NURSE ANESTHESIA

John J. Nagelhout
Karen L. Plaus

FIFTH EDITION

ELSEVIER

NURSE ANESTHESIA

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Foreword

Since the publication of the last edition of this textbook, we lost our mentor and dear friend John F. Garde. Without his encouragement and guidance, our anesthesia career paths would have been much different and no doubt much less rewarding. John encouraged the publication of the first edition of this text, two decades ago, as an important milestone in the evolution of the specialty of nurse anesthesia. He felt it showcased the breadth and depth of nurse anesthetists' contributions to research and clinical care. John transmitted his enthusiasm for the unique role of nurse anesthetists to everyone he encountered. He believed that anesthesia excellence was manifest when a clinician made a difference in the everyday lives of patients. He was without question the most consequential nurse anesthesia leader of his time. We reprint the foreword he wrote for the first edition of this textbook in his honor.

John J. Nagelhout
Karen L. Plaus

FOREWORD FOR *NURSE ANESTHESIA*, FIRST EDITION

As a new century dawns, nurse anesthetists continue to provide the highest quality anesthesia services to their patients. To put this into perspective, consider that nurse anesthetists safely and compassionately administered anesthesia throughout the entire last century and even prior to that. The writings of Alice Magaw, published between 1899 and 1906, provide a noteworthy benchmark. Magaw detailed the use of chloroform and other anesthesia with the open-drop technique in more than 14,000 surgical cases without a single fatality attributable to anesthesia. She was the first nurse anesthetist to publish articles on the practice of anesthesia and was considered "the mother of anesthesia" during a time when surgeons selected nurses to specialize in anesthesia to provide greater safety for patients requiring anesthesia.

Many pharmacologic and technologic changes in anesthesia have occurred, however, since those noble beginnings. The chapter titles of this textbook serve as an atlas to this expanded knowledge base: "Clinical Monitoring in Anesthesia," "Anesthesia Equipment," "Pharmacokinetics," "Inhalation Anesthetics," "Intravenous Induction Agents," "Local Anesthetics," "Opioid Agonists and Antagonists," and "Neuromuscular Blocking Agents, Reversal Agents, and Their Monitoring," to name a few. Look at the specialty components of anesthesia contained in this book: Cardiac Anesthesia; Respiratory Anesthesia; Thermal Injury and Anesthesia; Trauma Anesthesia; Outpatient Anesthesia; Regional Anesthesia; Anesthesia for Ophthalmic Procedures; Anesthesia and Orthopedics; Anesthesia for Ear, Nose, Throat, and Maxillofacial Surgery; Anesthesia and Laser Surgery; and the list goes on. The continuum for practice in the twenty-first century is that of professionals learning anew how to ensure the best possible care for their patients.

When Agatha Hodgins and other nurse anesthetist pioneers gathered in a classroom in the anesthesia department of the University Hospital of Cleveland on June 17, 1931, they established what was to become the American Association of Nurse Anesthetists (AANA). This group sought to place better qualified people in the field, to keep those already in nurse anesthesia abreast of modern developments, and to give protection and recognition to this group of professionals.

When the AANA values statement was adopted in 1995, it was not surprising that it reflected this earlier philosophy. The AANA values the following:

- Its members and the advancement of the profession of nurse anesthesia
- Quality service to the public through diverse practice settings based on collaboration and personal choice
- Integrity, accountability, competence, and professional commitment
- Scientific inquiry and contributions to the fields of anesthesiology, nursing, and related disciplines
- Participation in the formation of healthcare policy.

These value statements are supported by knowledgeable practitioners ever in pursuit of their craft

Nurse Anesthesia is a textbook that builds on a formidable knowledge base and draws on the expertise of CRNAs and other professionals practicing in today's fast-paced, ever-changing environment. I look upon this volume as a means to demonstrate the profession's growth and encourage CRNAs and student nurse anesthetists to read it and reflect upon the dynamic field they have chosen.

I would like to close with one of my favorite quotations from Ralph Waldo Emerson, which I believe reflects all professionals on their prospective journeys:

To laugh often and much; to win the respect of intelligent people . . . ;
to earn the appreciation of honest critics . . . ; to find the best in others . . . ; to leave the world a bit better. . . .
Bon voyage.

John F. Garde, CRNA, MS, FAAN

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Preface

This is a time of extraordinary advances in the accumulation, integration, and dissemination of medical knowledge. Technologic innovations that allow this textbook to be used in traditional as well as various electronic formats are now commonplace. We approach the 5th edition of *Nurse Anesthesia* with a clear intent to bridge these platforms while remaining true to our educational objectives. The volume of new information available to the clinician can be overwhelming, and keeping up-to-date in daily practice is an ongoing challenge. Since the conception of the first edition of this text over two decades ago, we continue to be guided by our original vision to fill the need for a scientifically based, clinically oriented work on which anesthesia practitioners and learners can rely to deliver excellent patient care. The need to integrate new concepts and findings into every patient encounter necessitates that we all commit to lifelong learning as one of the most basic tenets of our practice.

Our intent is to harness the vast knowledge that nurse anesthetists bring to clinical practice and provide a comprehensive, evidence-based resource for continuous learning. We are tremendously gratified that this textbook has become the seminal work of our specialty. This book is included in the Library of Congress's essential nursing textbooks for medical libraries throughout the United States and in national digital resource databases such as Mosby's Nursing Consult. We reach an international audience of nurses and nurse anesthetists and are always pleased when we hear of the positive impact we are having on anesthesia practice worldwide.

We are especially grateful to all of our new and returning authors who bring a wealth of expertise and experience to their respective areas. The majority of clinical anesthesia continues to be provided by nurse anesthetists, and this textbook is a testament to the leadership we bring to academic and clinical nursing. Each chapter has been extensively reviewed and revised to contain the most salient information available. The newest concepts, techniques, and areas of controversy in anesthesia are discussed in detail. This edition contains hundreds of new tables, figures, and boxes that add to the written materials. Effective anesthesia must be viewed as part of a therapeutic continuum of care. For this reason, we have been especially sensitive to include the latest medical and surgical information available from the specialties that impact our practice. Integrating new technology and knowledge in the basic sciences into clinical practice has allowed nurse anesthetists to continue to evolve as leaders in providing safe and comprehensive care.

As in past editions, we have completely revised our companion handbook that accompanies this text. It provides essential information regarding pathophysiology, surgical procedures, and drugs that can be easily accessed in both print and digital formats in the clinical setting.

Producing an educational resource of this size and complexity would not be possible without the tireless efforts of our authors and a broad array of experts. We would like to express our sincere gratitude to Retta Smith, who assisted in the production and editing of this textbook; our medical illustrator, Steve Beebe, Director of Multimedia Communications at Kaiser Permanente, who added dozens of new illustrations that greatly clarify the information presented; and Bryan Chen, computer graphics illustrator, Kaiser Permanente, who conceived numerous figures to illustrate the new material. We proudly carry over from the previous editions hundreds of anatomic figures that were specially hand drawn for this text by the renowned medical illustrator William E. Loechel. Special gratitude is expressed to the staff at Elsevier: Teri Hines Burnham, Executive Editor; Laura Selkirk, Senior Content Development Specialist; and John Gabbert, Project Manager.

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CHAPTER 1

Nurse Anesthesia

A History of Challenge

◆ *Bruce Evan Koch*

It is fitting to open a text on nurse anesthesia with a history chapter. Nurses were the first professional anesthetists in the United States; the vast majority of anesthetics provided in this country are administered by nurses. And nurses have contributed to progress in clinical anesthesia, patient safety, and the science, education, and public policies supporting anesthesia. By teaching what nurse anesthetists in the past have accomplished, oftentimes against great odds and with few or none of the resources available to us today, we fix in the pupil's mind the fact that anesthesia is a practice of nursing.

FIGURE **1-1** **A**, John F. Garde (1935-2009) and **B**, Ira Gunn (1927-2011).

People have known since the late eighteenth century that inhaling nitrous oxide or diethyl ether could produce euphoria. The English scientists Joseph Priestley and Humphrey Davy experimented on themselves and even partied with these substances. Davy famously speculated that nitrous oxide "may probably be used with advantage during surgical operations."[1]

At the same time, American medical students used ether and nitrous oxide recreationally. But almost 40 years would pass before they attempted to use these agents as adjuncts to surgery. Crawford Long, a Georgia physician, used diethyl ether for the removal of a small cyst in 1842. Unfortunately, he did not report his findings. At least two other men, the Massachusetts physician Charles Jackson and the Connecticut dentist Horace Wells, experimented with ether or nitrous oxide. Finally, on October 16, 1846, the Boston area dentist William T.G. Morton conclusively demonstrated the use of ether for surgical anesthesia in an operating room (now memorialized as the "Ether Dome") at Massachusetts General Hospital. So important was the event that the surgeon John Collins Warren, who had witnessed many prior failed attempts, reportedly exclaimed, "Gentlemen, this is no humbug." Another eminent surgeon who had been in attendance stated, "I have seen something today that will go around the world."[2] From their vantage point, optimism seemed justified; however, another half century would pass before the promise of painless surgery would be substantially fulfilled.

From the outset, Morton's discovery caused problems. People realized its value, and some wanted a piece of the action. Morton attempted to disguise ether so he could profit from it. He named the substance Letheon and applied for a patent. Long, Jackson, and Wells all claimed credit for Morton's discovery. The four men battled for years. The physician and writer Oliver Wendell Holmes, Sr. (father of the Supreme Court Justice) wrote to Morton, "Everybody wants to have a hand in a great discovery… All I want to do is give you a hint or two as to names." Rather than Letheon, Holmes suggested "anaesthesia from the Greek for insensible." But it seems Holmes too wanted something for himself. The term *anaesthesia*, according to historian Julie Fenster, "had been in use before to denote parts of the body benumbed but not paralyzed." She added that, "Holmes only borrowed the word for the new state of being, though he has received credit

for coining it."[3] As Robert Dripps dryly noted, "anesthesia was placed under a cloud."[4]

Nineteenth century anesthesia was problematic in other more important ways. Related infections and the careless administration of anesthesia vexed surgeons, plagued patients, and delayed progress in the field of anesthesia for decades. They led the historian Ira Gunn to term this era "the period of the failed promise."[5]

THE PROBLEM OF THE OCCASIONAL ANESTHETISTS

In the nineteenth century, physicians expanded surgery as a medical specialty, but not anesthesia, although there were calls for them to do so.[6] James Gather, the pioneer physician anesthetist, gave one explanation for this medical disinterest: "So intense had been the interest in surgery that anesthetics had been used only as a means to an end, and this fully explained the attitude of the profession on this subject in America at the present time." But money was also an issue. One physician commentator S. Simon doubted whether a physician "taking the work up as a specialty could make a living at it alone; and especially is this true in the smaller cities."[7] Indeed, the historian Marianne Bankert agreed: "Apart from the few physicians who had a genuine intellectual interest in anesthesia, it would also take years for the economics of anesthesia to make it an attractive area for their colleagues—if at first, only as a supplemental source of income."[8] The Philadelphia surgeon J.M. Baldy thought anesthesia unworthy of a physician's intellect: "Every physician obtains his medical education with the idea of practicing medicine, and it is only dire necessity which will compel him to give up such a future for the narrow one of anesthesia. Every physician who for a few years of his early and least busy life devotes a part of his time to anesthesia does so with the distinct idea of observing and learning surgery, with the result that he is shortly paying more attention to the technic [*sic*] of the operation than he is to the anesthetic, and within a year or so he is demanding an assistantship from the surgeon as a reward for his faithful service in what he considers a subordinate position and which he has all along filled under mental protest and only as a means to an end."[9] As a result, anesthesia remained a medical stepsister to surgery until well into the twentieth century.

The work of anesthesia was relegated to others. "Students, nurses, newly graduated physicians, specialists in other fields, and even custodians were called upon to be *etherizers*."[10] "Anesthesia could be anybody's business," wrote Virginia Thatcher.[11]

Lack of attention led to a degradation of knowledge and technique. "Within a few months (of the discovery) at the Massachusetts General Hospital, Morton's inhaling apparatus (which had worked well) was abandoned in favor of a small bell-shaped sponge, which was saturated with ether and applied directly over the nose and the mouth of the patient."[12] Not surprisingly, ether pneumonia resulted. Some surgeons therefore turned to chloroform, which had been discovered by James Simpson in England to have anesthetic properties. "But, very soon, a death occurred from chloroform, then another and another in quick succession. This led to its more careful and restricted use by some surgeons, to its total abandonment by others, but in 1855, the general mass of surgeons and physicians still continued its use…"[13] Thatcher cited one physician who, in 1859, wrote, "In some cases Dr. M. had seen chloroform administered by young gentlemen rather in a careless manner…In fact, he believed that most of the fatal cases can be traced to a careless administration of the remedy."[14]

Careless anesthesia persisted for decades. A cogent example was recorded in 1894 by Harvey Cushing, the founder of neurosurgery.* Almost fifty years after the discovery of anesthesia Cushing was a student at Harvard Medical School:

> *My first giving of an anaesthetic was when, a third-year student, I was called down from the seats and sent in a little side room with a patient and an orderly and told to put the patient to sleep. I knew nothing about the patient whatsoever, merely that a nurse came in and gave the patient a hypodermic injection. I proceeded as best I could under the orderly's directions, and in view of the repeated urgent calls for the patient from the amphitheatre it seemed to be an interminable time for the old man, who kept gagging, to go to sleep. We finally wheeled him in. I can vividly recall just how he looked and the feel of his bedraggled whiskers. The operation was started and at this juncture there was a sudden great gush of fluid from the patient's mouth, most of which was inhaled, and he died. I stood aside, burning with chagrin and remorse. No one paid the slightest attention to me, although I supposed I had killed the patient. To my perfect amazement, I was told it was nothing at all, that I had nothing to do with the man's death, that he had a strangulated hernia and had been vomiting all night anyway, and that sort of thing happened frequently and I had better forget about and go on with the medical school. I went on with the medical school, but I have never forgotten about it.*[i]

Surgeons began to appreciate the need for professional anesthetists. The need as Thatcher defined it was for anesthetists who would "(1) be satisfied with the subordinate role that the work required, (2) make anesthesia their one absorbing interest, (3) not look on the situation of anesthetist as one that put them in a position to watch and learn from the surgeon's technic [*sic*], (4) accept the comparatively low pay, and (5) have the natural aptitude and intelligence to develop a high level of skill in providing the smooth anesthesia and relaxation that the surgeon demanded." Some surgeons, particularly in the Midwest, "accepted in this capacity a class of persons for whom they had learned to have deserved respect and from whom they had obtained commendable assistance and service—the Catholic hospital Sister."[15] And so as a result of medical disinterest, poor delivery of anesthesia in general, and an overwhelming need, nurses were asked to give anesthesia.

HISTORICAL ANTECEDENTS OF THE NURSE AS ANESTHETIST

The Civil War provided the first opportunity for nurses to assume the duties of anesthetist. Evidence is found in three different accounts. Mrs. Harris from Baltimore, Maryland, took chloroform and stimulants to the Battle of Gettysburg. Harris "penetrated as near as possible to the scene of the conflict, ministering as much as in her power to the stream of wounded that filled the cars…"[16] It is not known whether Mrs. Harris was a nurse. A second report connects a nurse with administering chloroform. "Private Budlinger of the 76th Ohio Unit, after breathing it for a few minutes without any apparent effect, more chloroform was added and reapplied by a nurse in attendance."[17]

But the most convincing example was written *by* a nurse. Catherine S. Lawrence, a native of Skaneateles, New York, wrote a 175-page autobiography in which she recorded administering

*I am grateful to EI Eger, MD for this citation.

[i]Cushing HW, Letter to FA Washburn, Anaesthesia Charts of 1895, Treadwell Library, Massachusetts General Hospital, Boston MA, cited. In: Shephard DAE, *Harvey Cushing and Anaesthesia*, Canadian Anaesthetists Society Journal. Vol 12, no 5, September, 1965.

anesthesia as a Union Army nurse. Lawrence described her duties at a hospital outside Washington, D.C., during and after the Second Battle of Bull Run (1863). She administered medications, resuscitated with restoratives like ginger, tied sutures around arteries, and administered chloroform. "I rejoice that the time has arrived that our American nurses are being trained for positions so important. A skillful nurse is as important as a skillful physician."[18-21]

The early use of nurses as anesthetists was mostly an American phenomenon. However, a 1911 article revealed that "(In) the European hospitals female as well as male nurses…were taught how to give anaesthetics [*sic*] in the …(Franco-Prussian War of 1870-1871). Only the nurses gave anaesthesia in the ambulatory hospitals on the field."[22]

The First Civilian Nurses to Practice Anesthesia

Civilian nurses began to practice anesthesia during the 1870s in the Midwest. Sister Mary Bernard founded the Sisters of St. Joseph of Wichita, Kansas, and in 1877 entered St. Vincent's Hospital in Erie, Pennsylvania, to train as a nurse. A year later, she took over the anesthesia duties of the hospital. This practice was repeated throughout the Midwest. The Franciscan Sisters, who were active in the building and staffing of St. John's Hospital in Springfield, Illinois, were particularly successful in preparing hospital Sisters as nurse anesthetists and sending them out to other Midwestern hospitals. Having been prepared by another community of the Sisters of St. Francis (Syracuse, New York), Sister Mary Erhard went to Hawaii in 1886, where she administered anesthesia and performed other nursing duties on the island of Maui for approximately 42 years.

The St. Mary's Experience

In the summer of 1883, a very destructive tornado swept through Rochester, Minnesota. In its wake, wrote Helen Clapsattle, the tornado "left an idea in the mind of the mother superior of the Sisters of St. Francis." During rescue efforts, Mother Alfred paid a visit to Dr. W.W. Mayo. "Did he not think it would be well to build a hospital in Rochester?" Dr. Mayo thought the town too small to support a hospital, but "Mother Alfred had made up her mind. Quietly she overruled the Old Doctor's objections and said that if he would promise to take charge of a hospital, the sisters would finance it." St. Mary's Hospital was built and opened and although hospitals ranked low in the public's mind, their venture was a huge success. By 1904 it had expanded twice in order to keep up with demand and has endured until today as the Mayo Clinic. The Mayos (William Sr., William Jr., and Charles) won international acclaim for their surgery.

But how did the Mayos handle the administration of anesthesia? Like many surgeons, they were aware of its dangers, but unlike their colleagues on the East Coast they were quick to embrace the open drop method of ether when it was brought to the United States from Germany. They also differed from East Coast physicians in one other respect. "In employing a permanent full-time anesthetist, and that a nurse, the Mayos were unusual if not unique. In other hospitals anesthetizing was one of the duties of the interns."

Why would they give the job to nurses? "The Mayos had given the job to a nurse "in the first place through necessity; they had no interns. And when the interns came, the brothers decided that a nurse was better suited to the task because she was more likely to keep her mind on it, whereas the intern was naturally more interested in what the surgeon was doing."[23]

Nurses won the Mayo's admiration by improving anesthesia care. Alice Magaw could discuss "a hundred and one details as to signs of sufficient anesthesia and ways of recognizing and preventing impending disaster." Magaw, along with her pupil Florence Henderson, refined and advocated the dripping of ether. Ether anesthesia required vigilance and careful attention to detail and to the psychological care of patients to minimize the agitation that often led to disasters like the one described by Harvey Cushing earlier.

Florence Henderson described how this was done. "A modified Esmarch inhaler, which is covered with two layers of stockinet, is used…With the mask held about an inch from the face the ether is dropped upon it, slowly at first, and the patient is asked to breathe naturally through the nose. Then the mask is gradually lowered, and the rapidity of the dropping increased, care being taken not to give the ether fast enough to cause a sensation of smothering or suffocation. As soon as the jaw relaxes the head is turned to one side, because the patient usually breathes more easily with the head in this position." This was quite a contrast to the "crude" methods of most early anesthetizers.

And it was successful. Nancy Harris and Joan Hunziker-Dean, who investigated Florence Henderson's life, concluded that "through a delicate balance of interpersonal skills and technical expertise, (Henderson) was able to essentially eliminate the excitement phase of ether anesthesia and consistently used a fraction of the usual ether dose. She demonstrated to all who observed that the administration of ether anesthesia could be elevated to an art form."[24]

Magaw and Henderson made anesthesia safe. Magaw accounted delivery of over 14,000 anesthetics "without an accident, the need for artificial respiration or the occurrence of pneumonia or any serious results."[25] Included were anesthetics for abdominal, intraperitoneal gynecologic, urologic, orthopedic, ophthalmic, head and neck, and integument operations. Some were even conducted in the prone position.[26]

Thatcher wrote that it was Alice Magaw who "brought to the profession of nurse anesthetist as well as to the Mayo Clinic no little fame at a time when poor anesthesia was the major worry of most surgeons." Charles Mayo was so impressed by Magaw that he named her "The Mother of Anesthesia."[27] Surgeons who visited from Minneapolis, Iowa, Baltimore, Chicago, and England "sent selected nurses to Rochester to observe Alice Magaw and other nurse anesthetists at St. Mary's Hospital at their work."[27]

Magaw and Henderson introduced better teaching methods too. Early anesthesia education has been described by A.J. Wright as "on the spot training of any person available…" At Mayo sometimes the "nurses stayed for 2 or 3 months and learned to give ether under supervision."[27]

The Lakeside Experience

A second "Mecca" of nurse anesthesia developed in Cleveland, Ohio. In 1900 Agatha Hodgins, a Canadian nurse, went to Cleveland to work at Lakeside Hospital. Dr. George Crile chose her to become his anesthetist in 1908, and as such she became perhaps even more renowned than Alice Magaw. Together with Crile, Hodgins pioneered the use of nitrous oxide/oxygen anesthesia and introduced it in World War I, opened and led a prominent school for nurse anesthetists that endured the first major challenge from physician anesthetists, and in 1931 Hodgins alone founded the American Association of Nurse Anesthetists (AANA).

Hodgins' primary interest was in education. Like St. Mary's Hospital, Lakeside Hospital was the recipient of many requests for anesthetist training from both physicians and nurses. According to Thatcher, "Visiting surgeons eager to emulate

the Lakeside methods, customarily bought a gas machine (the Ohio Monovalve) and then sent a nurse to Cleveland to find out how it worked."[28] Hodgins recalled, "The number of applicants increased so rapidly that we felt some stabilizing of work necessary and the matter of a postgraduate school in anesthesia presented itself." In 1915, Hodgins opened a school at Lakeside Hospital. The Lake School was not the first formal postgraduate anesthesia educational program. That honor belongs to St. Vincent's Hospital in Portland, Oregon. But the Lakeside School is the only program for which original records still exist. There were admission requirements, the course included both clinical and didactic components, tuition was charged, and a diploma was granted. "The department of anesthesia encompassed the school, both being under the charge of Agatha Hodgins as chief anesthetist. She, in turn, worked under the jurisdiction of the superintendent of the hospital and the chief surgeon. For the supervision of the students she had 1 or 2 assistants until 1922 when the number was increased to 3."[29] The evolution of nurse anesthesia education into a more formalized, scientifically based discipline can thus be seen.

Although records do not exist, 54 similar programs were said have to existed at major hospitals in Chicago, Illinois; Worcester, Massachusetts; Milwaukee, Wisconsin; New Orleans, Louisiana; Baltimore, Maryland; Ann Arbor, Michigan; St. Louis, Missouri; Detroit, Michigan; Poughkeepsie, New York; Tacoma, Washington; and Minneapolis, Minnesota.[30]

The Proliferation of Nurse Anesthetists

Prior to World War I, anesthesia grew more sophisticated. Nitrous oxide was reintroduced, and with it came the first anesthesia machines. Surgeons and hospitals sought nurse anesthetists who were capable of using the machines. The first recognition of the value of formalized education also occurred at this time. Four postgraduate programs were developed: at St. Vincent's Hospital in Portland, Oregon (1909);[31] at St. John's Hospital in Springfield, Illinois (1912); at New York Postgraduate Hospital in New York City (1912); and at Long Island College Hospital, Brooklyn, New York (1914).[32] Other nurse anesthesia programs were developed as a part of the undergraduate nursing curriculum as a specialty option. Isabel Adams Hampton Robb, a pioneer nursing leader and the first superintendent of the Johns Hopkins School of Nursing, which had opened in 1889, had in 1893 published a nursing textbook titled *Nursing: Its Principles and Practices for Hospital and Private Use*; this textbook included a chapter titled "The Administration of Anaesthetics." By 1917, as a result of the "superior quality of anesthesia performed by nurse anesthetists,[33] they were given the responsibility for surgical anesthesia at Johns Hopkins Hospital in Baltimore, where a training program was established under the direction of Ms. Olive Berger.

But success bred resistance. Thatcher wrote that, "The rapid growth of postgraduate schools of anesthesia in which nurses were trained, as well as the increasing enthusiasm for the trained nurse anesthetists during World War I, did not escape the attention of physician specialists in anesthesia, and during the 1920s resentment against the nurse anesthetist culminated in attempts to legislate her out of existence."[34]

The Great War, a Small Battlefield

Nurse anesthetists played a very large role during World War I. Their involvement began in 1913, 4 years before the United States became involved militarily, and lasted until the armistice in 1918.

When America entered the war, the Army Nurse Corps numbered 233 regular nurses; it would grow to 3524 nurses by 1918. The number of nurse anesthetists is unknown because at the time nurse anesthetists formed part of the general nursing staff.[35] However, nurse anesthetists were credited with introducing nitrous oxide/oxygen, and teaching its administration to the English and French.[36] As a result of the superior performance of nurse anesthetists, both the Army and the Navy sent nurses for anesthesia training for the first time.

Several outstanding World War I–era nurse anesthetists have been remembered because they wrote of their work. Nurse anesthetists spent countless hours etherizing wounded soldiers as they arrived in "ceaseless streams for days at a time after battles," wrote Mary J. Roche-Stevenson. "Work at a casualty clearing station came in great waves after major battles, with intervals between of very little to do.…Barrages of gun fire would rock the sector for days, then convoys of wounded would begin to arrive by ambulance. Night and day this ceaseless stream kept coming on.… The seriously wounded, especially the ones in severe shock, were taken to a special ward, given blood transfusions and other treatments in preparation for surgery later. From the receiving tent, the wounded were brought to the surgery, put on the operating tables stretcher and all given an anesthetic, operated upon, picked up on their stretcher, and loaded on hospital trains for evacuation to base hospitals."[37] Terri Harsch,[38] who described the works of Roche-Stevenson and others such as Sophie Gran Winton, reported that 272 nurses were killed during the war.

In a paper about Miss Nell Bryant, who was the sole nurse anesthetist for Base Hospital Number 26 from the Mayo Clinic[39] we learn that chloroform and ether were in use, the physiology of shock was poorly understood, oxygen and nitrous oxide were given without controlled ventilation, and venipuncture involved a surgical cutdown.

Anne Penland was a nurse anesthetist with the Presbyterian Hospital of New York unit, Base Hospital Number 2. She had the honor of being the first U.S. nurse anesthetist to go officially to the British front, where she so won the confidence of British medical officers that the British decided to train their own nurses in anesthesia, ultimately relieving more than 100 physicians for medical and surgical work. Several hospitals were selected for this training of British nurses, including the American Base Hospital Number 2, with Penland as the instructor.[40]

Commenting in the *Bulletin of the American College of Surgeons*, Frank Bunts wrote, "The (First) World War demonstrated beyond any question the value of the nurse anesthetist."[41] George Crile speculated that "if the Great War had gone on another year, the British army would have adopted the nurse anesthetists right in the middle of the war."[42] Looking back after World War II, Lt. Colonel Katherine Balz, Deputy Chief of the Army Nurse Corps, credited nurse anesthetists for the fact that 92% of "battle wounded who reached Army hospitals alive were saved."[43]

ANESTHESIA: MEDICINE, NURSING, DENTISTRY, OR WHAT?

Although few physicians chose to specialize in anesthesia before World War II, one who did, Francis Hoeffer McMechan—a Cincinnati native—began a crusade to claim the field solely for physicians around 1911. McMechan had become disabled shortly after entering the field of medicine and did not practice. He and his wife undertook his mission through writing, publishing, and speaking. McMechan's first target was the high profile Lakeside School and its famous surgeon George Crile. He alleged that anesthesia was the practice of medicine, and he petitioned the Ohio Medical Board to take action. McMechan considered Ohio a "pivotal state in the national fight for the preservation of the status of the anesthetist as a medical specialist."[44]

The board acted. In a letter to Crile in 1916, the board claimed that no one other than a registered physician was permitted to administer anesthesia. Essentially, the board ordered Lakeside Hospital's School of Nursing to cease its anesthesia program or lose its accreditation. Not wanting to be responsible for the loss of the school's accreditation, Crile obeyed the order, pending the outcome of a hearing conducted in 1917. At the hearing, Crile took the position that Lakeside Hospital was only following the lead of many of the major clinics in the country. Crile managed to persuade the board of medicine to lift its order, and he was able to reinstitute his nurse anesthesia educational program and his use of nurse anesthetists.

But to protect nurse anesthetists, Crile took an additional step. In 1919, together with supporting physicians, he "introduced a bill into the (Ohio) legislature to legalize the administration of anesthetics by nurses."[45] An amendment to the legislation stated that nothing in the bill "shall be construed to apply to or prohibit in any way the administration of an anesthetic by a registered nurse *under the direction of and in the immediate presence of* (emphasis added) a licensed physician," provided that such a nurse had taken a prescribed course in anesthesia at a hospital in good standing.[46] Physician supervision, first mentioned here, would recur many times over.

A second attempt to legislate nurse anesthesia out of existence occurred in 1916. The Louisville (Kentucky) Society of Anesthetists passed a resolution proclaiming that only physicians should administer anesthesia. The attorney general concurred, and the Kentucky State Medical Association followed with a resolution stating that it was unethical for a physician to use a nonphysician anesthetist or to use a hospital that permitted nurses to administer anesthesia. These events prompted the surgeon Louis Frank and his nurse anesthetist, Margaret Hatfield, to ask the state board of health to join them in a suit against the Kentucky State Medical Association. In the lower court, they lost.

But on appeal, they won. In 1917 Judge Hurt of the Kentucky Court of Appeals not only confirmed the right of nurses to administer anesthesia, he also enunciated clearly that state licensure was meant to protect consumers, not professionals.

These two cases showed physicians they could not rely on the courts to end nurse anesthesia. But still they were not deterred. A California case (1933 through 1936) in which Dagmar Nelson, a nurse anesthetist, was charged with the practice of medicine has been considered as the defining test case of whether nurse anesthetists are practicing medicine or nursing when they administer anesthesia. This case was decided in favor of Dagmar Nelson at each level of the California civil court system. The California Supreme Court ruled again that the functioning of the nurse anesthetist under the supervision and in the direct presence of the surgeon or the surgeon's assistants was the common practice in operating rooms; therefore the nurse anesthetist was not diagnosing and treating within the meaning of the medical practice act.[47,48]

At the time, nurse anesthetists welcomed and embraced supervision. Gene Blumenreich, who has written extensively on the legal history of anesthesia, noted that "A number of states adopted statutes recognizing the practice of nurse anesthetists. Typically, these statutes followed the formulation in *Frank v. South* and provided that nurse anesthetists were to work under the 'supervision' or 'direction' of a physician." But, the statutes did not define supervision. "It is clear that the legislation was not attempting to create new duties and responsibilities but merely to describe what was already going on in practice…to explain why nurse anesthetists were not practicing medicine."[49] Decades later, however, supervision would become a battleground.

ORGANIZATION: "WE WHO ARE MOST INTERESTED"

In 1926 Agatha Hodgins called together a small group of Lakeside Hospital alumnae to form a national organization. Hodgins had been an educator since World War I, and she must have sought strength in numbers to address problems related to education. One hundred thirty-three names were submitted and tentative bylaws were drawn up. But, as Ruth Satterfield recalled, "much of what she (Hodgins) said fell on deaf ears."[50] The association failed to thrive. As Thatcher has noted, "It is only when common problems become too big for individual solutions that the average professional person becomes conscious of the protection that can be found in organization." The national organization of nurse anesthetists would only come to life after several problems coalesced in 1931.

Physician opposition to nurse anesthetists was one factor in this development. For example, California nurse anesthetists organized in 1929 after the Board of Medical Examiners alleged that Adeline Curtis was practicing medicine illegally. Curtis, a natural public speaker, went on the road with this refrain: "…we can get nowhere without an organization. We're in the minority of course but we must organize."[51] California held its first meeting February 3, 1930.[52] Other states followed suit, and by the end of the 1930s, 23 had established organizations.

Hodgins in 1935 noted that "the strongest objection of physicians during this period was against those nurse anesthetists who were working on a fee for service basis."[53] Hanchett,[54] who examined the *Chalmers-Francis v. Nelson* case (1933), concluded that plaintiff California physicians were motivated by economic factors. And Thatcher observed that "Miss Hodgins' concept (of an organization) might never have been sparked into action, and organizations of nurse anesthetists might have stayed at the local level if the collapse of the nation's economy had not revived the physician anesthetist's interest in protecting his income by eliminating competition from nurses…"[55]

But it was the poor state of anesthesia education that most motivated Agatha Hodgins. In 1931 she wrote to Adeline Curtis who was embroiled in the California dispute: "My chief interest is in education."[56] And with the previous factors compounding each other, Agatha tried again.

The National Association of Nurse Anesthetists (NANA) was born on June 17, 1931. Its name would be changed to the American Association of Nurse Anesthetists in 1933. The first meeting was held in a classroom at Lakeside Hospital and was attended by 40 anesthetists from 12 states.[57]

Right away, the new association set its sights on improving the quality of anesthesia by raising educational standards. The new president, in a letter to Marie Louis at the American Nurses Association wrote, "It is because of the increasing number of nurses interested in the particular work and growing realization of difficulties existing because of insufficient knowledge of, and proper emphasis on, the importance of education, that we who are most interested are taking the steps to insure our ability to define and help maintain the status of the educated nurse anesthetist."[58]An education committee was formed. Chaired by Helen Lamb, the committee crafted "recommended" curriculum standards for schools and ratcheted them up in 1935 and again in 1936.

But the fledgling association was weak. With few members and little money, it could not hold its first national meeting for 3 years, much less advance an agenda of education reform. In that period, Agatha Hodgins sustained a heart attack and "for all practical purposes bowed out as administrative leader." Gertrude Fife took over the day-to-day affairs. There grew the realization, attributed by Bankert to Helen Lamb and her Education Committee, that the problems were of such magnitude that an

alliance with a more influential professional association would be required. But which one?

Forming an alliance with a major professional organization would likely prove problematic, as divergent interests collide and trust is tested to its limit. The small young NANA would have to fight to maintain independence, while at the same time obtain much needed support. According to historian Rosemary Stevens, the AANA "made overtures to the American Board of Anesthesiology (ABA) in 1938 which might have enabled the two movements to combine and the anesthesiologists to take on the responsibility of the nurses' training." But at the time, the ABA was struggling to emerge from under the wing of surgery, and "the nurses were summarily rejected."[59]

So, instead, with the guidance and support of the American Hospital Association, Gertrude Fife and Helen Lamb planned the first meeting, which was held in Milwaukee in 1933. They also crafted a highly centralized organization to efficiently address the association's concerns. Thatcher listed those concerns: "(1) building up the membership so that there would be a creditable showing at the Milwaukee meeting; (2) arranging a program; (3) getting a constitution and the bylaws revised; and (4) launching the association's educational program."

Membership was to be a privilege, a mark of distinction. The bylaws required that an active member have graduated from an accredited school of nursing, have passed the required state board examination, and maintained an active license. Importantly, an applicant must "have engaged for not less than three years in the practice of the administration of anesthetic drugs prior to 1934, and must be so engaged at the time of making application for membership."[60] The founders meant business.

These accomplishments are all the more remarkable in light of the "most important event" of the year, the existential threat posed by the Dagmar Nelson trial in California.

But there were other strides made during this era. As membership surpassed 2500, a survey of schools using on-site surveyors evaluated courses being taught. An Anesthesia Records Committee was formed to create a standardized anesthetic record. And the credential "Member of the American Association of Nurse Anesthetists" was implemented. These strides served to show that the profession was coming of age. Then World War II erupted and stalled further progress.

WORLD WAR II AND NURSE ANESTHETISTS

When World War II began, nurse anesthetists once again distinguished themselves. They served at home and in all theaters of operations. Nurse anesthetists were serving in Hawaii when Pearl Harbor was attacked. Mildred Irene Clark, who was originally from North Carolina, joined the Army in 1938. Under Army auspices, she graduated from Jewish Hospital in Philadelphia, where Hilda Salomon was program director. Clark also received training from John Lundy and Florence McQuillen at the Mayo Clinic (Woodson MIC: personal oral communication to Ira Gunn, October 1994).

Clark was on assignment as a nurse anesthetist at the Schofield Barracks Hospital in Hawaii when Pearl Harbor was struck. Clark was among other nurse anesthetists on active duty who set up educational programs for preparing additional nurse anesthetists. Clark completed her career in 1967 as the Chief of the Army Nurse Corps, the first nurse anesthetist to hold this position.

Annie Mealer, another notable Army nurse anesthetist, was sent from Walter Reed Army Medical Center to the Philippines in 1941. She served as chief nurse and chief nurse anesthetist of the hospital on Corregidor.

For 3 years Mealor was held as a prisoner of war. Among the nurse anesthetists imprisoned with her were Denny Williams, Doris Keho, and Phyllis Arnold Iacobucci. They and 62 other Army nurses were imprisoned until February 3, 1945.

Marianne Bankert quotes at length a letter Annie Mealor later wrote in which she described her experiences. Mealer recalled housing President Quezon and his family, dodging "Jap bombs," and "giving anesthetics to one casualty after another" who "all needed help that only a nurse could give them." In Japanese custody aboard a troop ship, and sick with dengue fever, Mealer wrote, "I threw my cape down on the deck to lie on it and prayed that the wind would blow the fumes of the stale fish in another direction. I looked around at the nurses in the various uniforms of coveralls and skirts. They had grown slender as reeds, but were smiling over some secret rumor about liberation—not realizing they had nearly three more years of hard work and starvation."[61]

Wartime greatly expanded the need for anesthetists in both military and civilian hospitals. Lt. Col. Katherine Balz, the Education Consultant to the Army, estimated that "approximately 15,000,000 patients were admitted to Army hospitals during the war, and something had to be done to provide the anesthesia services needed for these patients' care." Rosemary Stevens reported that in 1942, nurse anesthetists outnumbered anesthesiologists by 17 to 1.[62] By the end of World War II, the Army Nurse Corps had educated more than 2000 nurse anesthetists, most (though not all) of whom were given an abbreviated 4- to 6-month curriculum patterned after that required by the AANA.[63] Lt. Col. Balz recalled a situation in which some volunteer nurses were placed into anesthesia service after only 90 days training! "At the end of that time, these volunteers were thrown into a situation in which 100 operations were being performed every 24 hours….there were not enough hours in the day to care for the patients and at the same time provide for formal instruction. In this hospital, over 5,000 anesthetics were given during a six months' period, and not one death or complication occurred as a result of anesthesia."[64]

The increased needs and the shortened training period posed "extraordinary complications" for the AANA. The quality of newly minted graduates had to somehow be addressed. To maintain standards, the AANA implemented a temporary "program of certification by exam and certification by waiver."[65] Accreditation of programs was postponed entirely. In 1943 the Annual Meeting was reduced to just 1 day; a quorum could not be met, so already elected officers remained on the board.

From her sick bed, Agatha Hodgins sent these words of encouragement: "The immense and vital part all branches of medical service will play in this continuing task can—because of its greatness—be now only dimly conceived. They will in very truth be a 'green island' in 'the wide deep sea of misery' now encompassing the earth." These were among her last words. Hodgins passed away in 1945. Her gravesite is located on Martha's Vineyard.[66]

As World War II drew to a close, the AANA's plans for instituting a certification examination for civilian membership were at last realized. The first examination was given in June 1945. It was completed by "90 women in 39 hospitals in 28 states, plus one in the Territory of Hawaii."[67] It would be hard to conclude that their "high type of service" during the two world wars did not account for this accomplishment.

Nationally, World War II was also associated with bringing about certain human rights advances. President Truman integrated the armed forces in 1948. And the first male nurse was commissioned in 1955, a step attributed to nurse anesthesia. The AANA admitted its first African-American member in 1944 and its first male member in 1947. The first two male nurses commissioned

in the Army Nurse Corps were nurse anesthetists, Edward L.T. Lyon of New York and Frank Maziarski of Washington, who later became the sixtieth president of the AANA.[68,69]

A SHORT-LIVED PEACE FOR NURSE ANESTHETISTS AND THE NATION

After the war the number of physicians in anesthesia greatly increased. In 1940 there were only 285 full-time anesthesiologists, 30.2% of whom were certified; in 1949 there were 1231, 38.3% of whom were certified.[70] Ira Gunn attributed the increase to wartime medical experiences "alerting physicians to the potential of anesthesia as a specialty.[71] Bankert listed as causes "the increased complexity of anesthetics, but also…a military structure that encouraged medical specialization and a GI Bill that supported medical residencies."[72] The country produced more physicians, and many were drawn into anesthesiology.

An "old problem" reappeared. For upon returning from military service, "medical (physician) anesthetists—*many of them trained in the Armed Services*—(in an effort) to establish themselves in a civilian economy, brought about a resurgence of activity against the nurse anesthetist."[73] One activity was to render "historically invisible" the contributions of nurses. For example, the centennial celebration of ether at the Massachusetts General Hospital made no mention of nurse anesthetists. (It would, in fact, be the impetus for Virginia Thatcher's seminal history book.) Bankert listed other similar efforts: "a myth is launched of the early superiority of British anesthetists—a land, so the story goes, which was never so foolish as to allow nurses to administer anesthetics; the national association of physician-anesthetists backdates its founding (from 1936) to 1905; a new word (*anesthesiologist*) is coined in the 1930s to distinguish the work of physician-anesthetists from nurse-anesthetists; 'historical' studies are published with titles such as *The Genesis of Contemporary Anesthesiology*, as though nothing of significance occurred in the field until the 1920s, when physician-anesthesia began to be effectively organized…"[74]

Then anesthesiologists launched a public relations effort to denigrate nurse anesthetists. Bankert reported that in 1947, several "major articles" appeared in *Look Magazine, Hospital Management, Reader's Scope,* and *This Week*. One excerpt railed, "Bad anesthesia causes more operating-room deaths than surgery. Now many hospitals have physician-anesthetists to protect you." And fear was a part of this campaign: "Until the operating rooms of our hospitals are brought into line with the clear requirements of modern anesthesiology, hundreds of Americans will continue to die needlessly on operating tables, sacrificed to ignorance and incompetence."[75] It is not known what if any evidence was offered to support this opinion.

These efforts did not accomplish their goal. Surgeons, the public. and "often the anesthesiologist himself" were not dissuaded from trusting nurse anesthetists. However, they did "discourage many capable nurses from entering the field," prompting the AANA to promote the profession and recruit nurses who had been frightened away.[76] And soon thereafter, the first quality of care study in anesthesia took place. The results according to Gunn "shocked and dismayed many anesthesiologists."

In 1954 Beecher and Todd published a prospective analysis of anesthesia outcomes collected between 1948 and 1952. Ten university hospitals contributed data for approximately 600,000 anesthetics. The nurse anesthetists' death rate was one half that of anesthesiologists. Furthermore, there was no difference in physical status between groups of providers. However, that did not stop the authors from surmising (without evidence) that anesthesiologists were anesthetizing more complex surgical cases.[77] Not surprisingly, more quality comparisons would be conducted in the coming decades.

In fact, as Gunn pointed out, nurse anesthetists at that time were second to no one. In 1948, for example, Olive Berger at Johns Hopkins reported 480 anesthetics for repair of cyanotic congenital heart disease, including tetralogy of Fallot.[78] Betty Lank at Boston Children's Hospital, pioneered the use of cyclopropane in pediatric anesthesia.[79]After the United States committed troops to South Korea, the National Women's Press Club named the Army nurse as its Woman of the Year (1953). An Army nurse anesthetist, Lieutenant Mildred Rush from Massachusetts, was designated to accept the award on behalf of all Army nurses.

And it was the Korean War that ultimately led to the accreditation of all nurse anesthesia education programs. During the war itself, the AANA had begun accrediting programs, but it had little clout, and within each state the Veteran's Administration had its own standards concerning 'so-called' accredited schools. To enforce proper standards, the AANA successfully appealed to the Department of Health, Education, and Welfare for recognition as the sole accrediting agency.[80] Within a few years, civilian schools either brought themselves into compliance with AANA standards, or quietly closed.

SETTING EDUCATION STANDARDS AND DEVELOPING AN APPROVAL PROCESS

The foundation for the formal education of nurse anesthetists was embedded in the 1933 bylaws of the NANA (later renamed the American Association of Nurse Anesthetists [AANA]). The newly formed association was directed "to develop educational standards and technique(s) in the administration of anesthetic drugs," as specified in Article II, Objectives.[81] This objective revealed the vision of early nurse anesthesia leaders for a formal educational process that has grown and matured throughout the twentieth and early twenty-first centuries.

By 1934 the NANA's Educational Committee had studied curricular outlines submitted to them by several schools of anesthesia as the basis for creating a standard curriculum that should be offered to all students. In addition to the detailed standard curricular outline, other guidelines for operating a school of anesthesia were developed, including the type of conducting institution, instructors, recordkeeping, and other activities.[82] During the first decade of its existence, the Educational Committee worked on developing a list of schools of anesthesia and establishing an inspection process to evaluate whether the schools were offering the recommended standard curriculum. By 1939 a national survey of 106 hospitals and institutions had been completed that identified 39 courses of instruction located in 18 states of the United States. There was also a plan to have a representative of the NANA visit all schools for the purpose of collecting information, coordinating training methods, and promoting quality education. Helen Lamb's work on developing the initial method for approving schools led to a formal accreditation process.[82]

Lamb, a former student of Agatha Hodgins, frequently addressed the value of a university education for nurse anesthetists. She was founder, then director, of the Barnes School of Anesthesia in St. Louis, Missouri, from 1929 to 1954.[53] In 1989 the AANA established an annual award in Lamb's name to honor outstanding educators.

With the advent of World War II, a shortage of anesthesia personnel became evident, and many hospitals began training anesthetists to meet their own needs. During the critical period, the professional organization encouraged the use of established schools of anesthesia that followed the association's standard curriculum

to train anesthetists, rather than the development of new schools that might use substandard methods of training.[82]

The publication of the 1945 *Essentials of an Acceptable School of Anesthesiology for Graduate Registered Nurses* containing information on the proper training of nurses was partially in response to the establishment of new schools with questionable quality during the manpower shortage in World War II. A standard curriculum was finally submitted to members of the board of trustees by the Educational Committee on July 11, 1945, for approval as part of the *Essentials*.[82]

The formal accreditation process for schools of nurse anesthesia was approved unanimously during the 17th Annual Meeting of the AANA in September 1950. Membership dues were also increased at that meeting to $20, with $5 of the assessment allocated for the accreditation program. The formal motion to approve the accreditation program included the rationale that the competency of past, present, and future graduate nurse anesthetists could be emphasized by having the schools of anesthesia inspected by qualified consultants, approved, and publicly endorsed. According to Helen Lamb, serving as chair of AANA's Advisory to the Approval Committee, "Such accreditation would vouch for the fact that graduate nurse anesthetists, who now occupy or who in the future enter our field from our standard courses of training, are irreproachably equipped, educationally and clinically, to meet the professional requirements and responsibilities that are inherent in the practice of our specialty."[82]

In 1975 the Council on Accreditation of Nurse Anesthesia Educational Programs (COA) was established as an outgrowth of the AANA's Approval of Schools Committee Recognition. The COA was established in response to major revisions of the United States Office of Education (USOE) recognition requirements. The revised USOE criteria mandated a structural change in the AANA that resulted in the formation of three semiautonomous councils—accreditation, certification, and practice. The formation of the original council structure with three separate councils was a major change in the operation of the AANA. The COA has been continuously recognized by the U.S. Department of Education (USDE). In addition, the COA has been recognized by the Council on Higher Education Accreditation (CHEA) or its successors since 1985.

THE NEW AGE OF NURSE ANESTHESIA: THE 1960s

When the 1960s began, the AANA had evolved into a more fully fledged professional organization. It was under the influential leadership of its first full-time executive director, Florence McQuillen, who was hired in 1948. John Lundy, the chairman of anesthesiology at the Mayo Clinic, worked with McQuillen and referred to her as "the best-read person on the literature of anesthesia." McQuillen exerted such a powerful influence at the AANA[83] that in 1965 she was named association executive of the year by the journal *Hospital Management*.

During McQuillen's tenure, other certification of graduates and accreditation of programs placed the association firmly within the regulatory and educational spheres of American health care. Membership grew considerably, and exceeded 10,000. All 50 states had associations affiliated with the AANA. And the members had approved the beginnings of continuing education.[84]

But the decade of the 1960s was a transitional period for everyone in health care, including nurse anesthetists. The United States, which had relied increasingly on employer-based health insurance since WWII, extended coverage to elderly and poor people through Medicare and Medicaid in 1965. These programs led to a greater need for health providers. Educational programs for all health professionals, including nurse anesthetists, increased accordingly.

Growth was embraced by anesthesiologists in ways that were not entirely welcomed by Certified Registered Nurse Anesthetists (CRNAs). Gunn recounted that "Anesthesiologists held meetings to define the future." Some sought an all-physician specialty. Others knew such a goal was unattainable because nurse anesthetists were "providing the majority of anesthesia care in the United States."[85] To resolve the manpower issue, two ideas gained prominence. Adherents of the first idea advocated support of nurse anesthesia educational programs.[86] Adherents of the second idea proposed another type of anesthesia practitioner based on a physician assistant model that the anesthesiologist could control.[87,88] Either option would be problematic.

Clearly there would be value in communication between the two groups. But since 1947, the American Society of Anesthesiologist's (ASA's) "Anti-Adriani Bylaw" had precluded communication with the AANA. According to Marianne Bankert, ASA President Albert Betcher (1963) initiated efforts to establish relations with nurse anesthetists, in light of the reality presented by "present and projected personnel needs."[89]

In 1964 the ASA and AANA established a liaison committee that met twice a year. Florence McQuillen articulated the Association's goals. Through dialogue, the AANA sought "no interference with the progress of educational programs of the Association, and a curbing of anti-nurse anesthetist activity and publicity."[90] After 3 years of meetings, the *AANA News Bulletin* and the *ASA Newsletter* published a joint statement that read in part, "It is, therefore, highly desirable that continued close liaisons be developed between these organizations for enhancing the quality and quantity of available personnel, for advancing educational opportunities, for determining ethical relationships and for the overall improvement of patient care." C.R. Stephens, a noted anesthesiologist who had worked with nurse anesthetists for many years, wrote in a 1969 report to the ASA, "Progress has not been rapid, but the dialogue has enhanced understanding."[91] That progress and understanding would be tested severely during the next decade.

THE 1970s: A TURBULENT DECADE

Long-term American involvements, such as the Vietnam War, and the era of progressive reforms became part of this country's history during the 1970s. As federal expenditures for health care rose, the government exerted greater scrutiny of health services. In 1974 the U.S. Commissioner of Education revised the criteria governing nationally recognized accrediting agencies, of which the AANA was one. The new criteria were intended to protect the public's interest by completely separating the professional obligations of an association from its proprietary concerns. The AANA would have to give up its roles in accrediting programs and certifying graduates, roles it had nourished and cherished since 1931. To divest itself of these operations, AANA undertook a wholesale reorganization. In 1975, largely through the work of Ira Gunn, assisted by Ruth Satterfield, Mary Cavagnaro, and Ed Kaleita, autonomous councils were established and granted accrediting and certifying functions.[92]

The process of governmental review and revision provided an opportunity for physicians to attempt to take control over CRNA education. The ASA proposed a competing accrediting organization, the Faculty of Nurse Anesthesia Schools, and it misused both the Joint Statement issued by the AANA/ASA Liaison Committee (1972) and a manpower study to justify their activities. After many tense months of strategizing, however, the Councils on Accreditation and Certification ultimately won the government's approval.

The struggle over accreditation and certification had several important outcomes. By separating out the accrediting and certifying functions, the AANA was free to pursue laws and policies that would protect CRNAs, without fear of creating a conflict between its private interests and its public duties. Secondarily, it revived the AANA's relationship with the American Nurses Association, but it "increasingly strained relations between the AANA and ASA."[93]

Ira Gunn recalled that some nurse anesthetists saw this episode as an opportunity to upgrade educational programs and move into universities and colleges. John Garde, Ira Gunn, Joyce Kelly, and Sister Mary Arthur Schramm were the CRNAs who pioneered programs in the baccalaureate and then graduate frameworks in the early 1970s.[94]

In another outgrowth of this era, state nurse anesthetist organizations sought explicit legal recognition, either within the state nurse practice act or as a separate law. Gunn traced this phase of licensure to a Department of Health, Education, and Welfare committee report of 1971 that "supported an extended scope of function for registered nurses." Other factors influencing its development included higher educational standards, increased complexity of practice, the women's movement, and the increased presence of men in nursing.[95]

Nurse anesthetists were soon addressed in one or more places within state statutes or regulations in all 50 states. However, according to Mitchell Tobin, the former Director of State Government Affairs for AANA, "Although it is clear that legitimacy of nurse anesthesia as a profession is widely accepted, the manner, type, and frequency of statutory and regulatory recognition of CRNA practice varies considerably."[96] In the following decade, the AANA would have to issue position statements to influence the ways in which CRNAs were treated under state nurse practice acts and boards of nursing rules.

And last, the AANA, in a rare offensive legal maneuver, sought direct reimbursement for CRNA services within the Medicare program (1976). President John Garde spoke of the rationale in his 1973 report to the members. "If a physician is paid for a procedure or care, and that same procedure or care is provided by the CRNA, why should it not be reimbursed through health insurance programs?"[97] The effort failed. However, coupled with the other challenges of the 1970s, this attempt alerted CRNAs to the need for an increased presence in Washington, D.C.

FEDERAL LEGISLATIVE INITIATIVES IN THE 1980s

By the end of the 1970s, American medicine had "suffered a stunning loss of confidence." So wrote Paul Starr in "The Transformation of American Medicine." "Slower economic growth and persistent inflation in the seventies undoubtedly lay behind the shift from a redistributive to a regulatory politics in health care." But, although the economy declined, medicine "seemed to pass from stubborn shortages to irrepressible excess." From 1970 to 1980, healthcare expenditures had grown from $69 billion to $230 billion. And "the reimbursement practices for hospitals and doctors were peculiarly designed to encourage higher costs.[98] Conservatives and some liberals in Congress aimed to cut that back.

Gunn described how this played out within anesthesia: "Anesthesiologists billed for services when they were not present in the hospital or even in town. Some chose not to come out at night or on weekends to supervise care provided in emergencies, yet they billed as if they had been present. Anesthesiologist supervision or billing capability for concurrent cases was not limited to any specific fixed numbers, permitting abuse. During this time, some surgeons were openly critical of the number of fees being paid to anesthesiologists for concurrent services, particularly when the anesthesiologists were not available. A number of these surgeons and other providers complained to both private insurers and Medicare. As a result, some private payers began limiting reimbursement to not more than two concurrent procedures, and Medicare's Inspector General focused on anesthesia reimbursement in the search for potential fraud. Around this time, Richard Verville, the AANA's Washington counsel, stated that a source in the Inspector General's office of what was then the U.S. Department of Health, Education, and Welfare had told him that approximately 25% of Medicare fraud and abuse investigations concerned anesthesia services."[99] Two federal efforts to control anesthesia costs and accountability had their genesis in these peculiar reimbursement practices.

TEFRA

The first federal effort to control anesthesia costs and accountability was the Tax Equity and Fiscal Responsibility Act (TEFRA), enacted in 1982. TEFRA was designed to control costs, and "ensure that an anesthesiologist demonstrated that he or she provided certain services as part of a given anesthetic to qualify for payment. Among other things, TEFRA limited payment to anesthesiologists for no more than four concurrent cases, and stipulated seven conditions that anesthesiologists must fulfill as part of a given anesthetic procedure to qualify for payment."[100]

However ,TEFRA had some adverse implications for CRNAs. The seven conditions were misconstrued by the ASA as standards of practice. Its *Guidelines to the Ethical Practice of Anesthesiology* (adopted October 25, 1978; effective February 12, 1979), made this clear.[101]

They separated reimbursement for anesthesiologists based on supervision or medical direction and specified payments on the basis of direction to be limited to not more than two concurrent procedures. Payment took two forms. When the CRNAs were employed by the anesthesiologist, each service was billed as though the anesthesiologist had administered each case. When the CRNAs were hospital employees, the time units for the anesthesiologist were cut in half. When the anesthesiologist's service was supervision and not direction (i.e., supervising three or more CRNAs), the payment was to be made under Part A of Medicare on the basis of a "reasonable charge." The hospital could still bill for the CRNA services of their own employees under Part A if the services were provided within the hospital and under Part B of Medicare if the services were provided in a surgical center.

An Existential Threat Leads to Direct Reimbursement

In early 1983, while the AANA was still dealing with TEFRA, without much fanfare and with less media exposure than usually accompanies such legislation, Congress passed a second cost control bill, the prospective payment system (PPS). The PPS revised the means of calculating Medicare payment from a cost-plus fee for service basis to prospective pricing based on diagnosis-related groups. This measure posed a much greater threat to CRNAs than TEFRA.

The PPS legislation was a powerful disincentive to the hiring of nurse anesthetists: (1) it would be impossible for the anesthesia component of payment to cover the full cost of hospital-employed CRNAs; (2) unbundling of services and payment was prohibited; and (3) anesthesiologists who had been billing for CRNA services under Medicare Part B could no longer do so. Taken together these caveats meant "CRNA services were, for all practical purposes,

nonreimbursable."[102] Hospitals would terminate CRNAs and rely entirely on anesthesiologists.

The very real threat posed by PPS mandated action. Either the reimbursement for both anesthesiologists and CRNAs would need to be placed under the same source, Medicare Part A, or AANA would have to seek direct reimbursement rights for CRNAs under Medicare Part B.

In the 1980s CRNAs were heavily recruited healthcare professionals. The majority were employed by hospitals or anesthesiologists, but a growing number of CRNAs practiced privately. Private practice CRNAs were unable to obtain reimbursement directly from Medicare, Medicaid, and many private insurance companies.

After a 3-year-long effort that Bankert described as "one of the greatest lobbying achievements not only of the AANA, but of the whole of nursing," President Reagan signed into law the Omnibus Budget Reconciliation Act of 1986. Since then Medicare and Medicaid have paid directly for all CRNA services, making nurse anesthetists the first nursing specialty to be so accorded. Of its importance, Dr. Judith Ryan, the executive director of the American Nurses Association, said that "The American Association of Nurse Anesthetists' achievement to secure direct reimbursement for CRNAs is a singular, notable contribution to identification and payment of the nurse as a provider of care, and nursing services as covered health benefits."[103]

Non-Legislative Legal Problems Arise

In the same decade, events of no less significance took place in civil law pertaining to anesthesia. The courts tested whether a surgeon is liable for the actions of a nurse anesthetist. Traditionally, surgeons have been considered "Captains of the Ship" and were therefore thought responsible for everything that occurred inside an operating room. Logically this theory was extended to mean that "nurses (and nurse anesthetists) become the temporary servants or agents of the attending surgeon during the course of an operation, and liability for their negligent acts may thus be imposed upon the surgeon under the doctrine of *respondeat superior*."[104] Blumenreich explained the danger to CRNAs of this theory: "When surgeons work with nurse anesthetists, the surgeons become liable for their mistakes—but when surgeons work with anesthesiologists, the surgeons do not have to worry about what happens at the head of the table." But, in fact, the theory is fallacious. Blumenreich went on to say, "First, surgeons are not always liable for the negligence of nurse anesthetists. Second, surgeons may also be liable for the negligence of anesthesiologists. Third, because a surgeon's liability, whether working with nurse anesthetists or anesthesiologists, depends on the particular facts of the situation, as a practical matter, the surgeon is likely to be included in the suit whether the surgeon is working with a nurse anesthetist or an anesthesiologist." In fact, no surgeon has been held liable in a court of law for the negligence of a nurse anesthetist. Courts have apportioned liability according to specifics facts of a case.[105,106]

A second area of civil law that effected anesthesia in the 1980s was antitrust. Nurse anesthetists, like other professionals, are subject to antitrust laws. However, they also can use those laws when they allege others have conspired to restrict CRNA practice. Two cases filed by CRNAs, Vinod Bhan (*Bhan v. NME Hospitals, Inc.*, 84-2256, DC No. CV-S-83-295 LKK [October 2, 1985]) and Tafford Oltz (*Oltz v. St. Peters Community Hospital*, 861 F2d 1440, 1450 [9th Cir 1988]), illustrated these points.

Oltz had held clinical privileges and had worked as a private practitioner at St. Peters Community Hospital in Helena, Montana. His privileges were terminated when the hospital gave an exclusive contract to a group of anesthesiologists. Oltz alleged, and the court agreed, that the hospital and the anesthesiologists had conspired to terminate his privileges so that the anesthesiologists would have access to his cases. The verdict turned on the fact that St. Peters Community Hospital had significant enough market shares within its service area to exert a monopoly, and that by awarding the exclusive contract to the anesthesiologists, the hospital damaged competition. By August 1994, more than 12 years and numerous appeals later, Oltz prevailed. Although nondisclosure was a condition of the final settlement of monetary damages in this case, the court awarded Oltz (the plaintiff) $1.6 million in attorney fees.[107]

A second antitrust case involved Vinod (Vinnie) Bhan, who practiced anesthesia in California. When his hospital terminated his privileges and replaced him with anesthesiologists, Vinnie sued. The defendants (both the hospital and the anesthesiologists) challenged Bhan's standing—that is, his legal right to file suit. They asserted that Bhan, as a nurse and nurse anesthetist, did not, in the eyes of the law, compete with physicians because of their different licensure.

Bhan lost the case because the hospital that terminated his privileges did not have sufficient market share in the community to restrain competition. One essential element of antitrust laws is that they exist to protect competition, not competitors. Bhan's ability to compete was not adversely effected, because there were plenty of other local hospitals where he could seek to practice.

However, the appellate court ruling that gave Bhan and CRNAs standing to sue anesthesiologists as competitors set a significant legal precedent for the profession. The Circuit Court concluded, *"No doubt the legal restrictions upon nurse anesthetists create a functional distinction between nurses and MD anesthesiologists. They do not, however, necessarily preclude the existence of a reasonable interchangeability of use or cross-elasticity of demand sufficient to constrain the market power of MD anesthesiologists and thereby to affect competition"* [emphasis added]. The court continued, stating that "as a matter of law, Bhan's allegations are sufficient to establish that he is a proper party to bring this antitrust action."[108,109]

And Blumenreich said, "The Bhan case was important because it gave to some extent the protections of the antitrust laws to nurse anesthetists. Hospitals could not boycott nurse anesthetists." Its results would be more "long-lasting."

Hyde v. Jefferson Parish Hospital District No. 2

A third antitrust case, *Hyde v. Jefferson Parish Hospital District No. 2* (1983; New Orleans, Louisiana) centered on whether an exclusive contract by a group of anesthesiologists was by itself (per se) a violation of the antitrust laws. At East Jefferson Parish Hospital, a group of anesthesiologists held an exclusive contract with the hospital and worked with hospital-employed CRNAs. Dr. Hyde was denied privileges solely on the basis of the exclusive contract. Hyde sued, claiming that a patient who was admitted for surgery in effect had no choice but to buy anesthesia from the hospital's exclusive group of anesthesiologists. He alleged that this situation represented a tying arrangement, which had previously been deemed in violation of the antitrust laws. (A tying arrangement would be similar to going to a store to buy bread but being unable to buy it by itself. Rather, one would be required to buy butter to get the bread, whether or not the purchaser used butter on bread.)

The Jefferson Parish Hospital District won the case at the lower court level. But Hyde appealed all the way to the U.S. Supreme Court.

The ASA also filed an amicus curiae brief, but in support of Dr. Hyde. The ASA opposed exclusive contracts, but attempted to link its opinion to the quality of care: "the elimination of competition through a classic tying arrangement is not simply a matter of dollars and cents. It can adversely affect the quality of medical care. ASA believes that in this setting, it is particularly important that competition be allowed to reward superior performance and innovation, while exposing the indifference to quality that may too often be the hallmark of a monopoly.[110]

The Supreme Court ruled unanimously in favor of the hospital's right to award an exclusive contract for anesthesia services. The ruling was favorable to CRNAs in what Blumenreich recalled was a "footnote in the court's opinion to the effect that 'there has been no showing that nurse anesthetists provide a lesser quality of care.' So we feel like we accomplished what we set out to do."[111] Shortly afterward, the AANA appointed Blumenreich General Counsel, a post he held until 2011. Gunn wrote that "the Hyde case alerted the AANA to the need to revitalize its public relations program, continue its watch for attempts to discredit CRNAs, and take action either to correct or to prevent further damage."

CRNA Achievements of the 1980s

Although much attention focused on events taking place on the legal front, other important areas of practice were advanced. For example, liability insurance coverage, first offered to CRNAs in 1974 by outside brokerages, was skillfully brought in house when the AANA bought the Glen Nyhan Agency. Renamed A+, and now called AANA Insurance, the agency has provided a steady stream of insurance to CRNAs since 1988.

The AANA Education and Research Foundation was established in 1981; it would be renamed the AANA Foundation in 1995. The Foundation has enjoyed enormous support. A 2011 report[112] listed scholarships, grants, and workshops in excess of $2.2 million given to 2275 individuals.

- 739 scholarships totaling more than $1 million to support nurse anesthesia
- 131 fellowships totaling $650,000 to assist CRNA students pursuing their PhD and DNP degrees
- 173 research grants to CRNAs totaling more than $531,000
- 39 student research grants totaling $31,000
- 1193 poster presentations at AANA annual meetings totaling more than $50,000

The Conductor

No review of the 1980s would be complete without mention of the ascendance of John Garde, who served the profession from 1957 through 2009.

Mr. Garde's career at the AANA stemmed from being an educator. From 1964 to 1975, John was Program Director, Associate Professor, and then Chairman of Anesthesia at Wayne State University. Mr. Garde went to work for the AANA in 1980 as the Education Director and then in 1983 was appointed Executive Director. This was his post until retiring for the first time in 2000, and from which he would become an "iconic figure in the healthcare community."[113]

Under Mr. Garde's executive leadership, the profession prospered. Evidence for this includes the previously described legal and regulatory victories and educational advancements. The AANA also expanded to include AANA Publishing, AANA Insurance Services, AANA Management Services, the AANA Foundation, a Government Relations Office in Washington, D.C., and (not least) the AANA Archives. (John was "steeped in history.")

Because John "knew everyone," relations between the AANA and outside organizations flourished. According to Rita Rupp, "John facilitated and led in the formation of the National Federation of Nursing Specialty Organizations and later a national nursing executive directors group."

Nurse anesthesia even globalized during this era: the International Federation of Nurse Anesthetists was formed, and the AANA supported volunteerism in developing nations through Health Volunteers Overseas.

Mr. Garde had attended the venerable Alexian Brothers Hospital School of Nursing in Chicago, and the St. Francis Hospital School of Nurse Anesthesia in La Crosse, Wisconsin. According to Patrick Downey who was a contemporary of John's, the program director at St. Francis, Sister Yvonne Jenn, became his "mentor for life." "John was the student she waited for; she selected him to administer anesthesia for the first pneumonectomy at St. Francis…Their mutual trust was so strong. She taught John never to act on an impulse. Think things over. They glowed when they were together." (Personal communication, 2011).

As Executive Director, John practiced the lessons he learned from Sister Yvonne. Rita Rupp, who was John's executive assistant, said, "John had been (AANA) president, so he knew how it felt. As executive director he had an unwritten rule, defer to the president, but act as a mentor. He got involved with each president, and created a sense of comfort" (Personal communication, 2011).

With characteristic modesty, John later recalled that he saw himself as "the conductor of a great orchestra." Past President Larry Hornsby elaborated: "The president was the soloist. John used the orchestra to make the soloist sound the very best…(as president) you could not fail…He catered to each president's needs and strengths to make you the leader that the organization needed at the time" (Personal communication, 2011).

THE CALL FOR HEALTHCARE REFORM IN THE 1990s

Cost Containment in Health Care

Bill Clinton was elected president in 1992 with a promise to reform health care. The president's healthcare reform package was aimed at universal coverage and reflected a major shift in healthcare delivery toward managed care.

Clinton brought hope to CRNAs, who took note of the fact that the President's mother was a retired CRNA.[114] A component of President Clinton's healthcare legislation would have removed legal barriers to practice for advance practice nurses, permitting them to more directly compete with physicians to reduce costs. This provision would also have provided the legal authority for APNs to render services without physician supervision (in some instances collaborating with or referring patients to physicians).

For a variety of reasons, Clinton's healthcare plan was defeated. In its place, the health insurance industry, in conjunction with the major businesses that provided health insurance to their employees, forced a form of "managed care" on a large portion of the insured population. Because of the cost savings projected for a managed care system, the U.S. government offered Medicare beneficiaries certain incentives to instead accept a managed care version of Medicare. And some states began to pattern their Medicaid programs after the managed care concept, permitting managed care groups to bid to cover Medicaid patients.

Managed care, in theory, was intended to (1) move the healthcare system from a disease treatment to a health-maintenance system; (2) do away with incentives found in the fee-for-service system—that is, the more services provided, the more money made—and thereby reduce unnecessary health services;[115,116]

(3) promote a cost-effective workforce by emphasizing primary care providers and nonphysician professionals; and (4) promote a shift from independent practice patterns to greater use of salaried personnel. Some anesthesiologist groups found that under managed care their workload declined by 40%.[117] Physicians thus scrambled to protect autonomy and income, while patients sought to preserve some choice of provider.

When CRNAs won direct reimbursement rights in 1986, they agreed to accept as payment in full for each anesthetic, no more than the amount Medicare assigned for the service. In other words, CRNAs do not "balance bill." Payment schedules were then devised for anesthesiologists working alone, CRNAs working alone, and anesthesiologists medically directing CRNAs in team practice settings. In the early 1990s, a Government Accounting Office (GAO) study[118] revealed that payments for anesthesia services under the medical direction arrangement were 120% to 140% greater than payments for CRNAs or anesthesiologists working alone. This payment scheme served as a strong incentive for anesthesiologists to employ CRNAs, but it was not budget neutral, which had been the intent of Congress. The GAO recommended payment of only one anesthesia fee, totaling no more than when an anesthesiologist performed the service alone. Furthermore, the study recommended that payment for anesthetic procedures under the medical direction model be split 50% for the CRNA service and 50% for the anesthesiologist service, a significantly reduced portion for both the anesthesiologists and the CRNAs. The AANA chose to support the single-payment plan. The ASA opposed it. The single-payment reimbursement plan was implemented, and tension between the two groups again was exacerbated.

Attempts to Measure Quality of Care

In the second half of the twentieth century, physicians first, and then nurses, attempted to evaluate the quality of anesthesia care by measuring death rates. The first attempt was published in 1954 by Beecher and Todd.[119] The Beecher and Todd study looked at nearly 600,000 cases gathered at university medical centers nationwide. It was notable for shedding light on the "not yet entirely clear, nor completely appreciated" cardiovascular dangers of curare, with which there was an associated "six-fold difference, unfavorable to curare" in the death rate.

As mentioned earlier, Beecher and Todd compared outcomes between physician specialists, residents in anesthesia, and nurse anesthetists. Although there was "comparability of good and poor risk cases in the three groups," and "although the physician specialist anesthetizes only half as many patients as the nurse, he is charged with an equal number of anesthesia deaths." In other words, they found a glaring difference.

Two decades later amid complaints about the Veterans Administration (VA) healthcare system, the U.S. House of Representatives mandated a study by the National Science Foundation regarding the care given to veterans. At the time, much of the anesthesia administered at VA facilities was provided by nurse anesthetists. The reviewers reported back to Congress in 1977 that there were no significant differences in the outcomes of anesthesia based on the providers of that care.[120]

In 1980 an anesthesiologist, W.H. Forrest, published a portion of an institutional differences study conducted by the Stanford Center for Health Care Research. Forrest divided the institutions between those predominantly served by nurse anesthetists and those predominantly served by anesthesiologists; he concluded—using conservative statistical methods—that there were no significant differences in anesthesia outcomes between the two anesthesia providers.[121] (Ira Gunn wrote that she "spoke with Dr. Forrest regarding his study, and he mentioned that he had been castigated by his colleagues for reporting these results.")

A North Carolina retrospective study of anesthesia-related mortality from 1969 to 1976 (performed by a committee from the North Carolina Society of Anesthesiologists) was published in 1981. The findings based on providers (e.g., CRNAs working alone, anesthesiologists working alone, and CRNAs and anesthesiologists working together as a team) were similar. But no test of significance was made in this study.[122]

Subsequent studies deserve attention because they were used to support the claim that CRNAs should be anesthesiologist supervised.

Between 1992 and 2003, studies by Abenstein and Warner; Silber et al; Wiklund and Rosenbaum; and Vila et al were published and promoted as evidence that the "the utilization of anesthesiologists improves anesthesia outcomes." These studies and their rebuttals were summarized in "Quality of Care in Anesthesia," a 2009 publication by AANA.[123] The article by Abenstein and Warner "purported to analyze the quality of care…but failed to mention the key conclusion." For example, the authors claimed that there were "differences in the outcomes of care based on type of provider, *not withstanding that the actual researchers came to the opposite conclusion*." (Emphasis original.) The Silbur study "examined the death rate, adverse occurrence rate, and failure rate of 5972 Medicare patients. One analyst concluded this data was, in fact, not "specific to anesthesia staffing," and "the type of anesthesia provider does not appear to be a significant factor in the occurrence of potentially lethal complications." Two studies attributed to Wiklund and Rosenbaum were also found to be irrelevant. The reviewer pointed out that Wiklund and Rosenbaum, by attributing safer anesthesia to a federal decision to "support training in clinical anesthesiology" had left "the path of unbiased review of the specialty to make unsubstantiated or misleading comments about the unilateral contributions of anesthesiologists to the advancements achieved."

The Silbur study stirred up "serious questions of objectivity." "Reportedly, both the *Journal of the American Medical Association* and the *New England Journal of Medicine* declined to publish" it. The timing of its publication led to questions about its motivation. "The abstract was published in the midst of the controversy between anesthesiologists and nurse anesthetists over HCFA's [Health Care Financing Administration] proposal to remove the physician supervision requirement for nurse anesthetists in Medicare cases." The AANA reviewer concluded, "The timing of the publication in the ASA's own journal was politically motivated" to influence the Health Care Financing Administration (now known as the Centers for Medicare and Medicaid Services [CMS]). However, CMS ultimately "dismissed all claims" made by the authors in this study.

The Vila study compared outcomes at ambulatory surgery centers (ASCs) with those in office operating rooms (a practice for many independent CRNAs). It claimed that "the risk of adverse incidents and deaths was approximately 10 times greater in the office setting than in an ASC, and that if all office procedures had been performed in ASCs, approximately 43 injuries and six deaths per year could have been prevented." It concluded with the hopeful remark that "the presence of anesthesiologists in ASCs 'may be a factor in more favorable outcomes.' "

But the AANA analyst pointed out flaws in both its methodology and conclusions. The study "does not specifically mention CRNAs," yet it "makes the unsupportable assertion that office surgery may not be as safe when an anesthesiologist is not present."

Misuse of outcomes research was extensive during this era. Gunn wrote that "in the medical literature in the 1990s, serious questions were raised regarding the quality and relevance of published research, the peer review system, and the selection of articles for publication."[124] A 1993 review concluded that 95% of the medical research being published in journals was either flawed or irrelevant.[125]

The Federal Supervision Regulation

Recall that in 1919 surgeon George Crile and some of his colleagues secured legislation in Ohio that for the first time codified the practice of nurse anesthesia.[126] An amendment to that legislation made mention of physician supervision: "the administration of an anesthetic by a registered nurse *under the direction of and in the immediate presence of* a licensed physician."[127] Nurse anesthetists welcomed this development and sought similar legislation in other states.[128]

In the 1980s, there emerged physician oversight regulations within the Medicare Rules for Participating Hospitals. The regulations stemmed from the aforementioned Tax Equitability and Federal Responsibility Act (TEFRA) of 1982. They pertained only to anesthesia. And because they were federal, they preempted any state laws that permitted CRNAs to practice without supervision.[129]

At the same time TEFRA took effect, the number of anesthesiologists tripled. Increased competition in the anesthesia marketplace prompted Blumenreich to write that supervision became

> *the springboard for yet new attacks. In 1985, H. Ketcham Morrell, president of the American Society of Anesthesiologists (ASA) wrote: "…the operating surgeon or obstetrician who purports to provide medical direction of the nurse, in the absence of an anesthesiologist, carries a high risk of exposure, on a variety of legal theories, for the acts of the nurse."*[ii]

An unknown number of surgeons opted for anesthesiologists as a result. Imagined liability among surgeons became such a crisis that Blumenreich wrote "no subject has received more of my attention…"[iii]

Removing supervision from the Medicare Rules was an obvious remedy, because it would impact practice across the country. From 1994 to 2001, HCFA and AANA attempted to do just that. The struggles that ensued were chronicled by Patrick Downey. Legislation was introduced in both houses of Congress that would remove the supervision requirement and address reimbursement issues. Both the AANA and ASA responded with grassroots public relations campaigns, and the legislation went nowhere. Then in December 1997, HCFA proposed a major change in its *Hospital Conditions of Participation*, and it included the elimination of physician supervision of CRNAs. Nursing organizations lined up in support of the change, but medical opposition was fierce. Nullifying legislation was proposed, as were safety studies to delay its consideration. More public relations were deployed, and the controversial claims of the Silbur study (that outcomes are better when CRNAs are supervised by anesthesiologists) were invoked. In March of 2000, HCFA ruled that CRNAs could practice without physician supervision, and in its ruling, HCFA deemed the Silbur study "irrelevant." But the new rule was not implemented until the final days of the Clinton administration. And the Bush administration, as all new administrations do, placed a moratorium on late-term regulations. In November 2001 the Bush administration restored the earlier rule containing supervision.

The "final" rule contained an escape clause, a proviso allowing state governors to opt out.[130] Between 20 and 31 states (opinions varied) had no laws specifying supervision of CRNAs, which meant governors might be inclined to provide an opt-out. Before long, some governors did. Iowa was the first. Then a number of rural Western states opted out. To date, governors in 17 states have done so. These include Iowa, Nebraska, Idaho, Minnesota, New Hampshire, New Mexico, Kansas, North Dakota, Washington, Alaska, Oregon, Montana, South Dakota, Wisconsin, California, Colorado, and Kentucky. Depending upon one's interpretation, that was at least 50% of eligible states.

Two prominent health economists, Brian Dulisse and Jerry Cromwell, studied Medicare data between 1999 and 2005.[131] They found "no evidence that opting out of the oversight requirement resulted in increased inpatient deaths or complications." This came as no surprise to the AANA and CRNAs. The authors concluded, "We recommend that CMS return to its original intention of allowing nurse anesthetists to work independently of surgeons or anesthesiologist supervision without requiring state governments to formally petition for an exemption."

Other contemporary studies supporting this assertion were collected in the publication *Quality of Care in Anesthesia*.[132] Simonson, Ahern, and Hendryx (2007), and Needleman and Minnick (2008) found no significant differences between CRNAs and anesthesiologists with respect to obstetric (OB) anesthesia outcomes. Pine, Holt, and Lou (2003) studied Medicare outcomes for patients in 22 states between 1995 and 1997. Their findings were mortality rates were similar for CRNAs and anesthesiologists working individually; no statistically significant difference in the mortality rate for team versus solo practice; and no statistically significant difference in mortality for hospitals without anesthesiologists versus hospitals where anesthesiologists provided or directed anesthesia care. However, the Institute of Medicine, the health arm of the National Academy of Sciences, weighed in with a report entitled "The Future of Nursing: Focus on Scope of Practice."[133] The report came as a powerful endorsement of nurses as high-quality clinicians. Its conclusion reads, in part: "Now is the time to eliminate the outdated regulations and organizational and cultural barriers that limit the ability of nurses to practice to the full extent of their education, training, and competence. The U.S. is transforming its healthcare system to provide quality care leading to improved health outcomes, and nurses can and should play a significant role. The current conflicts between what APRNs can do based on their education and training and what they may do according to state and federal regulations must be resolved so that they are better able to provide seamless, affordable, and quality care. Scope-of-practice regulations in all states should reflect the full extent not only of nurses but of each profession's education and training. Elimination of barriers for all professions with a focus on collaborative teamwork will maximize and improve care throughout the health care system."

Doctoral Preparation of Nurse Anesthetists Achieved

Upgrading Nurse Anesthesia Educational Requirements

The upgrading of academic credentials for CRNA educators and their graduates has always been closely tied to the goals of the professional association to advance the art and science of anesthesia.[82] Nurse anesthesia leaders have been responsible for increasing requirements for curricular content, faculty qualifications, and academic credentials for graduates since early in the twentieth century. Over time, schools of anesthesia have changed from

[ii]Blumenreich G: Supervision. *JAANA*, October 2000.
[iii]Blumenreich G: Another Article on the Surgeon's Liability for Anesethesia Negligence. *AANA Journal*, April 2007.

apprenticeships at hospitals into degree-granting institutions fulfilling the vision of early anesthesia leaders for a university education for nurse anesthetists. This movement into academia required identifying the location of schools of anesthesia in the nation, determining the essential characteristics of better schools, agreeing on curricular requirements, inspecting schools, and developing a school approval process.

Doctoral Degrees. Beginning in the mid-1980s, the AANA and the COA have continually assessed the need for and feasibility of practice-oriented doctoral degrees for nurse anesthetists. In June 2005 the AANA board of directors convened an invitational summit meeting to discuss interests and concerns surrounding doctoral preparation for nurse anesthetists. Following the summit, the Task Force on Doctoral Preparation of Nurse Anesthetists (DTF) was formed and charged with developing options relative to doctoral preparation of nurse anesthetists that the AANA board could consider.[134] The DTF's final report and options were presented to the AANA board of direction in April 2007, and in June 2007 the board unanimously adopted the position of supporting doctoral education for entry into nurse anesthesia practice by the year 2025. This decision was based on more than 2 years of investigation to thoroughly explore the interests and concerns surrounding doctoral preparation of nurse anesthetists.

Setting a requirement for doctoral education followed in October 2009 when the Council on Accreditation of Nurse Anesthesia Education Programs adopted a position that "The COA will not consider any new master's degree programs for accreditation beyond 2015: and that students accepted into an accredited program on January 1, 2022, and thereafter must graduate with doctoral degrees." The position became part of the Standard on Accreditation of Nurse Anesthesia Educational Programs and the basis for drafting new standards for practice doctorate programs.[134]

CRNA PRACTICE TODAY

Demographic information collected from CRNAs by AANA in 2010 indicated there were about 40,000 members of the AANA. CRNAs are 56% female and 44% male. Their average age was 49.8 years. Of currently practicing CRNAs, 42% planned to retire by 2022. Ninety-six percent of CRNAs reported they practice clinical anesthesia, whereas only 2% worked in either management/administration or education. Median annual total compensation for CRNAs, including salary and benefits, was $165,571. CRNAs worked in all states and in every clinical setting using every anesthetic modality (general, regional, sedation, pain management). The data point out that American CRNAs are very productive and make an enormous contribution to the care of patients under anesthesia. And CRNAs are fulfilled by their work; only 10% expressed job satisfaction of 3 or less on a scale of 1 to 5.

The United States is currently a country at war, and so CRNA contributions to military anesthesia are particularly significant. The U.S. Army, Navy, and Air Force commission approximately 1100 CRNAs serving on active duty. Others work within the Department of Health and Human Services for the U.S. Public Health Service and Veterans Administration. Increased deployments of active duty CRNAs have disrupted the lives of many.

CRNAs are proving to be very versatile, filling more than clinical duties in today's military. They are also leaders and in some cases soldiers on the line. CRNAs Major Steve McColley and Captain Mitchell Bailey earned Bronze Star Medal nominations for acts of courage in Iraq. Major Jeffrey Roos, a CRNA stationed at Fort Benning, Georgia, earned a Bronze Star from the Army for his lifesaving efforts during Operation Anaconda, the first major U.S. offensive launched in Afghanistan after the September 11, 2001, attacks on the World Trade Center. A CRNA was in the news for extricating Private Jessica Lynch from a hospital in Iraq.

Deployments of CRNAs to Afghanistan and Iraq have reduced anesthesia staffs at stateside hospitals. No figures exist to describe the overall impact of the latest escalation on anesthesia services in stateside hospitals. However, the impact of deployments has been mitigated somewhat following a recent policy change in the Navy. Navy CRNAs are now considered "licensed independent practitioners" (LIPs), a term coined by The Joint Commission (TJC). According to Captain Annette Hasselbeck, NC USN, LIP status has enabled the Navy's medical planners to use global sourcing of CRNAs. In other words, CRNAs are used interchangeably with anesthesiologists, based on skills, seniority, and availability. This had always been the practice pattern, but defining CRNAs as LIPs has kept practice in compliance with TJC policy. According to Captain Ron Van Nest, NC USN (retired), the policy was changed in 2000 to reflect the facts that CRNAs very often deploy alone and capably make independent clinical decisions that affect anesthetic management. Recognizing CRNAs as LIPs has also kept morale high; all billets are filled and retention of Navy CRNAs is at 100% as of this writing.

International Federation of Nurse Anesthetists

The International Federation of Nurse Anesthetists (IFNA) is a federation of national associations of nurse anesthetists. It is an affiliate member of the International Council of Nurses and a Nursing Partner of the World Health Organization. The IFNA represents more than 50,000 nurse anesthetists worldwide and is a growing organization with members in both developed and developing countries (S. Quellette and J. Rowles written communications, January 21, 2012). The first organizational meeting was held in September 1988, and 11 countries were admitted as charter members in 1989. A World Congress is held every 2 years and is hosted by a member country.

To date there are 36 members countries. The IFNA has developed international standards for education, standards of practice, standards for patient monitoring, and a code of ethics for nurse anesthtists.[135] An anesthesia approval process for entry level programs was launched in 2010 offering three levels of awards: Registration, Recognition, and Accreditation. The goal of the Anesthesia Program Approval Process is to encourage programs to comply with the IFNA's *Educational Standards for Preparing Nurse Anesthetists* through an approval process that takes cultural, national, or regional differences into consideration.[135]

Progress in Anesthesia

Progress in anesthesia has occurred in all areas of the discipline. The AANA Foundation lists and describes hundreds of recent and ongoing CRNA-led research projects.[136] These projects range from basic and applied sciences to clinical anesthesia, education, and economics.

A *Special Research Edition* of the *AANA Journal* published in August, 2011, featured a "select and eclectic" group of articles all based on applied and basic research. The *Special Edition*, and some of the research, was funded by the AANA Foundation, whose president, Louise Herschkowitz, CRNA MSHA, wrote, "As our profession evolves, and as more CRNAs grow through doctoral education, the quantity and quality of both clinical and basic science research is rapidly expanding."

The Editor-in-Chief of the *AANA Journal*, Chuck Biddle, CRNA PhD, in an editorial wrote, "Of great pride to me is the quality and diversity of work that I see emerging from colleagues

nationwide, research that is altering the landscape of anesthesia care. I believe that strongly held views based on belief rather than sound evidence still exert too much influence on healthcare decision making. The age of evidence-based practice is upon us, and we should actively embrace the opportunity that it provides to merge research, skill, intuition, and humanitarianism."

EMINENT NURSE ANESTHETISTS FROM HISTORY

Olive L. Berger (1898-1981)

Olive Berger made her mark in clinical anesthesia at Johns Hopkins in Baltimore, Maryland, where she received her anesthesia training and held the position of chief anesthetist from 1931 until her retirement in 1967. She administered the anesthesia for the first total pneumonectomy performed at Johns Hopkins, and Miss Berger was the first nurse anesthetist to administer anesthesia to infants for the repair of tetralogy of Fallot. Berger and Helen Lamb, of Barnes Hospital, St. Louis, Missouri, developed an endotracheal technique for intrathoracic surgery. She served as president of the American Association of Nurse Anesthetists (AANA) from 1958 to 1960, and was awarded the Agatha Hodgins Award for Outstanding Accomplishment in 1980.

Margaret G. Boise (1883-1972)

While employed at Presbyterian Hospital in New York City, Margaret Boise traveled to St. Mary's Hospital in Rochester, Minnesota, in 1910, to be trained in ether anesthesia by Florence Henderson. She then trained other nurses at Presbyterian Hospital, and later at Johns Hopkins. In 1913, Samuel J. Crowe, head of otolaryngology at Johns Hopkins, employed Boise to provide anesthesia to his patients. She soon was also employed by urologist Hugh H. Young, and they collaborated on a gas-ether machine known as the Boise-Young apparatus. She also created a simple anesthesia machine for tonsillectomies. Boise also gave anesthetics to most of chief surgeon William Stewart Halstead's patients and was appointed head anesthetist in the surgical department.

Catholic Sisters (late 1800s to early 1900s)

Catholic Sisters around the United States played a prominent role as early nurse anesthetists. Because healing of the sick was part of their religious vocation, they established hospitals and nursing schools across the county. Many of these early nurse anesthetists were discovered by Virginia S. Thatcher while doing research for a history of nurse anesthesia. In 1877 Sister Mary Bernard, a nurse at St. Vincent's Hospital in Erie, Pennsylvania, was the first nurse known to specialize in anesthesia. The Hospital Sisters of the Third Order of St. Francis at St. John's Hospital in Springfield, Illinois, gained prominence starting in 1880 when Sister Aldoza Eltrich and others were trained in open drop ether and chloroform. Their nursing school first began to teach anesthesia to Sisters in 1912, and in 1924 the nurse anesthesia school was open to lay nurses under the direction of Sister Rudolpha, a devoted educator until her death in 1969. The AANA presented the 1954 Award of Appreciation to the Order in 1954 for their longtime contribution to the education of nurse anesthetists. Other sisters of note include Sister Mary Cyrilla Erhard, who journeyed to Hawaii in 1886 and administered anesthesia at a Maui hospital for 42 years.

Col. Mildred Clark (1915-1994)

Mildred Clark had a long and distinguished career in the Army Nurse Corps (ANC). She took her anesthesia training at Jewish Hospital, Philadelphia, 6 months after joining the ANC in 1938. She was stationed at Schofield Barracks when Japan bombed Pearl Harbor in 1941, and later served in numerous leadership roles both in the United States and at the 382nd Station Hospital in Korea. In 1947 she became the Director of Nurses of the XXIV Corps in Korea and less than a year later, Chief Nurse of the Far East Command in Tokyo, Japan. Her assignment as Procurement Officer in the Surgeon General's Office tested her skills and creativity to recruit nurses during a nationwide nursing shortage. In 1963 she was the first nurse anesthetist to be appointed as Chief of the Army Nurse Corps, and she served in this position until her retirement in 1967.

Mary Alice Costello (1943-2001)

Mary Alice Costello, a nurse anesthesia educator, founded the Cincinnati General Hospital School of Nurse Anesthesia (later the University of Cincinnati School of Nurse Anesthesia) in 1945 and served as its director for 27 years. Costello was one of the first nurse anesthetists to become adept at the administration of regional anesthesia and instructed nurse anesthetists from around the country in regional techniques. She also dedicated a large part of her career to the AANA and the Ohio Association of Nurse Anesthetists, serving as president of both organizations as well as serving on numerous committees. She was awarded the AANA's Helen Lamb Outstanding Educator Award in 1987.

Adeline Curtis (1897-?)

Adeline Curtis was employed as staff anesthetist from 1921 to 1928 at the Johnston-Wickett Clinic in Anaheim, California, to give anesthetics to patients of three surgeons working in Orange County hospitals. She resigned in 1928, when the California Board of Medical Examiners published a resolution alleging that nurse anesthetists were not licensed to provide anesthesia. She believed that she was within her scope of practice and employed an attorney who received a statement by the state attorney general that there was no law in California prohibiting a nurse from giving anesthesia. She resumed giving anesthetics at the clinic, and her experience prompted the Los Angeles nurse anesthetists to band together and form the California Association of Nurse Anesthetists. This was the first attempt to limit anesthesia by nurses in the state, and Curtis would later provide financial support to Dagmar Nelson when she was taken to court over the same charge in 1933.

Gertrude L. Fife (1902-1980)

Gertrude Fife was a dedicated leader of the AANA whose work provided a foundation for subsequent growth of the organization. Upon graduating from Lakeside Hospital School of Anesthesia in Cleveland, Ohio, in 1925, she was immediately appointed a member of the staff. Fife was appointed director of the school in 1934 and she served in that position, and as director of University Hospitals' anesthesia department, until her retirement in 1946. Fife worked closely with cardiac surgeon Claude S. Beck, and the "mechanical control of respiration during intrathoracic operations originated with" Beck, Fife, and F.R. Mautz. Fife virtually took over the running of the newly formed AANA in 1933 when president Agatha Hodgins fell ill and planned the first annual meeting in less than 6 months. She was a farsighted educator who implemented and extended many of Hodgins' educational goals. She promoted the idea of accreditation of schools in her address at the first annual meeting, and advocated a national board examination for nurse anesthetists. Her dedication to the AANA was unwavering. She was a charter member of the AANA and served as AANA's second president, AANA's journal editor from 1933 to 1944, and treasurer from 1935 to 1950. She was the recipient of AANA's Award of Appreciation in 1950 and the Agatha Hodgins Award for Outstanding Accomplishment in 1978.

John F. Garde (1935-2009)

John Garde's career spanned 44 years, including serving as the director of the Wayne State University School of Anesthesia, Detroit, Michigan, and as AANA's education director (1980-1983) and executive director (1983-2001). Additionally, he served a term as AANA president (1972-1973), which made him the first male to hold that position. Among the most notable accomplishments during Garde's tenure at AANA were the advancement of nurse anesthesia education programs to a graduate framework; the development of AANA public policy and a federal government affairs office in Washington, D.C.; and attainment of Medicare direct reimbursement for CRNAs. He received AANA's Helen Lamb Outstanding Educator Award in 1981 and the Agatha Hodgins Award for Outstanding Accomplishment in 2000. In 1994 he was named a Fellow of the American Academy of Nursing (AAN) and was posthumously inducted into the AAN Hall of Fame in 2009, the first nurse anesthetist to receive that honor.

Ira Gunn (1927-2011)

Ira Gunn was a polymath who saved and advanced nurse anesthesia several times. As an educator, Gunn established anesthesia educational programs at Tripler and Walter Reed Army Medical Centers. In the mid-1970s, together with Ruth Satterfield and Mary Cavagnaro, Gunn developed the AANA councils that assured the autonomy of accreditation and certification processes. Gunn is credited with mending the rift between organized nurse anesthesia and other nursing associations. She also was vitally involved with federal government relations during the 1980s when AANA secured legislation to assure "pass through" payment for CRNA costs and direct reimbursement for CRNA services. Gunn had exceptional writing abilities. She published many articles and edited journals. She was a coauthor of the AANA amicus curiae brief to the U.S. Supreme Court in the case of *Jefferson Parish Hospital v. Hyde*. Her many accolades included Fellow of the American Academy of Nursing (1981), the Agatha Hodgins Award (1983), the Order of Military Medical Merit (2001), and the American Academy of Nursing Living Legend Award (2003).

Edith Graham (1871-1943)

Edith Graham was the first anesthetist at St. Mary's Hospital in Rochester, Minnesota. In fact, she was the first trained nurse in the community, having received her nursing instruction at Women's Hospital in Chicago; she also taught nursing to the Sisters of St. Francis who staffed the hospital. Graham provided safe anesthesia for patients of Dr. Charles M. Mayo and Dr. William J. Mayo from 1889 to 1893, her career ceasing with her marriage to Charles Mayo. She was the only anesthetist during those years; as testament to her skills, of the 655 patients who were operated upon, 98.3 percent left the hospital alive.

Margaret Hatfield (dates unknown)

Although little is known about Margaret Hatfield, it was her administration of anesthetics for patients of Louisville surgeon Louis Frank that was the center of the 1917 legal case, *Frank v. South*. After the Kentucky State Medical Association passed a resolution instructing its members not to employ nurse anesthetists because they deemed it was a violation of the practice of medicine, Frank decided to take the issue to the courts. On appeal, the case was decided in favor of the plaintiffs and confirmed that nurse anesthetists were not engaged in the practice of medicine.

Florence Henderson (1876-1956)

Florence Henderson was another prominent nurse anesthetist who was hired by the Mayo brothers at St Mary's Hospital in Rochester, Minnesota. She provided safe anesthesia to patients of Dr. Charles Mayo from 1904 to 1917 and was a specialist in the administration of ether. She disseminated her knowledge by speaking at medical societies and publishing articles. In 1913 she read her paper, "Ether Anaesthesia," before the Southern Minnesota Medical Association, where she was the only nurse to speak. Her paper was published the next year in the *St. Paul Medical Journal*. In 1917 she moved to California and provided anesthesia for patients of a group of surgeons until her retirement in the 1920s.

Agatha Hodgins (1877-1945)

In 1908 surgeon George Crile asked Agatha Hodgins to be his anesthetist at Lakeside Hospital, Cleveland, Ohio. Her skills as an educator emerged, and soon Hodgins began to instruct nurses in the administration of anesthesia. In 1914 she served with Crile and others from Lakeside Hospital in France during World War I; together they introduced nitrous oxide/oxygen anesthesia to those performing war surgery, and Hodgins trained many in its safe administration. Hodgins formalized the Lakeside Hospital School of Anesthesia in 1915 after her return from France, and served as director from 1915 to 1933. She saw the need for nurse anesthetists to band together, and in 1931 she founded the AANA and was elected the first president (1931-1933). She was committed to improving educational standards and helped lay the groundwork for the association's program to accredit schools of nurse anesthesia, implemented after her death. Among Hodgins' publications are a chapter on nitrous oxide/oxygen anesthesia in Crile's *Anoci-Association* and two articles in the *Archives of Surgery*.

Alice Hunt (1880-1956)

Surgeon Philemon Truesdale asked Alice Hunt to be his anesthetist in 1908, and she received training in open drop either and nitrous oxide/ether. In 1917 she went to Peter Bent Brigham Hospital in Boston, where she trained both nurses and medical interns in the administration of anesthesia and gained recognition for her skillful administration of nitrous oxide/oxygen anesthesia. In 1920 an article she co-authored with surgeon Elliot C. Culter on postoperative complications was published in the *Archives of Surgery*. After the war ended, she became the anesthetist to Samuel Harvey, professor of surgery at Yale. She also was appointed as instructor of anesthesia with university rank in 1922. Later she was promoted to assistant professor in 1930 and taught nurses and medical students for 26 years. In 1949 she became the first nurse anesthetist to author a book, *Anesthesia: Principles and Practice*.

Helen Lamb (1899-1979)

Helen Lamb is an example of the productive collaboration between nurse anesthetists and surgeons. She developed and administered the anesthetic for the world's first successful pneumonectomy in 1933, performed at Barnes Hospital in St. Louis, Missouri, by surgeon Evarts Graham and contributed a chapter on endotracheal anesthesia to Graham's *Thoracic Surgery*. She also collaborated with Richard van Foregger in the development of the van Foregger anesthesia machine used at Barnes. In addition to her clinical work, Lamb founded the school of anesthesia at Barnes Hospital, St. Louis, Missouri, in 1929, and served as director until 1951. She was a charter member of the AANA and served as the fifth president (1940-1942). She was chair of the AANA Education Committee for over 10 years and tirelessly worked to establish the curriculum and minimum standards for schools of nurse

anesthesia. Lamb also organized the Missouri Association of Nurse Anesthetists and was its first president.

Betty E. Lank (1904-2001)

Betty Lank was a nurse anesthetist at Children's Hospital in Boston, Massachusetts, for 34 years (1935-1969) and was an early specialist in pediatric anesthesia. She quickly adopted cyclopropane for pediatrics in 1938 and published an article on its benefits the next year. Lank worked closely with renowned surgeon Robert E. Gross and safely administered the anesthesia while Gross divided the first patent ductus arteriosis in 1938; she also administered the anesthetic for the first successful esophageal atresia repair performed by William Ladd in 1939. Lank advanced pediatric anesthesia through the development of pediatric-sized anesthesia mask and ventilation bags. She also assisted in the design and creation of the hospital's first postanesthesia recovery room.

Alice Magaw (1860-1928)

In 1893 Alice Magaw became the anesthetist for Drs. William J. and Charles H. Mayo at St. Mary's Hospital in Rochester, Minnesota, a position she held until 1908 when she married Dr. George Kessel. Charles Mayo bestowed upon her the name "Mother of Anesthesia" for her mastery of open drop ether. In 1899, Magaw became the first nurse anesthetist to be published when the *Northwestern Lancet* printed her article "Observations in Anesthesia." Five more articles would follow. She spoke before a number of medical societies, unusual for a nurse at that time, detailing her safe administration of anesthetics. Many surgeons around the country sent their nurses to Magaw for anesthesia training. She gained a reputation for quietly talking the patient to sleep, without the struggle seen so often elsewhere.

Agnes McGee (1885-?)

Agnes McGee established the first postgraduate course in anesthesia at St Vincent's Hospital in Portland, Oregon, in 1909. The training included instruction in anatomy, the physiology of the respiratory track, and the pharmacology of anesthetic agents. McGee also taught third-year students at the University of Oregon Medical School. For her work as an educator, the AANA bestowed upon her the 1953 Award of Appreciation.

Florence McQuillen (1903-1981)

In 1927 John S. Lundy invited Florence McQuillen to join his staff at the Mayo Clinic. She worked closely with Lundy as chief nurse anesthetist and as a clinical instructor, and collaborated with him in editing and abstracting articles for *Anesthesia Abstracts*. In 1948 she became the first AANA executive director, a position she held until her retirement in 1970. In her 22 years with the AANA, McQuillen was influential in virtually all areas of the AANA's growth and expansion. Under her guidance, the U.S. Department of Health, Education, and Welfare officially recognized the AANA's authority to grant accreditation for nurse anesthesia programs and to grant certification for nurse anesthetists. She also instituted the AANA's voluntary continuing education program, which made the AANA the first professional nursing organization to recognize the need for continuing professional education; this eventually led to the adoption of a mandatory continuing education (CE) program. She received the AANA Award of Appreciation in 1970.

Ruth M. Nash (1882-?)

Ruth Nash, a graduate of the New York Post-Graduate Hospital, one of the early postgraduate schools of anesthesia, which was established in 1912, took over the postgraduate school of anesthesia in 1917. She was also appointed special lecturer on anesthesia for the department of physiology and pharmacology of the Long Island College of Medicine in 1927.

Jack Neary (1945-2009)

Jack Neary was a pioneer in pain management education and practice. He practiced for 23 years at Cottage Hospital, Woodsville, New Hampshire, and served as the anesthesia department director beginning in 1985. He expanded the department, began offering epidurals for labor and delivery, and developed a postoperative pain service. He extensively lectured and taught pain management and regional anesthesia techniques throughout the country. He also was an adjunct clinical faculty member and associate professor at the University of New England School of Anesthesia where he inspired and mentored many students. A strong political advocate, Neary fought for nurse anesthetists' practice rights throughout his career and worked with the AANA on policy and regulatory issues surrounding pain management. He received the AANA's Alice Magaw Outstanding Clinical Practitioner Award in 1999 and the Agatha Hodgins Award for Outstanding Accomplishment in 2009 (posthumously), and the New Hampshire Nurse Practitioner of the Year Award in 2006.

Dagmar Nelson (1892-1958)

Dagmar Nelson received her anesthesia training at St. Mary's Hospital, Rochester, Minnesota, where she worked for a short time; she later went to Los Angeles at the request of surgeon Verne Hunt, who was working at St. Vincent's Hospital. Nelson was the hospital's sole anesthetist. In 1933 she became the defendant in a landmark legal case, *Chalmers-Francis v. Nelson*, which alleged she was violating the California Medical Practice Act by administering anesthesia, that is, practicing medicine without a license. A lower court found in her favor and upon the plaintiff's appeal, the case went to the California Supreme Court. The judgment rendered in 1934 again found in favor of Nelson and confirmed the legality of nurse anesthesia practice.

Anne Penland (1885-1976)

In 1912 Anne Penland was trained in anesthesia by Margaret Boise at Presbyterian Hospital in New York City. During World War I, Penland was the only nurse anesthetist with the New York Presbyterian Hospital Unit (Base Hospital No. 2) and was the first official nurse anesthetist on the British front. Penland's demonstration of her anesthesia skills contributed to the decision by the British to train their nurses in anesthesia; Base Hospital No. 2 was one of the training centers for the British nurses and Penland served there as instructor. After the war, Penland served as Presbyterian Hospital's chief anesthetist for 20 years.

Hilda Salomon (1895-1983)

Hilda Salomon's career as a nurse anesthetist educator took place at Jewish Hospital in Philadelphia. She was appointed chief of the anesthesia department in 1924, and she founded the Jewish Hospital School of Anesthesia in 1929 and served as its director until her retirement. While director, she instituted regular local meetings among the students and faculty of the many schools of anesthesia then functioning in Philadelphia. She was a charter member of the AANA and was its third president (1935-1937). During her AANA presidency, she promoted several ideas that were considered radical for the time. In particular, she called for a

proposal permitting the membership of male and African-American nurse anesthetists. She also helped organize the Pennsylvania Association of Nurse Anesthetists and also served as president. In recognition of her service, she received AANA's Award of Appreciation and the Agatha Hodgins Award for Outstanding Accomplishment.

Col. Ruth Satterfield (1913-2008)

Ruth Satterfield dedicated her life to the development and advancement of nurse anesthesia education. The majority of her career was spent in the Army Nurse Corps, which she joined in 1940. She served as education director of all army schools of nurse anesthesia and director of the Army Nurse Corps Anesthesia Course at Walter Reed General Hospital in Washington, D.C. She concluded her army career as consultant to the Army Surgeon General. She also continued her work as Education Consultant to the AANA (1968-1981). Her honors include the second Oak Leaf Cluster to the Army Commendation Medal for her work as Special Course Director, Anesthesia, William Beaumont General Hospital; the prestigious Order of Military Medical Merit for her "sustained contributions to the betterment of Army medicine;" and the first AANA Annual Agatha Hodgins Award for Outstanding Accomplishment.

Sister M. Yvonne Jenn (1910-2002)

Sister Yvonne was a dedicated educator. She founded the St. Francis School of Anesthesia in La Crosse, Wisconsin, in 1942 and served as its director until her retirement in 1981. She also served as the director of anesthesia for the hospital. Sister Yvonne worked to ensure her students learned about new and innovative techniques and anesthetic agents, and she included ethics in schools curriculum long before it was popular. She was a pioneer in the field of respiratory therapy and served 12 years as registrar for the American Association for Respiratory Care. She received the AANA's Agatha Hodgins Award for Outstanding Accomplishment in 1982 and the Helen Lamb Outstanding Educator Award in 1995.

Helen Vos (1914-2007)

Helen Vos's career was marked by her dedication to the education of nurse anesthetists both in the United States and abroad. After serving 4 years in the Army Nurse Corps in the 1940s, she became the first director of the anesthesia program at Hurley Hospital in Flint, Michigan, and discovered her passion for teaching. She taught anesthesia in Lahore, Pakistan, for 4 years, and also served as Educational Director at the anesthesia program at Barnes Hospital, St. Louis. Most notably, she was the second director (1963-1977) of the North Carolina Baptist Hospital School of Anesthesia, Winston-Salem, North Carolina, where she was also appointed Assistant Professor, Allied Health Programs, Bowman Gray School of Medicine. She also traveled throughout the country presenting continuing education lectures and taught countless numbers of CRNAs the meaning of the "three-lead EKG." She served as the 1966-1967 AANA president and was presented with the AANA's Agatha Hodgins Award for Outstanding Accomplishment in 1979 and the Helen Lamb Outstanding Educator Award in 1996.

Sophie Jevne Winton (1887-1989)

A practitioner in anesthesia for more than 50 years, Sophie Winton began her career at Swedish Hospital in Minneapolis where she was trained in anesthesia. In 1918 she joined the Nursing Corps, then part of the Red Cross, and was assigned to Mobile Hospital No. 1 in the Chateau-Thierry area, often giving as many as 25 to 30 anesthetics a day with open drop ether and chloroform. She received the Croix de Guerre and six overseas service bars for her service on the front lines. In 1933 she lent her financial support in a test case (*Dagmar Nelson v. Chalmers-Frances*) in California that was to have far-reaching effects on the practice of nurse anesthesia. Winton was an early independent practitioner and managed her own dental and plastic surgery clinic in California until 1960. She was awarded honors by the Mexican Dental Association in conjunction with the International Dental Association for her advancement in the delivery of dental anesthesia. In 1984 she was presented with the AANA's Agatha Hodgins Award for Outstanding Accomplishment.

SUMMARY

Nurses were recruited into the field of anesthesia by surgeons in the latter half of the nineteenth century because inexpert clinical anesthesia administration by others often resulted in morbidity and mortality. The Civil War was the earliest documented use of nurses as anesthetists, and it became a trend afterward. By the 1890s, nurse anesthesia was well established, having spread from Midwestern Catholic hospitals to cities on both coasts. Before the turn of the twentieth century, nurse anesthetists provided gratuitous training to others. The first hospital-based anesthesia educational program opened in 1909. During World War I, nurse anesthetists were widely credited with significantly reducing combat-related surgical morbidity and mortality. By 1920, nurse anesthesia had become well established and well accepted.

Nurse anesthetists formed a national organization in 1931. Dedicating themselves to advancing anesthesia education and patient safety, nurse anesthetists implemented a number of firsts: annual meetings, a monthly bulletin, and a journal. In 1945 the first certification examination for graduates was implemented. As a result of service in the mid-century wars, nurse anesthetists earned officer's status, and men gained the right to join the military's nurse corps. When the military demanded that its nurse anesthetists pass the AANA certification examination, civilian hospitals soon followed suit. By the 1950s, nurse anesthetists worked with surgeons and engineers to pioneer anesthesia machinery, ventilators, and anesthesia for pediatric cardiovascular surgery. During this era, accreditation of anesthesia training programs was achieved.

The second half of the twentieth century was marked by a closer involvement between the profession and government. As Medicare paid for a larger proportion of clinical anesthesia services, the government in turn exerted increasing control over how those services were rendered and at what cost to taxpayers. Because federal dollars also went for nursing education, government exerted a measure of control over accreditation. Independent councils on accreditation, certification, recertification, and public interest evolved from this.

In the 1960s and 1970s, state governments modernized nurse practice acts to account for new subspecialties in advanced practice nursing. CRNAs had to participate even though they had long predated other advanced practice nurses. The 1980s and 1990s brought about governmental efforts to "reform" health care by extending services and containing costs. Quality of care entered the debate, and CRNAs ultimately proved what had been shown 50 years earlier: anesthesia outcomes are no worse and perhaps better when a CRNA administers the anesthetic. For CRNAs, constant vigilance and a presence in federal and state government

centers were essential because each of the aforementioned policy changes presented organized anesthesiologists with an opportunity to threaten nurse anesthesia. As a result, state nurse anesthetist associations became stronger, and the AANA established an office in Washington, D.C.

Progress in nurse anesthesia has occurred over many decades and resulted in an extraordinary record of patient safety. CRNAs have undertaken hundreds of clinical, scientific, and policy research projects to further professional and public understanding of nurse anesthesia.

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CHAPTER 2

Nurse Anesthesia Specialty Practice and Education in the United States

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In existence for nearly 150 years, the specialty practice of nurse anesthesia has become one of the most challenging and rewarding areas of advanced nursing practice. Nurse anesthetists, together with their professional association, the American Association of Nurse Anesthetists (AANA), have been role models for members of other nursing groups and allied health organizations. This chapter describes current educational requirements to become a Certified Registered Nurse Anesthetist (CRNA), the roles of the CRNA, and the roles the councils and the AANA play for the profession.

NURSE ANESTHESIA EDUCATIONAL REQUIREMENTS

The upgrading of academic credentials for CRNA educators and their graduates has always been closely tied to the goals of the professional association— advancing the art and science of anesthesia.[1] Nurse anesthesia leaders have been responsible for increasing the requirements for curricular content, faculty qualifications, and academic credentials for graduates since early in the twentieth century. Over time, nurse anesthesia programs have moved from apprenticeships at hospitals into degree-granting institutions fulfilling the vision of early anesthesia leaders for a university education for nurse anesthetists. This movement into academia required identifying the locations of programs in the nation, determining the essential characteristics of programs, agreeing on curricular requirements, inspecting programs, and developing a program approval process.

Nurse Anesthesia Education Today

Nurse anesthesia programs are governed by the *Standards for Accreditation of Nurse Anesthesia Educational Programs*.[2] The processes used to accredit programs are focused on ensuring compliance with the *Standards* and the Council on Accreditation of Nurse Anesthesia Educational Programs' (COA) *Accreditation Policies and Procedures*.[3] Revisions to the *Standards* and the accreditation policies occur periodically to ensure they continue to reflect the current requirements to prepare graduates for entry into practice, meet U.S. Department of Education (USDE) and the Council for Higher Education Accreditation (CHEA) recognition requirements and promote improvement in nurse anesthesia education.[4] In 2011 the COA initiated a major revision of its standards with the purpose of establishing new practice doctorate standards. The new standards will be used by the COA to assess programs transitioning to award practice doctoral degrees. The COA requires all students accepted into an accredited nurse anesthesia program on January 1, 2022, and thereafter to graduate with doctoral degrees (refers to Standard III, Criterion C2).[2]

Nurse Anesthesia Program Requirements

Nurse anesthesia programs are required to demonstrate compliance with the *Standards* and the *Accreditation Policies and Procedures*. The requirements include the need for programs to assess their integrity and educational effectiveness through ongoing evaluation and assessment. Programs must continually monitor and evaluate their didactic and clinical curriculum, including, but not limited to, curricular content, admissions policies, faculty, and clinical sites used for student educational experiences. In addition to programs' internal assessment processes, programs must submit annual reports to the COA, complete self-studies and host onsite COA visits at a maximum of every 10 years. The COA monitors programs' indicators of success and the attainment of their stated outcomes. This includes programs' pass rates on the National Board of Certification and Recertification for Nurse Anesthetists' (NBCRNA) national certification examination (NCE). Programs must demonstrate graduates take the NCE examination and pass it in accordance with the COA's pass-rate requirement.[3] The COA also monitors programs' attrition and employment rates. Programs are required to post their first-time NCE pass rates, attrition rates, and the employment rates of its graduates on their websites and to link their websites to the COA's list of recognized programs.[5] These stringent requirements help ensure the effectiveness of nurse anesthesia clinical and didactic education and also that the public is being provided with accurate information related to student achievement.

The COA has requirements related to the administration of nurse anesthesia programs. The requirements include programs' management of faculty and students, fiscal management, maintenance of COA accreditation and other higher-education accreditation requirements of the universities, faculty continuing education, and program evaluations. The COA Standards require that nurse anesthesia programs employ Certified Registered Nurse Anesthetists (CRNAs) with graduate degrees in the roles of program administrator and assistant program administrator. In addition, programs must demonstrate they provide an extensive educationally sound curriculum combining both academic theory and clinical practice. Programs must develop and implement policies and procedures that use outcome criteria to promote student learning while simultaneously enhancing the programs' quality and integrity.

The COA Standards also identify the minimum admission requirements. Admission to nurse anesthesia programs requires graduation from a school of nursing, a baccalaureate degree, current licensure as a registered nurse, and at least 1 year of professional experience in a critical care setting. The critical care experience must provide experiences for the registered nurse to develop as an independent decision maker capable of using and interpreting advanced monitoring techniques based on knowledge of physiologic and pharmacologic principles. Programs determine what types of work experience are acceptable for admission. Typical critical care areas include surgical, cardiothoracic, coronary, medical, pediatric, neurologic, and neonatal intensive care units.

Nurse Anesthesia Program Curriculum

The didactic curricula of nurse anesthesia programs are governed by the COA Standards and help ensure students are provided with the scientific, clinical, and professional foundation upon which to build sound and safe clinical practice. Based on the 2011 COA Annual Report data from all nurse anesthesia programs, the number of graduate semester credits for nurse anesthesia programs are greater than other graduate degrees in health professions.[6] The curriculum of graduate nurse anesthesia programs includes courses in anatomy, advanced physiology/pathophysiology, advanced health assessment, advanced pharmacology, chemistry, biochemistry, physics, professional issues, equipment, technology, pain management, research, clinical conferences, chemical dependency, and wellness (refer to Standard III, Criterion C14 and C21).[2] Courses in nurse anesthesia practice provide content such as induction, maintenance, and emergence from anesthesia; airway management; anesthesia pharmacology; and anesthesia for special patient populations such as obstetrics, geriatrics, and pediatrics. In addition, students are instructed in the use of anesthesia machines and other related biomedical monitoring equipment. Programs must evaluate students' knowledge and skills to ensure they are meeting the programs' stated objectives as they progress in the program.

The methods used to deliver nurse anesthesia curricula are changing as new technologies are being applied in higher education. Based on COA 2011 Annual Report data, more than 60% of nurse anesthesia programs use some form of distance education in their provision of didactic instruction.[6] Programs' distance education offerings vary from several core courses to programs in which the majority of the didactic curriculum is provided using distance education. In addition, 98% of programs report having access to some form of simulation (e.g., simple models, computer, full-body patient simulation).[6] The involvement of individual programs ranges from the use of simulation to supplement traditional content delivery methods to the utilization of simulation to entirely deliver curricular content.

The clinical curriculum of nurse anesthesia education provides students with an opportunity to apply didactic knowledge in clinical practice. Programs prepare graduates with the knowledge and skills to administer all types of anesthesia, including general, regional, and selected local and moderate sedation to patients of all ages for all types of surgeries. Students use a variety of anesthesia drugs, manage fluid and blood replacement therapy, and interpret data from sophisticated monitoring devices. Additional clinical responsibilities include the insertion of invasive catheters, the recognition and correction of complications that occur during the course of an anesthetic, the provision of airway and ventilatory support during resuscitation, and pain management. To meet COA Standards and be eligible to take the NCE, a student must have performed a minimum of 550 anesthetics, which must include specialties such as pediatric, obstetric, cardiothoracic, and neurosurgical anesthesia.[2] The anesthesia experiences include the care of not only healthy but critically ill patients of all ages for elective and emergency procedures. In most programs, the minimum number of clinical experiences is surpassed early in the clinical practicum. Based on 2011 certification transcript data, nurse anesthesia programs provide an average of 846 cases, 1683 hours of anesthesia clinical experience, and 2519 total clinical hours for each student.[7]

During students' clinical experiences, they must be supervised by CRNAs or anesthesiologists who provide instruction in the administration and monitoring of various techniques, including both general and regional anesthesia. The clinical faculty evaluates the technical and critical thinking skills of students. The entry into practice competencies for the nurse anesthesia professional are those required at the time of graduation to provide safe, competent, and ethical anesthesia care to patients for diagnostic, therapeutic, and surgical procedures (refer to Standard III, Criterion C21).[2] The entry into practice competencies should be viewed as the structure upon which the nurse anesthetist continues to learn new facts, obtain and refine knowledge, and develop skills along the practice continuum that starts at graduation (competent), and continues throughout their entire professional career (expert).

Future Specialization

Although nurse anesthesia entry-level education prepares individuals for the full scope of nurse anesthesia practice, certain areas of specialized practice are currently available to promote interested CRNAs to further develop additional post-entry knowledge and skills related to their preparation in specific areas of nurse anesthesia practice. One example of this type of specialization preparation is a postmasters certificate in pediatric anesthesia available through Wayne State University in Detroit, Michigan. This program provides selected CRNAs and/or graduate nurse anesthesia students with the opportunity for continued focused preparation in the practice area of pediatrics through an arrangement with Children's Hospital of Michigan.[8]

Another area of specialization that has been developed for practicing certified registered nurse anesthetists is in the area of nonsurgical (chronic) pain management. In 2008 the AANA assembled a group of CRNA practitioners who were identified as devoting most or all of their clinical practice to this specialized area. Through the input and guidance of this group of leaders, a theoretical foundation for pain practice was operationalized, and subsequently work was initiated to formalize the continuing education content for nurse anesthetists expressing an interest in nonsurgical pain management. Although the short-term goal was to develop comprehensive continuing education in this content area, the longer-term goal was to develop the preparation of these practitioners into a more formalized educational framework. Hamline University in St. Paul, Minnesota, was identified as possessing the traits and resources necessary for an ideal academic partner to house and offer a formal higher education program in advanced pain management for the nurse anesthesia community. The final product of this partnership was a four-semester/15 month postmasters educational program in advanced pain management.[9] Although other specialty groups could eventually avail themselves of this education, the commitment was to first focus on the nurse anesthesia community and to expand enrollment to other practice disciplines over time, based on demand and the adequacy of educational resources. The first class of students enrolled in this landmark educational undertaking began their program of study on February 1, 2012.

Also, at the time of this chapter's publication, no post-National Certification Examination for Nurse Anesthetists had been developed for either of the two areas of educational specialization noted previously. However, the NBCRNA is committed to "…continue to explore strategies to meet its goals and the needs of the profession. The future requirements for recertification and the possibility of specialty credentialing for subspecialty areas (pain management, pediatric, cardiac, and other clinical specialties) are under consideration."[10] Essential to this consideration will be the preparation of adequate numbers of individuals who have successfully completed post-entry level educational programs. Until an acceptable number of individuals are prepared and in the workforce, it is unlikely that any certifying examination would be considered for development.

Equally important to the development of new and varied areas of specialized post-entry to professional nurse anesthesia education is the need to remain mindful of the APRN Consensus Model.[11] This model for education, accreditation, and certification for advanced practice nursing specifically identifies that areas of educational specialization within advanced practice nursing that occur beyond the levels of role and/or practice foci are not to be used as sources for regulation of practice, but rather to serve the individual nursing practitioners in their delivery of care and services.[11] Therefore, future examination for specialty areas of practice by the certified Registered Nurse Anesthetist, above the *role of nurse anesthetists* and the population foci of *across the lifespan* should not be used as a gate-keeping mechanism to prevent any CRNA from engaging in any subspecialty practice. As long as a CRNA can demonstrate he or she has obtained the knowledge, skills, and abilities necessary to engage in a specialized area, the individual practitioner should not undergo regulation via additional professional licensure.

THE CERTIFIED REGISTERED NURSE ANESTHETIST

CRNAs are anesthesia specialists who administer approximately 32 million anesthetics annually to patients in the United States.[12] As an advanced practice nurse, a CRNA can serve in a variety of capacities in daily practice, such as clinician, educator, administrator, manager, and researcher. CRNAs furnish anesthesia services to patients, using all anesthetic techniques, for all types of surgical, obstetric, diagnostic, and chronic pain management procedures. CRNAs practice in urban hospitals, critical access designated hospitals, ambulatory surgical centers, and U.S. military, public health services, and Veterans Administration healthcare facilities. CRNAs also practice in the offices of dentists, podiatrists, ophthalmologists, and plastic surgeons. In some states, they are the sole anesthesia providers in almost 100% of all rural hospitals, which enables these medical facilities to provide obstetric, surgical, diagnostic, and trauma stabilization services.[12]

CRNAs have a variety of employment possibilities available to them. The largest percentage of CRNAs are employed by hospital facilities; however, others are self-employed or are employees of anesthesiologists, academic institutions, military installations, or clinics. CRNAs provide anesthesia services in collaboration with other qualified practitioners, such as physicians (e.g., surgeons, obstetricians, or anesthesiologists), dentists, or podiatrists.[13] To become a CRNA, an individual must comply with the following requirements[11]:

- Hold a current and unrestricted state licensure as a registered professional nurse
- Graduate from a nurse anesthesia educational program accredited by the COA or its predecessor
- Successfully complete the NCE administered by NBCRNA or its predecessor

To maintain the CRNA credential, the individual must meet the requirements as set forth by the NBCRNA concerning continuing education, document substantial anesthesia practice, maintain current state licensure, and certify that he or she has no conditions that could adversely affect the ability to practice anesthesia.[14] More information regarding maintenance of certification may be found at the NBCRNA website: www.nbcrna.com.

CRNA Activities

Professional certification indicates that an individual has met predetermined criteria that measure the knowledge, skills, and abilities necessary for entry-level practice in a specialty area. Certification affords the public an awareness of the qualifications and capabilities of its healthcare providers. The credential CRNA indicates that the individual who holds it has fulfilled prescribed criteria and is qualified to provide the services described within a CRNA's scope of practice. The AANA publishes a scope of practice for CRNAs (Box 2-1).

BOX 2-1

Scope of Practice for Nurse Anesthesia Practice

CRNA scope of practice includes, but is not limited to, the following:

1. Performing and documenting a preanesthetic assessment and evaluation of the patient, including requesting consultations and diagnostic studies; selecting, obtaining, ordering, and administering preanesthetic medications and fluids; and obtaining informed consent for anesthesia
2. Developing and implementing an anesthetic plan
3. Initiating the anesthetic technique, which may include general, regional, and local anesthesia and sedation
4. Selecting, applying, and inserting appropriate noninvasive and invasive monitoring modalities for continuous evaluation of the patient's physical status
5. Selecting, obtaining, and administering the anesthetics, adjuvant and accessory drugs, and fluids necessary to manage the anesthetic
6. Managing a patient's airway and pulmonary status using current practice modalities
7. Facilitating emergence and recovery from anesthesia by selecting, obtaining, ordering, and administering medications, fluids, and ventilatory support
8. Discharging the patient from a postanesthesia care area and providing postanesthesia follow-up evaluation and care
9. Implementing acute and chronic pain management modalities
10. Responding to emergency situations by providing airway management, administration of emergency fluids and drugs, and using basic or advanced cardiac life-support techniques

From *American Association of Nurse Anesthetists* (AANA): *Scope and Standards for Nurse Anesthesia Practice*. Park Ridge, Ill: AANA, 2010. Accessed January 18, 2012 at http://www.aana.com/resources2/professionalpractice/Documents/PPM%20Scope%20and%20Standards.pdf.

Individual state or facility rules and regulations may influence CRNA scope of practice; therefore, it is the CRNA's responsibility to ensure that he or she is practicing within his or her scope of practice when providing anesthesia care. More information regarding CRNA scope of practice is available on the AANA website at www.aana.com.

In addition to defining CRNA scope of practice, the AANA also publishes expected standards for nurse anesthesia practice that describe CRNA behaviors concerning informed consent, monitoring, and documentation of care, to name a few. These standards apply to all anesthetizing locations and are intended to encourage high-quality care. The standards for nurse anesthesia practice are available at www.aana.com. CRNAs are consulted on a 24-hour basis and are an integral part of the healthcare team, lending their expertise in airway management, respiratory care, management of fluid and electrolyte problems, pain management, resuscitative efforts, and other related clinical activities.[12]

Apart from a clinical practice role, CRNAs often function in many other capacities. CRNAs hold administrative or other managerial positions; participate in quality improvement processes; lead research activities; collaborate in interdepartmental activities; and participate on various state and federal governmental agencies.

A large number of CRNAs are involved with the education of nurse anesthesia students and other healthcare professionals (e.g., flight nurses, medical students).

AANA ORGANIZATIONAL STRUCTURE AND FUNCTION

The American Association of Nurse Anesthetists (AANA) is a professional association that represents the majority of CRNAs and students nationwide. According to 2011 AANA data, more than 90% of CRNAs in the United States are members of the AANA.[11] The AANA was first incorporated in Ohio on March 12, 1932, as the National Association of Nurse Anesthetists (NANA). It was reincorporated in the state of Illinois on October 17, 1939, and was designated as a tax-exempt organization in accordance with subsection 501(c) of the Internal Revenue Code, and that same year the organization's name was changed to the American Association of Nurse Anesthetists.

Configurations and Relationships of Councils

In the 1970s, the AANA bylaws were revised to allow for the establishment of four separate autonomous councils under the corporate structure of the AANA: the Council on Accreditation of Nurse Anesthesia Educational Programs (COA), the Council on Certification of Nurse Anesthetists (CCNA), the Council on Recertification of Nurse Anesthetists (COR), and the Council for Public Interest in Anesthesia (CPIA). In recent years significant changes have occurred in the structure of the councils. In 2007 the CCNA and COR incorporated to form the National Board of Certification and Recertification for Nurse Anesthetists (NBCRNA). The COA separately incorporated in 2009, and in 2010 the AANA members voted on a bylaws change at the August 7, 2010, AANA annual business meeting to not continue to recognize the CPIA. Subsequent to that action the CPIA chose to not continue its activities and has since been dissolved. The COA and the NBCRNA are solely responsible for their own internal affairs, including the election of officers and the direction of financial activities. In accordance with their bylaws, membership on these councils includes CRNAs, students, hospital administrators, and members of the public.[15]

The councils have been established with the intention of informing and assuring the public that accreditation, certification, and recertification activities are within the discipline of nurse anesthesia and are separate from and not unduly influenced by the national professional association (i.e., AANA). Communication between the AANA, COA, and NBCRNA takes place through scheduled leadership meetings that facilitate discussion of issues of mutual concern. A CRNA executive director serves the COA, NBCRNA, and the AANA. More information on the COA and NBCRNA can be found at their websites: home.coa.us.com and www.nbcrna.com, respectively.

Today, AANA's bylaws, available at www.aana.com, are essentially the AANA's working constitution, which dictates how the association functions. The bylaws address the different classes of membership, decision-making procedures, responsibilities of the AANA's elected officials, the staff role and responsibilities of the Executive Director, the configuration of committees, functions of committee members, and the AANA's relationship with state nurse anesthesia associations.[15]

The AANA board of directors (BOD) is elected by voting-eligible members of the AANA and serves as the administrative authority for the AANA.[15] The BOD includes the president, president-elect, vice president, treasurer, and seven region directors. The BOD develops organizational policy; oversees the budget and related financial affairs; promulgates clinical standards and guidelines; participates in legislative activities; and serves as a liaison with external governmental and professional agencies. In addition, the BOD receives and considers the reports from the AANA staff, the various committees of the association, and the autonomous councils and makes recommendations as needed.

As of 2012, the AANA organization resides in three offices from Park Ridge, Illinois, to Washington, D.C., and employs over 128 people. The AANA Executive Director manages the daily activities of the Association with the assistance of the Deputy Executive Director and the senior directors of the various divisions. Collectively, the AANA staff carries out objectives as established by the elected AANA BOD and consistent with the AANA's mission statement to "advance patient safety, practice excellence, and its members' profession." With this in mind, the AANA supports advocacy activities at the local, state, and federal levels on behalf of its members and the public. The AANA's organizational structure and more information regarding the AANA divisions and its advocacy efforts are available at www.aana.com.

AANA Subsidiary

The AANA owns one subsidiary, the AANA Association Management Services (AAMS), which provides non–dues-related sources of revenue, as well as services for the general membership. There are currently two divisions within the AAMS. These divisions provide services related to insurance and housing (hotel rooms and lodging arrangements in association with meetings and events of the AANA) to both internal and external clients.[16]

SUMMARY

With the ongoing dedication of its members, volunteer leaders, and staff, the nurse anesthesia profession has been growing and evolving for well over a century. As they encounter the challenges resulting from healthcare growth and change, all CRNAs must take an active role in securing their future, because a profession is ultimately the sum of its members.

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Legal Concepts in Nurse Anesthesia Practice

CHAPTER 3

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Few issues in nurse anesthesia practice cause the type of consternation that legal issues do. Perhaps it is that they are not known to nurse anesthetists as well as the issues surrounding the actual administration of anesthesia. This chapter attempts to demystify some basic issues surrounding the interaction of the legal and anesthesia worlds. This chapter is not intended to give specific legal advice.

SOURCES OF LAW

The source for all American law is the Constitution of the United States.[1] All governmental power, state and federal, stems from that document. The Constitution cannot be changed by legislation nor can the President act in contravention of the Constitution. The Constitution can be changed only by amendment, a difficult process.[2] The final authority on the interpretation of the Constitution is the Supreme Court of the United States.[3]

The Supreme Court of the United States, however, makes rulings only on laws in reference to federal law. State laws are interpreted by their respective state courts, unless those laws violate the Constitution of the United States or other federal laws. If the state law violates the U.S. Constitution or other federal law, the federal law supersedes.[4]

Laws may come from any of the three branches of government set out in the Constitution, the legislative, the executive, or the judicial branch. The legislative branch, in the federal system also known as the Congress, creates laws that are known as *statutes*. These statutes must be passed by both houses of Congress, the Senate and the House of Representatives, after which they are presented to the President. If the President signs the bill, it becomes law. If the President vetoes the bill, Congress can override that veto by a vote of two thirds of both houses of Congress. States have similar procedures, but the exact process varies slightly between states.

Regulations are promulgated by administrative agencies. On the federal level these include agencies such as the Food and Drug Administration (FDA), the Occupational Safety and Health Administration (OSHA), and other agencies. On the state level, regulations are promulgated by agencies such as boards of nursing, medicine, and dentistry. Administrative agencies create regulations, and they also may have the function of determining whether regulations and statutes were violated. In this quasijudicial function, a license may be revoked or a person may be fined by the administrative agency. The actions of administrative agencies are reviewable by courts. Courts will review the process used and whether an agency's actions were within its statutory powers, but they generally do not review decisions based on their expertise in their respective fields.

Nurse anesthetists must maintain an awareness of what regulations apply to them. Failure to adhere to the board of nursing regulations and standards of care may result in actions against a nurse anesthetist's license, up to revocation of the license and fines. In 2003 a nursing board in Oklahoma revoked a nurse anesthetist's license and imposed a $99,000 fine for unsafe injection practices that resulted in 699 probable hepatitis C virus (HCV) infections and 31 probable hepatitis B virus (HBV) infections. The Board of Nursing's action occurred after the CRNA was reported by registered nurses working in his pain control clinic.[5] Other regulatory agencies such as the Centers for Disease Control and Prevention also make standards that courts may apply to nurse anesthetists.[6]

Courts also have a law-making function in their role of interpreting statutes and regulations. If there is any ambiguity in the way that a statute or regulation is worded, courts will interpret those laws according to the intention of the writers of the statute or regulation, as best as that can be determined. Courts will also interpret whether the statute or regulation in question violates the state or federal Constitutions. Thus, not only must statutes and regulations be viewed to determine what the laws are but also courts' interpretations of those regulations and statutes must be considered.

In the United States, court systems exist at both the state and federal levels. The state systems deal primarily with issues of state law. This includes most malpractice cases, licensure issues, and contracts. Federal courts deal primarily with federal law issues. However, overlap can occur in both areas. Sometimes federal issues are addressed by state courts that are in the process of dealing with a case concerning primarily state issues; the reverse also occurs. Further confusing the issue, many cases dealing with federal law may be brought in a state court. A federal court may hear a case that is solely a state law issue because the parties to the lawsuit are residents of different states and the amount under dispute meets the requirement for federal jurisdiction.

The federal court system and most state systems have three levels. The first level is the trial level. In the federal system, this is known as the district court. States refer to courts of this first level by many names, such as district courts, juvenile courts, small claims courts, and county courts. New York calls its trial level courts supreme courts. Once a case has been tried, the court's decision may be appealed to the intermediate appellate court. In the federal system this is the United States Court of Appeals. Parties to lawsuits usually have a right to appeal the case to the intermediate appeals court. Appellate courts consider only whether trial courts made mistakes of law. For example, an appellate court can overturn a trial court's decision because it improperly allowed evidenced to be entered that altered the outcome of the case. In this instance, the appellate court would remand the case to the trial court for retrial. An appellate court does not go over testimony or evidence in the case to determine whether it would have decided the case differently.

The highest level of court is the supreme appeals court. In the federal system, this is the United States Supreme Court. In some states, the name of the highest court is different. For example, in New York, the trial court is called the Supreme Court, the

intermediate appellate court is the supreme appellate court, and the supreme appellate court is the New York Court of Appeals. Some states also have two separate supreme courts, one for civil cases and one for criminal cases.

In the federal and in many state systems, parties in a lawsuit do not have a right to have a case heard by the supreme appellate court. For a case to be appealed to the United States Supreme Court, a petition called a *writ of certiorari* is sent to the Court requesting that it hear the case. The Court then decides whether the case deserves review. Many states use this method but also have additional mechanisms for obtaining state Supreme Court review. Some states allow a trial judge or intermediate appellate court to certify a question for state supreme court review.

CRIMINAL LAW

Law in the United States' legal system can be divided into two basic types: criminal law and civil law. Criminal law is the body of law established to protect society from harm, declaring what conduct is criminal and establishing punishment for violation of the law. Civil law is the body of law concerned with private rights and remedies. Civil law applies to torts (private wrongs other than a breach of contract) and breaches of contract.

Nurse anesthetists usually are more concerned with civil law issues than with criminal law issues. However, nurse anesthetists can violate criminal laws in several instances. Fraudulent filing of insurance or Medicare claims can violate federal and state laws. Nurse anesthetists who knowingly sign forms indicating that procedures were performed when they actually were not or stating that anesthesia providers were involved with a case when they were not can be subject to fines and imprisonment for Medicare or insurance fraud. A nurse anesthetist who is asked to sign or fill out false forms by an employer is not freed from criminal liability by virtue of the employment relationship. A nurse anesthetist who practices without appropriate licensure or who knowingly employs an unlicensed person to practice anesthesia can be criminally prosecuted. The misuse of controlled substances is another area of criminal law that concerns nurse anesthetists.

At the time of this chapter's writing, two nurse anesthetists are being prosecuted for racketeering, insurance fraud, and neglect of patients in the Las Vegas hepatitis cases.[7] Nurse anesthetists must be aware that billing one patient for a single-use vial of medication that is used on more than one person may constitute insurance fraud. Likewise, charging both patients for medication from a single-use vial may constitute insurance fraud.

CIVIL LAW

Malpractice (Torts)

Malpractice is part of a greater area of the law called *torts*. A tort is a civil wrong committed against a person or property independent of a contract. Torts include two types of civil wrongs: intentional torts and unintentional torts. Intentional torts are actions deemed to be violations of the civil law when they are performed intentionally. Intentional torts include assault, battery, and false imprisonment. The legal area of greatest concern for nurse anesthetists is malpractice, which is a form of negligence. The term *malpractice* refers to professional misconduct or the consequences of unreasonable lack of skill of nurses, doctors, lawyers, and accountants. Malpractice is an unintentional tort—that is, the person who commits malpractice did not intend to cause the harm that resulted from negligence. Although healthcare providers can also be sued for improper medical care in some states, according to a theory of breach of contract, many states disfavor or statutorily eliminate this option.

Four elements constitute every cause of action for malpractice. There must be (1) a legal duty that the practitioner owes the patient; (2) a breach of that duty by the practitioner; (3) a reasonably close causal connection between the breach of duty and the damages that result; and (4) actual damages to the persons owed the duty.

Duty

The anesthetist's duty begins when a provider-patient relationship is established. This relationship is considered a type of contract. The anesthetist agrees to care for the patient in return for a fee, and the patient agrees to pay a fee in order to receive the anesthetist's professional care. This contract does not have to be in writing—in fact, it does not even need to be spoken of by the two parties. The contract is formed when the patient allows the anesthetist's care and the anesthetist agrees to care for the patient. The law implies a contract for professional care in return for a reasonable fee by the actions of the two parties. The situation is analogous to the case of a homeowner calling a plumber to fix a clogged drain. The two parties have shown by their conduct that they intended to have services rendered for payment of a fee. The law assumes that a reasonable person does not expect an anesthetist (or a plumber) to perform services for free and implies a contract based on the conduct of the parties. The law terms this an *implied-in-fact contract*.

The anesthetist's duty can begin even though all of the preceding terms are not met. The beginning of the provider-patient relationship is not dependent on the payment of fees for the services. Even if both the anesthetist and the patient expect that no fee will be paid, the duty begins with the rendering of services. The patient's lack of mental or physical capacity to enter into the relationship does not prevent the creation of a provider-patient relationship. The anesthetist who cares for an unconscious patient has a duty to that patient even though the patient is unaware of the care being rendered. The law refers to this as in *implied-in-law contract*, because the law implies that a reasonable patient would have agreed to be cared for had he or she not been unconscious.

Standard of Care. The law presumes that people follow a minimum standard of conduct. The driver of a car is expected to stop at red lights and to drive on the right side of the road. The driver need not be the best driver on the road but must act in a manner in which a reasonable driver would act. Thus determining the minimum standard of conduct is objective. What is reasonable is not what the driver thinks is reasonable, but rather what an average reasonable driver believes to be reasonable. For the nurse anesthetist, failure to act according to the standard of care is one of the elements of negligence. The nurse anesthetist must act as a reasonable and prudent nurse anesthetist would act under similar circumstances. It should again be noted that determination of this standard is objective. It does not matter that one particular nurse anesthetist may have had less knowledge than most practitioners and thus acted in a reasonable and prudent manner for the amount of knowledge that he or she possessed. All nurse anesthetists are charged with the duty of acting as would average, reasonable, and prudent nurse anesthetists.

At one time, the standard of care was based on how other practitioners in the community where the alleged malpractice took place would have acted. Today, courts hold healthcare professionals to standards that are relevant for the entire country. Nevertheless, courts still allow for differences related to the size of the community and the equipment available to the anesthetist. For example, although a rural hospital with 25 beds might not be expected to have an anesthetist in-house 24 hours a day

or to have equipment available for extremely specialized tertiary care, a 1000-bed urban tertiary care medical center would. However, the nurse anesthetist in both situations is expected to work at the same level given the limitations of the available equipment. For example, a nurse anesthetist in a small rural hospital might not have the same equipment for the rapid transfusion of blood that a nurse anesthetist in a large urban trauma center had. If a patient were exsanguinating, however, the rural anesthetist would be expected to recognize this and transfuse as rapidly as possible with the equipment available to him or her.

The general rule is that the expert testimony must be used for determining the standard of care in a case of professional malpractice. An expert is a person who has a special skill and knowledge about a subject. An expert need not have the exact same training as the defendant in the case but may be a nurse anesthetist, medical doctor, pharmacologist, or other person with special knowledge. The requirement may be waived only under limited circumstances—for example, if the deviation from the standard is so obvious that it is easily understood by a lay person. Anesthesia textbooks may be used in court as a method of determining the standard of care.

Standards promulgated by professional organizations may be used as evidence of a standard of care. In some jurisdictions, courts view the standards as evidence of the standard of care. In other jurisdictions, they are considered as conclusive proof. Nurse anesthetists should be familiar with the *American Association of Nurse Anesthetists (AANA) Standards for Nurse Anesthesia Practice*. Nurse anesthetists must also adhere to published standards such as the *AANA Position Statement on Syringe Safety*.[8] Deviations for the patient care standards during an anesthetic procedure should be documented and the reason for the deviation explained. In addition, nurse anesthetists should be familiar with the policies of the institutions in which they work. Those policies also can be used as evidence of the standard of care. Deviations from institutional policies should be documented and explained.

Nurse anesthetists must stay abreast of new and emerging standards of care. One emerging area is the issue of distractions in the operating room, particularly reading, texting, and surfing the Internet during patient care. Some institutions have created policies forbidding the use of such devices in patient care areas. However, there is a general move in society against such distractions when driving, flying, and engaging in other important tasks. Train drivers and boat pilots have been held liable both criminally and civilly for injuries that were the result of these distractions.[9,10] Two Northwest Airlines pilots lost their licenses after flying past their scheduled airport while working on their laptop computers.[11] Even though there may not be published standards forbidding all texting and Internet surfing in the operating room, nurse anesthetists must be aware of how their behaviors would be viewed by regulatory agencies and juries. Even if it is common practice, it may be viewed as a deviation from the standard of care. As Judge Learned Hand said,

> *Indeed in most cases reasonable prudence is in fact common prudence; but strictly it is never its measure; a whole calling may have unduly lagged in the adoption of new and available devices. It never may set its own tests, however persuasive be its usages. Courts must in the end say what is required; there are precautions so imperative that even their universal disregard will not excuse their omission.*[12]

Informed Consent. Nurse anesthetists must obtain patients' consent before they can begin treatment. In a much quoted 1914 decision, Justice Cardozo stated, "[e]very human being of adult years and sound mind has a right to determine what shall be done with his own body."[13] Consent is the patient's agreement to undergo a specified treatment. A nurse anesthetist who treats a patient who has not agreed to treatment might be liable to that patient. For example, if a patient was undergoing an elective procedure under local anesthesia and the surgeon asked the nurse anesthetist to give the patient a general anesthetic, the nurse anesthetist and the surgeon might be liable for treatment without consent, even though general anesthesia had never been discussed with the patient. Informed consent, as opposed to consent, is the process in which the practitioner tells a patient not only about the diagnosis and the proposed procedure but also about the probability of the procedure's success and its associated risks, as well as about reasonable alternatives to the procedure. If more than one type of anesthesia is possible—for example, epidural versus general—nurse anesthetists have an affirmative duty to explain both to the patient. The nurse anesthetist may make recommendations on the basis of experience and the surgeon's and anesthetist's personal preferences. However, they should avoid making unsubstantiated statements—for example, that one type of anesthesia should be administered because it is not associated with complications, or that desired results are guaranteed with the use of a particular anesthetic or surgical procedure.

In addition to the ethical and moral desirability of informed consent, its importance to the practitioner lies in the fact that the failure to obtain informed consent can transform a faultless complication into a damage award against the practitioner. In one case, a patient was told by an anesthetist that the only potential problem that could happen from her upcoming spinal anesthesia for a hysterectomy was postdural puncture-related headache. The patient suffered some paralysis on the left side and problems with bowel and bladder control. The Supreme Court of Kansas stated that "While there does not necessarily have to be negligence in the administration of the spinal anesthetic for the resultant damage which [the patient] experienced, the risk was still present…. [W]e find [the anesthetist] failed to obtain the informed consent of [the patient] to the spinal anesthetic prior to its administration."[14] The case illustrates that merely telling the patient what type of anesthesia will be administered or obtaining a signature on a consent form does not constitute informed consent. Nurse anesthetists must understand that informed consent is a process that goes well beyond its objective manifestation (i.e., the patient's signature on a form).

Some risks, however, need not be disclosed. If a patient is aware of a risk or if a risk is common knowledge and the patient's awareness can be presumed, no disclosure is necessary. An anesthetist is not liable for failing to disclose risks that were not known in the anesthesia community at the time of the anesthetic procedure. Risks that are problems only if the anesthetic procedure is performed negligently need not be explained. If a patient specifically asks not to be informed of risks, they need not be disclosed. In this instance, however, the nurse anesthetist should note the request in the chart. A final instance in which an anesthetist may withhold information about risks is known as *therapeutic privilege*. If revealing the information about risks would jeopardize the outcome of the treatment or have an adverse effect on the patient's well-being, then the information can be withheld. The anesthetist must document the reasons for nondisclosure before the procedure. Although therapeutic privilege was used successfully as a defense in a 1955 anesthesia-related case, today it should be used with great caution.[15]

Actions alleging a lack of informed consent have been brought under either of two legal theories: negligence and battery. Battery is the unwanted touching of an individual, and assault is placing

someone in fear of an unwanted touching. Although assault and battery describe both a civil offense and a criminal offense, this section deals primarily with the civil offense of battery—that is, the unwanted touching of a patient. Criminal battery charges against a healthcare provider for failure to obtain informed consent are possible but unlikely.[16]

The pressing of battery charges was the traditional method for seeking a damage award for treatment without consent. However, battery is an intentional tort. The practitioner must have intentionally touched the patient without the patient's consent. The intent need not have been malicious or hostile; the fact that no consent was obtained for the intentional touching is the determining factor. Typically, the patient consents to a certain anesthetic or surgical procedure, but another is performed. Again, the fact that the surgeon and anesthetist acted to help the patient does not prevent the patient from being able to sue for battery. Battery may still be used in some jurisdictions; however, many jurisdictions have eliminated assault and battery actions in cases of lack of consent. These jurisdictions view the failure to obtain proper consent as a form of negligence, and an action as a form of malpractice.

The modern approach to failure to obtain informed consent is the seeking of damages under a malpractice (negligence) theory. A major distinction of the new approach is that the patient who is suing on the basis of battery does not have to prove damages because the unwanted touching is actionable even if it caused no harm. On the other hand, a patient suing under a negligence theory must prove damages. The extent of the duty to disclose varies from state to state. Some states have no requirements of an affirmative duty of the provider to disclose risks, whereas others have specific requirements detailing what must be disclosed. However, even in those states in which the nurse anesthetist does not have an affirmative duty to disclose risks, withholding or misrepresenting information when the patient asks can result in an action against the nurse anesthetist.

Just as the contract between the patient and provider can be implied, in many situations, informed consent also can be implied. If a nurse anesthetist is called to a patient care area to insert an intravenous catheter, the provider typically does not give the same depth of information that is given to a patient undergoing an anesthetic procedure. The anesthetist's purpose is stated, and the patient allows the procedure to continue. Consent is implied by the patient's failure to object to the care.[17] Although consent for a minor procedure on an awake patient may be implied without specific discussion about the procedure, it is unlikely that a court would use implied consent to find that an awake, competent patient had consented to anesthesia and surgery without specific discussion about the procedure.

The other situation in which consent is implied is a medical emergency in which the patient is unable to respond with regard to matters of consent. The person must be unable to respond because of injury, intoxication, or illness and the procedure to be performed must be life saving or health saving. If the procedure can be postponed until effective consent can be given by the patient or another appropriate person without the risk of additional injury, then consent must be obtained.

As alluded to earlier, there are times when persons other than those undergoing treatment can authorize consent. These persons can be (1) relatives of minors or incapacitated persons; (2) persons designated by the patient before being incapacitated; and (3) persons designated by a court as able to consent to treatment for the patient.

Traditionally, a minor cannot consent to medical treatment.[18] For nonemergency, elective treatment, this rule still applies. Consent by the parents or evidence of legal guardianship must be obtained, even if the child is brought for care by an adult relative.

In emergencies, consent of the parents to treatment is implied. The definition of emergency is broad. If the minor's health is in immediate danger (i.e., the minor has a fractured limb that must be set under anesthesia), then consent is implied. Nevertheless, anesthetists and surgeons should attempt to contact the parents or guardians to obtain consent. Even if the parents are not found, the attempt to contact them shows that the providers made a good faith effort to obtain informed consent. Although the emergency exception is broad, anesthetists must be sure that the situation is a bona fide emergency. If the parents were to question the existence of an emergency, the burden of proving that an emergency existed would rest with the providers.

In certain situations, a minor may consent to treatment. Some states have statutes or case law acknowledging the concept of the emancipated minor. An emancipated minor is one who, for the purposes of law, is not a minor despite his or her being younger than the usual age of majority. If a minor lives on his or her own, is married, or is the parent of a child, then the minor may consent to treatment. Some states have specific laws that allow a minor parent to consent to the care of his or her own child. Even in those states without a specific statute, a minor may consent to his or her child's medical treatment because a child's parent may consent to the child's treatment. States differ widely on whether a minor may consent to care for sexually transmitted diseases, contraception, and abortion. Practitioners are advised to determine what their particular laws allow with respect to these areas.

A problem can arise when a parent refuses to consent to medical care for a child. If a treatment would be considered life saving, the providers can petition the court for an order to allow treatment. A common example of this occurs when the parents of a child refuse to consent to a blood transfusion because of a religious belief. Normally, courts order such a treatment to be given if it is deemed life saving. It should be noted that the amount of time necessary to obtain such an order should not be long. Most cities and even many rural areas have a judge on call for emergency warrants or orders. Court orders can be obtained in as little 15 to 30 minutes. Hospital administrators and attorneys should be aware of the procedure for obtaining an emergency order.

As discussed earlier, consent for emergency treatment is implied if the patient is unable to give consent. In nonemergency situations, however, a person authorized by law must give consent for the patient. Who is authorized to give consent for an incapacitated person varies from state to state. Some states allow relatives to give consent for treatment to designated relatives. Other states require that a court order treatment or appoint a guardian who is empowered to give consent. There is, however, a good practical reason to obtain consent from the relative of an incapacitated person even in a state that does not specifically provide for consent by relatives. It serves as evidence of the providers' good faith in the performance of care and aids in the development of a relationship with the family that might lessen the likelihood of a lawsuit. Although this action would not prevent a suit by the incapacitated person for lack of informed consent, it would be difficult for the relative who gave consent to later file a suit for lack of consent on behalf of the patient.

The mere fact that a person is undergoing general anesthesia allows neither a relative to consent nor a surgeon to invoke implied consent to additional nonemergency surgical procedures on the patient. If a surgeon discovers a problem that necessitates subsequent surgery, or if the scheduled surgery cannot be performed without additional unplanned surgery, the unanticipated

procedure should be delayed until consent can be obtained. No matter how good the intention of the surgeon and how correct the diagnosis of the unanticipated problem, if the life or health of the patient is not at risk, the procedure should be delayed.

Persons may be designated by a living will or durable power of attorney as representatives of an incapacitated person before his or her incapacitation. A power of attorney is an instrument authorizing one person (not necessarily an attorney) to act as the legally authorized representative of another with regard to a designated matter. Traditionally, powers of attorney automatically became invalid upon the death or incapacity of the person delegating the power. A durable power of attorney, however, is made with the specific intent that it remains valid after the patient's incapacity. Durable powers of attorney were traditionally devices for controlling the use of property after incapacity; however, many states allow binding durable powers of attorney for healthcare decisions.

A person who lacks the capacity to make decisions about his or her own health care may have a guardian appointed by a court. A guardian is legally able to make decisions concerning the person's affairs. If the guardianship is extended to cover decisions concerning health care, the guardian may consent to the treatment of that person. The guardian may even consent to surgical treatment over the patient's objections, if the guardian clearly was given the power to make healthcare decisions by the court. It is up to the providers to ascertain the veracity of the representation that the guardianship extends to healthcare decisions. An inspection of the court order granting guardianship should be performed.

Breach of Duty

A breach of duty occurs when an anesthetist's practice does not meet the level required by law. The breach may be an error in the performance of an act during the administration of anesthesia care. Such an error is known as an *error of commission*. The error may also be an *error of omission*—that is, the failure to perform an act that should have been performed. This act is the standard of care discussed earlier.

The plaintiff in a malpractice suit has the burden of proving that a deviation from the standard of care occurred. Breach of duty and standard of care are usually proven simultaneously. Frequently, it is not whether the anesthetist acted in a particular manner that is in dispute, but rather whether the action deviated from the standard of care. For example, in one case, neither the plaintiff nor the defendant anesthetist disputed that 15 mg of tetracaine was administered intrathecally to a patient for a cesarean section. The only question was whether the administration of this amount constituted an overdose and deviated from the standard of care.

Causation

It is not enough to prove that a practitioner deviated from the standard of care. Even if the deviation from the standard of care and the presence of damages (see later in this chapter) are undisputed, the plaintiff must still prove that the damages were caused by the defendant anesthetist's negligent act. Two types of cause must be understood: *but for causation*, which is sometimes referred to as cause in fact; and *proximate cause*, which is also referred to as legal cause.

With but for causation, what is of importance is whether the damage would have occurred had the defendant not breached the duty—that is, "but for" the defendant's action the damage would not have occurred. This test eliminates negligent acts that did no harm to the plaintiff, even though some other damage occurred. Consider the example of an anesthetist who negligently failed to obtain a preoperative hemoglobin value or hematocrit for a patient whose hemoglobin and hematocrit results would have been within the normal range. The patient subsequently suffered laryngospasm and pulmonary edema. Although the failure to obtain the laboratory results was clearly negligent, it had no relationship to the subsequent problem. Had the negligence not occurred, the subsequent event would still have followed.

But for causation, however, is lacking in several respects. It is unfair to the plaintiff whose injury was caused by several factors. For example, consider the case of a patient who is negligently extubated by an anesthetist while still partially paralyzed because he or she had been administered nondepolarizing muscle relaxants; as a result, the patient subsequently decompensates. The postanesthesia recovery room nurse is unable to manage the patient and negligently fails to call soon enough for help. If only the but for causation test were used, the plaintiff could not prove malpractice because there is more than one cause. If the anesthetist had demonstrated greater skill in the recovery room, the mistake would not have caused harm.

Conversely, but for causation can be unfair to defendants because minor breaches of duty could lead them to be found liable for unrelated acts. For example, an anesthetist negligently pulls out a patient's intravenous catheter on the way to the operating room. Because of the negligence, the patient is in the operating room for 15 minutes longer than he or she would otherwise have been. During the additional quarter hour, a sudden earthquake destroys the part of the hospital housing the operating room but does not affect the postanesthesia recovery room. If only but for causation were used, the anesthetist (or the anesthetist's estate) could be held liable for the patient's earthquake injuries because, but for the anesthetist's negligence, the patient would have been safe in the recovery room.

Because of these problems, the *substantial factor test* is added to the but for causation test. With the new test, the defendant's negligence must be proved to be a substantial factor in the causation of the plaintiff's injuries. The substantial factor allows for a just result in both of the preceding cases. In the first case—that of the patient extubated negligently—both the anesthetist's and the postanesthesia nurse's actions can be found to have been substantial factors in the patient's death. In the second case, the negligent removal of the intravenous catheter was not a substantial factor in the patient's death during the earthquake, even though the but for causation requirement was satisfied.

Once the plaintiff in a case has proved that the defendant breached a duty and that the breach was the cause in fact of the plaintiff's damages, it must be proved that the defendant should be liable for the damages. This is referred to as *proximate* or *legal cause*. The issue of proximate cause is not a factual determination; rather, it is a question of policy. The law does not hold a person responsible for consequences that are considered remote and unforeseeable or for those that would not have caused damage without the presence of a remote, independent, intervening factor.

The differences between what constitutes sufficient foreseeability and what does not, what degree of remoteness precludes liability, and how independent a subsequent intervening cause must be in order for it to preclude liability fill many books. It is sufficient for the practitioner to remember that the issue of proximate cause does not arise until cause in fact is established.

Thus, in the examples described, neither the recovery room nurse's negligence nor the earthquake would be charged to the anesthetist if the anesthetist's negligence did not cause the patient to be in that situation in the first place. If the anesthetist was negligent in both situations, there would be no liability in the case of the earthquake injuries because it is not a foreseeable consequence

of pulling out an intravenous catheter. It is sufficiently remote from that action to remove the anesthetist from any legal responsibility. However, it is foreseeable that a patient who was negligently left in the recovery room with an inadequate airway might suffer from further negligence by subsequent caretakers.

Damages

The last element of a malpractice action involves damages. The plaintiff must prove that the negligent actions caused actual harm or damage, whether it be financial, physical, or emotional. Damages can be special, general, or punitive.

Special damages are those that are the actual result of an injury and which, in fact, follow it as a natural and proximate consequence. Special damages include past and future loss of income, medical expense, and funeral expenses. General damages are pain and suffering that are a direct result of the injury. The courts assign a cash value to special and general damages in an attempt to compensate a patient for the injuries. Some states have put a limit on the amount of pain and suffering compensation a plaintiff can receive in a medical malpractice suit.

Punitive damages are awarded by courts to punish defendants for outrageous conduct (e.g., violence, oppression, malice, fraud, or wanton and wicked conduct). The punitive damages awarded are in excess of the actual harm caused. States vary on what happens with the proceeds of punitive damages. In some states, part of the proceeds goes to the plaintiff and part goes to the state. Also, some states do not allow attorneys to collect their contingency fees from the punitive damage award. Punitive damage awards in medical malpractice suits are rare.

Burdens of Proof and Res Ipsa Loquitur. The plaintiff must prove all of the individual elements of negligence. Legal cases must be proved in accordance with several standards. The first is *beyond a reasonable doubt*. This is the standard that the state must meet if someone is to be found guilty in a criminal case. It is the most stringent standard of proof used. The second, intermediate level is *clear and convincing evidence*. The clear and convincing standard is occasionally used only in special civil cases, such as cases involving fraud, reformation of a contract, or civil commitments. The standard by which the plaintiff must prove the case in an action for malpractice (and most other civil actions) is the lowest of the three standards. This is the *more likely than not preponderance of evidence standard*. This standard requires that the evidence prove the case by more than 50%. Thus the plaintiff must prove that the damage was more likely than not caused by malpractice. It should be noted that a mere possibility that the defendant's action caused the injury is insufficient.

The importance of which party has the burden of proof should not be underestimated, because if the burden of proof is not met, then the party with the burden loses. If the plaintiff cannot find evidence of all the elements of malpractice, then the case fails. Because of the importance of the burden of proof and the potential harshness of the rule, there are exceptions to this requirement. One exception is the case of multiple negligent defendants. This situation arises if the plaintiff can prove that the damage was caused by the action of more than one negligent defendant—for example, the negligence of both an anesthetist and a recovery room nurse. The defendants then have the burden of proof and must determine the liability of each defendant.

A second instance of burden shifting is *res ipsa loquitur*. Res ipsa loquitur is a doctrine that allows the plaintiff to use circumstantial evidence to prove negligence. It also shifts the burden of proof of negligence from the plaintiff to the defendant. The reason for the doctrine of res ipsa loquitur (which is Latin for "the thing speaks for itself") is best explained with a description of the case from which it evolved. In 1863 a pedestrian in England was walking down the street in front of a warehouse. As he walked, a barrel of flour fell out of the warehouse window and struck him on the head causing him injuries. The plaintiff did not see what caused the barrel to fall; thus he could not prove negligence under the traditional rule that places the burden of proof of negligence on the plaintiff. The court determined that it was unlikely that the barrel would have fallen in the absence of negligence. In such a situation, the plaintiff should be allowed to recover damages unless the defendant can prove that no negligence occurred.

The res ipsa loquitur doctrine has evolved since that case. Now, three conditions must be satisfied before the plaintiff can use this doctrine. First, the event causing injury must be of a type that does not normally occur in the absence of negligence. Second, the damage must be caused by something which is in the complete control of the defendant. Third, the damage must not have been due in any part to negligence of the plaintiff. Some courts add a fourth condition: that the evidence of the event be in the hands of the defendant.

The first condition that implies more than a bad outcome must have occurred for the doctrine to be invoked. The plaintiff still has the burden of proving that the event does not normally occur in the absence of negligence. Events such as operation on the wrong patient or on the wrong extremity and burns from the use of an electrosurgical unit have usually been the events that allow the use of res ipsa loquitur. Showing that an event is unusual or unexpected is not sufficient. For example, an instance of malignant hyperpyrexia in a patient who gave no personal or family history of the condition is not enough to invoke re ipsa loquitur, because malignant hyperpyrexia is not an event that is normally the result of negligence. It should be noted that the patient can still attempt to prove that the anesthetist's response was negligent; however, the burden of proving negligence remains with the plaintiff.

After satisfying the requirement that the events do not normally happen in the absence of negligence, the plaintiff must prove that the instrumentality was within the exclusive control of the defendant. The term *control* refers to a right to control rather than an actual physical control. An unconscious anesthetized patient does not need to prove the identity of the person causing the injury. In a landmark case in this area, a patient undergoing an appendectomy sustained a traumatic injury to his shoulder. The court allowed the use of the doctrine of res ipsa loquitur against all of the operating room personnel even though it was obvious that not all could have been responsible. This is different from the case of multiple negligent defendants because, in this case, res ipsa loquitur was used against both negligent and non-negligent defendants' being liable for damages. The rule is a result of a policy determination that states that it is better to have operating room personnel be forced to prove their lack of negligence than to have anesthetized patients forced to prove negligence that occurred when they were unconscious, which is nearly impossible. The non-negligent defendant can attempt to prove that another defendant should be liable for the damages.

In order for res ipsa loquitur to be invoked, the injury must not have been the result of contributory negligence. A patient who failed to disclose a previous allergic reaction or case of malignant hyperpyrexia should not be allowed to use the doctrine to find the anesthetist negligent for administering the triggering agent. It has been suggested that it is unlikely that an anesthetist defendant would be successful in preventing the use of res ipsa loquitur on this basis.

The final requirement in some jurisdictions is that the evidence be more accessible to the defendant than to the plaintiff. This, however, is the least important of the elements of the doctrine. It has been suggested that it is not actually a requirement. Rather, it is another argument for justifying application of the doctrine.

Defenses to Negligence. When the plaintiff brings an action for medical malpractice, the defendant may defend in several ways. First, he or she offers evidence rebutting the plaintiff's evidence about the elements of the suit—namely, duty, standard of care, breach of duty, causation, and damages. Even if the plaintiff is to prove the elements of negligence, several defenses can prevent the placement of legal liability on the defendant. These include statutes of limitations, contributory or comparative negligence, and Good Samaritan statutes.

Virtually all civil lawsuits must be instituted within the specified time period after an incident or they will be barred in accordance with *statutes of limitations*. The policy behind the rule is that after a certain period it is difficult to gather the evidence to defend the lawsuit. For medical malpractice lawsuits, most states allow a period of 2 years; particular states may have statutes allowing more or less time.

Some states measure this period from the time of injury to the time that the lawsuit was instituted. Under these statutes, when the injury appears is not important; if the time period is 2 years and the plaintiff does not discover the injury until 3 years have passed, then the action is barred. Because the rule as applied is very restrictive, most states suspend the beginning of the statutory period until the time when the injury was discovered. Thus if malpractice caused an injury that was not discovered for 4 years, then the plaintiff would still have another 2 years to institute a lawsuit for medical malpractice. Some states use a hybrid statute that allows for a time period after the date of discovery but still places a cap on the total length of time from the date of injury. For example, a state may require that the suit be instituted within 2 years of the time of discovery but no later than 4 years from the date of injury.[19]

Two other situations may lengthen the statute of limitation. One is *fraud* or concealment of injury by the provider. If the reason for the plaintiff's failure to institute the action within the period specified is the provider's willful concealment of the event, the defense of statute of limitation may be disallowed because of the defendant's unclean hands.

Most states do not begin the time period if the patient is a minor. Thus infants or children who are injured as a result of medical malpractice have until the number of years allowed by the statute of limitations after their eighteenth birthday to initiate a lawsuit for recovery from any damages caused.

In the previous discussion of res ipsa loquitur, it is mentioned that the defense of res ipsa loquitur cannot be used if contributory negligence is involved. Traditionally, contributory negligence could be used as a complete bar to an action in negligence. If a plaintiff's negligence is responsible for 10% of the damages and the defendant's negligence for 90%, the plaintiff is prevented from collecting anything.

Because contributory negligence could produce very harsh results, most jurisdictions have adopted a doctrine of comparative negligence. In comparative negligence, the damage award is reduced by the amount of the plaintiff's negligence. Thus if the plaintiff was 10% at fault, the award would be reduced by 10%. Some states place a limit on the percentage of fault that the plaintiff is allowed before recovery is barred. If the plaintiff is either 50% or 51% at fault, depending on the state, recovery is barred. Thus if the plaintiff is 60% at fault and the defendant is 40% at fault, there is no recovery.

Another defense to malpractice is the use of a *Good Samaritan statute*. Most states protect providers who render emergency aid to sick or injured persons outside the hospital. If the provider cares for the patient in good faith, there is no liability unless gross, willful, or wanton negligence occurred. There is dispute among the states concerning whether emergency care rendered in the hospital is covered by the statute. In the absence of statutes limiting the liability of providers of emergency care in hospitals, the Good Samaritan acts normally do not apply to hospital care.

Vicarious Liability. Agency is the "relation in which one person acts for or represents another by the latter's authority."[20] The person who is represented is known as the principal and the person acting for the principal is the agent. Vicarious liability describes the legal theory that is used to hold the principal liable for the agent's action; it also is referred to by the Latin name *respondeat superior*. The principal need not have committed any negligent act to be liable for the agent. In the medical malpractice arena, the principal is held vicariously liable for the agent's negligent acts. It is important to understand that vicarious liability is a method of increasing the liability of principals and is not used for defending the agent. One who commits a negligent act is always responsible for the results. Thus a nurse anesthetist who is employed by a hospital or corporation that carries no malpractice insurance or has inadequate malpractice insurance can be held legally responsible for payment of damages. If both the employer and employee are named in the lawsuit, they are jointly liable for the amount of the judgment. Nurse anesthetists who depend on their employer's malpractice insurance should make themselves aware of the specifics of those policies and should be satisfied that the coverage limits are sufficient.

The most common and easiest relationship in which to find vicarious liability is the employer-employee relationship. An employer-employee relationship exists if the employee has been hired to perform services in the affairs of the employer and if he or she is controlled, or the subject of a right to be controlled by another. Normally, an employer is responsible for the negligent acts of its employees but not for their intentional acts. However, in certain cases employers may be held liable for intentional acts of employees if they knew or should have known of the employee's propensity toward those violent acts. That liability is not based on vicarious liability but on negligence in hiring or supervising the employee.

Generally, vicarious liability does not apply to the negligent acts of an independent contractor. An independent contractor is one who performs contracted work in his or her own way. The independent contractor is subject to the employer's control only in reference to the outcome, not to the methods used. However, the determination of whether someone is an independent contractor is a question of fact. It is determined not only by the characterization that the contractor and the employer give the relationship but also by all the facts and circumstances of the case. Hospitals can be held liable for the acts of independent contractors if the facts prove that the employer had control over the contractor. A nurse anesthetist may be an independent contractor for tax purposes but an employee under malpractice law if the facts prove that to be so.[21]

Even if a person is an independent contractor, liability remains with the employer for his or her own negligence. If a hospital or anesthesia group contracts with a nurse anesthetist but failed to have a proper credentialing procedure to assure that the nurse anesthetist was properly licensed and certified and if damage occurred due to the unlicensed person's practice as a result, the employer could be held liable for negligence.

The borrowed servant rule pertains to situations in which an employer "loans" an employee to another employer. An anesthesiologist who controls a nurse anesthetist is liable for the nurse anesthetist's negligence, even if the nurse anesthetist is an employee of the hospital. When applied to the operating room, however, vicarious liability has confused surgeons, anesthesiologists, nurse anesthetists, lawyers, and judges. Courts fashioned a species of vicarious liability referred to as the *Captain of the ship doctrine*.[22,23] The doctrine's premise is that the surgeon is ultimately responsible for all that occurs in an operating room. The doctrine has been used to hold surgeons responsible for the acts of nurse anesthetists and anesthesiologists.

A surgeon's liability for the case is related to his or her involvement in the decision-making process. If the surgeon makes independent decisions that affect the anesthesia, he or she is liable for those decisions. For example, an orthopedic surgeon insists that a patient scheduled for an emergency repair of a fractured ankle be given a general anesthetic. This is done despite the anesthetist's recommendation that a nerve block be performed because the patient has not been fasting long enough. If the anesthetist proceeds with the general anesthetic and aspiration pneumonitis results, then the anesthetist and the surgeon would share any liability that might result. This hypothetical case should not suggest that there is any liability; if loss of limb function is a possible outcome of the injury, it might be the correct decision to proceed and to use a general anesthetic because of the type of repair that must be accomplished. This only demonstrates that if the surgeon participates in the decision making for anesthesia, he or she may be liable for any injuries if that decision is proven negligent. The point to be taken is that the liability that might result would be there whether the anesthetist is an anesthesiologist or a nurse anesthetist. The doctrine of Captain of the ship has been eroding over the years and has been shown to be specifically so in several cases because it no longer represents an accurate portrayal of the relationships between professionals in the operating room, if it ever did.[24-26]

THE DOCTRINE

Organization of a Lawsuit

A lawsuit begins when the attorney for the complaining party, the plaintiff, files the complaint with the court. A copy of the complaint also is sent to the party being sued, the defendant, or to the party's attorney. Depending on the jurisdiction in which the lawsuit is filed, the complaint may be sent to the defendant by mail or be personally delivered. The defendant's attorney responds to the complaint by submitting an answer. A complaint, or any other type of legal summons, should never be ignored. Failure to answer a properly served complaint within the permitted time period can result in a default judgment against the defendant. That means that the plaintiff automatically wins the lawsuit and is granted the damages sought.

Discovery

After the complaint and answers are filed, the parties begin pretrial discovery. Pretrial discovery includes depositions and interrogatories. Depositions are question and answer sessions during which the lawyers for both sides question witnesses. Both parties and nonparties to the lawsuit can be deposed. The depositions are usually held in one of the attorneys' offices. This should not lead the person being deposed to believe that the depositions are informal or off the record. A court reporter is present and records everything that is said, except when the parties agree to go off the record. The deponents are under oath, and testimony given at deposition can be presented during the trial either as evidence of malpractice or to contradict the deponent's subsequent testimony in court. Interrogatories are written questions submitted to the parties to a lawsuit. They must be answered fully in writing and are also under oath. As with the complaint, a subpoena or notice of deposition should never be ignored. Failure to answer a subpoena or to appear after a notice of deposition can result in a fine of imprisonment for contempt of court. A party to a lawsuit also may be forced to pay the other party's expenses because of the failure to respond. Additionally, a party may have part of the pleadings struck from the case, may have the case dismissed, or in the most egregious instances, may have a default judgment entered.

The scope of discovery, which encompasses both depositions and interrogatories, is very broad. Questions may be asked that would be inadmissible in court because of irrelevance or other reasons. A nurse anesthetist involved in a lawsuit must attempt to put aside the emotional feelings associated with a lawsuit and answer questions in a truthful and professional manner. The attorney examining the witnesses can use the witnesses' anger to obtain additional information or to make the witness look bad before a jury, The nurse anesthetist's attorney should be relied on to make the appropriate objections. Again, at time of trial, the attorney can object to testimony taken in a deposition and subsequently prevent its presentation to the jury.

Trial

The trial is a difficult and stressful time for all involved in it. The nurse anesthetist should remain calm and professional and follow the advice of his or her attorney closely. The court's rules of decorum should be followed completely. The most important person in the courtroom is the judge, and any violation of the court's rules can be seen as a challenge to the judge's authority. Violations can not only anger the judge but also alienate the jury. The jury identifies more closely with the judge than with anyone else in the courtroom. Disagreements with testimony or with the court's rulings should be handled by the attorneys in the appropriate manner. Outbursts, groans, and other expressions of displeasure can only adversely affect the nurse anesthetist's case.

In addition to being truthful and professional, a nurse anesthetist who is a witness during discovery or trial should never hesitate to answer that he or she has no recollection of an event. Guessing about situations or giving answers that show uncertainty afford a skilled trial attorney opportunities to find inconsistencies. Few things appear worse to a jury than testimony that is inconsistent and appears to have been calculated to deceive the jury or to make the witness look better. A witness's credibility is his or her most valuable resource. Testimony during lawsuits is likely taken several years after the event, and it is understandable that a witness may not remember every precise detail.

SUMMARY

Fortunately, anesthesia is safer than ever, and the number of lawsuits involving anesthesia care has decreased in the past several decades. Improvements in monitoring technology, drugs, and diagnostic tests and the greater knowledge and skill of anesthesia providers all play a role. When an untoward incident does happen, however, the consequences can be devastating for the patient, their family, and the provider. Patient safety should be a primary factor on a daily basis in every decision made and technique performed. Processes that incorporate safety into the workflow of the modern anesthesia department must be constantly reassessed and updated. This chapter has explained some of the current legal concepts underlying anesthesia practice. It is important to remember

that ignorance of the law is no excuse for improper practice judgments. Know the laws and regulations that govern your practice. Know and follow your professional standards and guidelines. Document accurately and in a timely manner. Find a lawyer now that you can rely on; don't wait for a crisis to occur and then not have time to conduct a thorough search. It is better to have an attorney and not need one than to not have an attorney and need one. Seek attorney advice before a problem arises.

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CHAPTER 4

Nurse Anesthesia Research

Science of an Orderly, Purposeful, and Systematic Nature

◆ *Chuck Biddle*

The certified registered nurse anesthetist (CRNA) brings a wealth of knowledge to the clinical arena. Although this knowledge comes from a variety of disciplines, including physiology, pharmacology, physics, nursing, medicine, and psychology, it should be appreciated that research and critical thinking first and foremost make this knowledge possible. Evidence-based practice greatly enhances credibility within the clinical setting.

Research represents a rational approach to the making of practice choices among initially plausible alternatives and provides direction and a means for validating these choices. Whether selecting one intravenous opioid over another or choosing one particular pediatric induction technique instead of another, CRNAs rely on research to provide a solid foundation for clinical decision making, thereby avoiding fads and inferior alternatives.

The impact of research on the day-to-day activities of the CRNA has become an especially relevant topic. Before the mid-1970s the vast majority of nurses functioned without much consideration of research or publication of their ideas. In the late 1970s we experienced a period of punctuated evolution. Major driving forces behind this evolution included movement into a graduate educational framework, a more sophisticated appreciation of the scientific underpinnings of our specialty, recognition of the importance of evidence-based practice (EBP; see the discussion of this topic later in this chapter), national attention to issues of patient outcome and patient safety, and a growing self-awareness of nurse anesthetists not only as providers of excellent clinical care but also as active participants as scholars in the field.

Because CRNAs primarily function with a practice-oriented perspective, the recommendations of Brown et al[1] seem especially relevant. These scholars suggested that four characteristics of research are essential for the development of a scientific knowledge base for a discipline such as nurse anesthesia. First, research should be actively conducted by the members of the discipline. Second, research should be focused on clinical problems encountered by members of the discipline. Third, the approach to these problems must be grounded in a conceptual framework—that is, it must be scientifically based, emphasizing selection, arrangement, and clarification of existing relationships. And finally, the methods used in studying the problems must be fundamentally sound.

WAYS OF KNOWING

The term *research* can be broadly defined as the application of a systematic approach to the study of a problem or question. However, we do not know all the things we claim to know on the basis of systematic inquiry. For example, tradition and custom are important sources of human knowledge. Those who live in the United States are raised in a democratic society and are taught that democracy is the best and most advanced form of government. This is a powerful and efficient route for communication of knowledge because it excuses individuals from initiating an independent effort to come to grips with the concept of democracy. In the absence of evaluation for validity, however, such a route may lead to blind acceptance.

Another source of our knowledge is authority. We know something to be true because an authoritative person such as a parent, educator, clergyman, physician, or teacher tells us it is true. Yet, despite the fact that authorities are fallible, the knowledge they pass on often remains unchallenged. Should we not ask the basis for what we are being told?

Personal experience (the trial-and-error method) represents a powerful source of knowledge. We make observations (e.g., that placing a hand on a hot stove causes a burn) and on their basis make predictions (e.g., that a stove may be hot) and future behavioral decisions (e.g., to avoid touching a stove). However, a risk remains: Not only are certain events perceived differently by different people, but one person's experience may be too narrow to serve as the basis for the development of a reasonable and unbiased understanding of a given phenomenon. Although this mechanism is a practical way of knowing, it is highly fallible and represents a coarse and inefficient way to gain knowledge.

Logical reasoning is yet another way of knowing. The reasoning method has two components: inductive reasoning and deductive reasoning. Inductive reasoning results in generalizations that are derived from specific observations. Consider the following line of reasoning using a character in many action and adventure movies, James Bond, for example. We observe that James Bond is mortal; we observe that a number of other people are mortal as well; on this basis, we conclude that all people are mortal. Deductive reasoning is the development of specific predictions from generalities. In this case, we see the following line of reasoning: we know that all men are mortal; we know that James Bond is a man; therefore we conclude that James Bond is mortal. Both methods are useful, but the former offers no mechanism for evaluation or self-correction, and the latter is not in itself a source of new information.

Perhaps the most advanced way of knowing is reflected in the scientific method. Although it too is fallible, the scientific method is more reliable and valid than other methods. It provides for self-evaluation with a system of checks and balances that minimizes bias and faulty reasoning. In essence, it is a systematic approach to solving problems and enhancing our understanding of phenomena. It has, at its foundation, the gathering and interpretation of information without prejudice.

THE NATURE OF RESEARCH

Research is by definition a dynamic phenomenon. Whether it is directed purely at the acquisition of knowledge for knowledge's

BOX **4-1**

Research Scenario: Internal Versus External Validity

Internal Validity

The extent to which results can be accurately interpreted and the degree to which the independent variable (that which is manipulated) is responsible for a change in the dependent variable (that which is measured).

For example, the patient's blood pressure is measured. A combination of propofol, midazolam, isoflurane, and a new muscle relaxant is used for induction of anesthesia. A postinduction blood pressure is recorded, and the researcher concludes that the new muscle relaxant lowers blood pressure.

Questions

Has the researcher isolated the effect of the muscle relaxant from those of the other agents?

Are there plausible or competing alternative explanations?

Analysis

Internal validity is low because the results cannot be interpreted with any degree of certainty.

External Validity

The extent to which the results can be generalized; this issue relates to the question "To whom can the results be applied?"

For example, 35 obese men who are nonsurgical volunteers are anesthetized with a standard dose of a new induction drug. The clinical half-life of the drug is determined with plasma drug sampling and brain wave activity monitoring. The researcher concludes that future patients receiving the standard dose of the new drug will experience a clinical half-life of 11 minutes.

Questions

Is it reasonable to assume that obese patients might respond differently than their nonobese counterparts?

Might women respond differently than men?

Could surgical manipulation or other drug therapy have an impact on the pharmacokinetics of the new drug?

Analysis

External validity is low because the results cannot be generalized to any other individuals except those similar to the subjects in the study.

sake (basic research) or at the specific solution of problems (applied research), it is a process that can be conceptualized in terms of at least four characteristics.

First, research can assume many different forms. Second, research must be valid, both internally and externally (Box 4-1). Internal validity is necessary but not sufficient for ensuring external validity. Third, research must be reliable. *Reliability* refers to the extent to which data collection, analysis, and interpretation are consistent and to which the research can be replicated. Fourth, research must be systematic. The elements of a systematic approach include the identification of the problem or problems, the gathering and critical review of relevant information, the collection of data in a highly orchestrated manner, an analysis of the data appropriate to the problem or problems faced, and the development of conclusions within the study's framework.

Science is not a routine, cut-and-dried process. Rather, scientific knowledge emerges from an enterprise that is intensely human; as a consequence, it is subject to the full spectrum of human strengths and limitations. The scientific discovery and understanding that attend participation in research and its results can be professionally exhilarating and satisfying.

THE EIGHT CRITICAL STAGES IN THE RESEARCH PROCESS

Research accords several personal freedoms to those who engage in it: the freedom to pursue those opportunities in which one is interested, the freedom to exchange ideas with other interested colleagues, and the freedom to be a *deconstructionist*—that is, one who challenges existing knowledge. Yet, despite these freedoms, research must be logical, must progress in an orderly manner, and ultimately must be grounded within the framework of the scientific method. If research is a way of searching for truths, uncovering solutions to problems, and generating principles that result in theories, we must come to understand the process of research.

The research process can be described in many different ways. For purposes of simplicity, this process is defined as consisting of the following eight distinct stages:

1. Identification of the problem
2. Review of the relevant knowledge and literature
3. Formulation of the hypothesis or research question
4. Development of an approach for testing the hypothesis
5. Execution of the research plan
6. Analysis and interpretation of the data
7. Dissemination of the findings to interested colleagues
8. Evaluation of the research report

Stage 1: Identification of the Problem

The selection and formulation of the problem constitute an essential first step in the research process. The researcher decides the general subject of the investigation, guided principally by personal experience and by inductions and deductions based on existing sources of knowledge. The researcher makes the general subject manageable by narrowing of the focus of the problem. The following criteria must be met at this phase of the research process:

- The problem area should be of sufficient importance to merit study.
- The problem must be one that is practical to investigate.
- The researcher should be knowledgeable and experienced in the area from which the problem has emerged.
- The researcher should be sincerely motivated and interested in studying the problem.

We constantly encounter problems and situations that can be studied. At clinical anesthesia conferences, one might hear remarks such as the following:

"It seems to me that a tiny dose of thiopental given just before propofol alleviates virtually any pain on injection."

"Do you think there is less nausea and vomiting in outpatients who are deliberately overhydrated?"

"I find that the use of the waveform generated by my pulse oximeter gives me valuable information about depth of anesthesia."

"I believe that the inspiratory pause mechanism on the Ohmeda 7810 ventilator significantly improves arterial oxygen tension in my patients with chronic obstructive pulmonary disease."

"I am convinced that sleepiness is a major cause of anesthesia accidents."

A study could emerge from each of these situations, built on ideas, hunches, or curiosity. A problem that lends itself to research often materializes from personal observations and in the sharing of ideas and experiences among those who are familiar with the phenomenon in question.

Once identified, the problem should be stated in terms that clarify the subject and restrict the scope of the study. Defining the terms involved in the problem statement also is critical, as demonstrated in Box 4-2.

BOX **4-2**

Research Scenario: Stating the Problem

Poor
I am unsure of the effectiveness of etomidate in patients.

Better
I am unsure at what dose etomidate induces unconsciousness in patients undergoing hysterectomy and what impact it has on heart rate, blood pressure, and vascular resistance.

Comments
- The problem should be focused.
- The terms should be clarified.
- The relationships should be understood.
- The problem should not be so narrow as to be trivial.

The wording of the problem statement sets the stage for the type of study design used. Each step in the research process subsequently influences later steps, and this should be kept in mind at all times. A mistake made early inevitably creates difficulties at some later stage in the process. The novice researcher may be surprised to find that this first stage in the research process often consumes a large portion of the total time invested in the research effort. Yet the time is well spent, because research should not commence until a problem has been identified and formulated in a thoughtful and useful manner.

Common Mistakes

At this stage of the process, pitfalls can include an overly ready acceptance of the first research idea that comes to mind and selection of a problem that is too broad or vague to allow effective study.

Stage 2: Review of the Relevant Knowledge and Literature

Once the problem has been identified, information is needed for putting the problem into proper context so that the research can proceed effectively. A well-conducted literature review provides the researcher with the following:

- An understanding of what has already been accomplished in the area of interest
- A theoretic framework within which the problem can be optimally stated, understood, and studied
- An appreciation for gaps in current understanding of the phenomenon
- Information for avoiding unanticipated difficulties
- Examples of potentially useful or poorly constructed research designs and procedures
- A background for interpreting the results of the proposed investigation

The knowledge that influences the problem originates from three general sources: personal files and experience, personal contacts with experts, and the library and Internet. Both manual indexes and computerized databases should provide the researcher with immediate and full access to the world's published literature. Additional literature searches may be required at different times throughout the research process.

Common Mistakes

At this stage in the research process, mistakes include hasty review of the literature, overly heavy reliance on secondary (book) rather than primary (journal) sources, lack of critical examination of the methods by which conclusions were reached, and incorrect copying of references, for example, mistakes in noting the volume number or misspelling an author's name, which makes it more difficult to locate them again with ease.

Stage 3: Formulation of the Hypothesis or Research Question

In its most elemental form, a hypothesis is either a proposition of the solution to a problem or a stated relationship among variables. It establishes and defines the independent variable (the variable that is to be manipulated or is presumed to influence the outcome) and the dependent variable (the outcome that is dependent on the independent variable). The hypothesis is declarative in nature and assumes one of the following three forms:

1. A *directional hypothesis:* Patients premedicated with midazolam have less anxiety on arrival in the operating room than do those who were not premedicated.
2. A *nondirectional hypothesis:* Patients premedicated with midazolam experience a difference in anxiety on arrival in the operating room when compared with those who were not premedicated.
3. A *null hypothesis:* Patients premedicated with midazolam experience no difference in anxiety on arrival in the operating room compared with those who were not premedicated.

Research questions are generally reserved for investigations that are descriptive or exploratory in nature or for when the relationships among the variables are unclear. A research question might be more appropriate than a hypothesis in a study that proposes to determine the beliefs of anesthesia providers who interact with patients under specific circumstances. For example, consider the following research question: What are the attitudes of CRNAs in the northeastern United States who care for patients with acquired immunodeficiency syndrome (AIDS)?

Common Mistakes

At this point in the process, mistakes include use of a vague or unmanageable hypothesis and development of a research question that cannot be answered reasonably.

Stage 4: Development of an Approach for Testing the Hypothesis

After the research idea has taken shape in the form of a formal hypothesis or research question, a plan of attack is developed. The research proposal represents the stage at which the ideas of the project crystallize into a substantive form. The proposal includes the following:

- A problem statement and clarification of the significance of the proposed study
- The hypothesis or research question
- A sufficient review of the literature for justification of the study
- A description of the research design
- A careful explanation of the sample to be studied
- The type of statistical analysis to be applied

A research proposal is a useful and efficient way for the researcher to determine the completeness of the plan and is usually required if the researcher is to obtain departmental or institutional approval or is applying for financial support.

Research Methods

The research method is the way the truth of a phenomenon is coaxed from the world in which it resides and is freed of the biases of the human condition. A variety of research methods are at our disposal,

and researchers are not inflexibly wedded to any particular approach. Researchers do not follow a single scientific method but rather use a body of methods that are amenable to their fields of study.

Some of the methods available are highly recognizable, permanent components of the researcher's armamentarium, whereas others have evolved not only with respect to time but also in response to the specific needs of a particular problem or discipline. The research method can be influenced by the way a researcher views a problem. For example, a researcher can test a hypothesis, search for a correlation, ask "why" or "how" questions, or probe a phenomenon on the basis of "what would happen if" suppositions.

The researcher can view the method on the basis of the fundamental task that it will accomplish. For example, two broad categories into which research efforts can be divided are basic research and applied research. Basic research adds to the existing body of knowledge and may not have immediate, practical use. Applied research is oriented toward solving an immediate, specific, and practical problem.

The research method can be characterized in terms of its temporal relationship to the problem. A retrospective study is the process of surveying the past; the thing in which we are interested has already occurred, and we are simply looking to see what did occur. In contrast, a prospective study looks forward to see what will happen in a given situation; here, the collection of data proceeds forward in time.

It is important to understand several terms fundamental to the research process. As mentioned previously, the dependent variable is the object of the study, or the variable that is being measured. The independent variable is the one that affects the dependent variable and is presumed to cause or influence it. Another way of looking at this relationship is that variables that are a consequence of or are dependent on antecedent variables are considered dependent variables.

Another set of variables consists of control variables, also known as *organismic*, *background*, or *attribute* variables. Control variables are not actively manipulated by the researcher, but because they might influence the relationships under study, they must be controlled, held constant, or randomized so that their effects are neutralized, canceled out, or at least considered by the researcher (Box 4-3).

The term *blinding* refers to the process of controlling for obvious and occult bias arising from subjects' or researchers' reactions to what is going on. In a single-blind design, the patients are unaware of which treatment or manipulation is actually being given to the subjects. In the double-blind design, neither the researcher nor the subject is aware of which treatment or manipulation the subject is receiving. Whereas randomization attempts to equalize the groups at the start of the study, blinding equalizes the groups by controlling for psychological biases that might arise apart from any effect of the treatment. Many factors influence the decision to use a single-blind or a double-blind design. For example, in some situations, it may not be feasible to disguise a particular treatment or intervention.

Operationalization is the process of making the characteristics inherent in a given variable, condition, or process familiar or clear to others. If researchers do not operationalize the terms, phrases, and manipulations in the study, the net effect could be an ambiguous study. For example, in a study examining the effects of epidural anesthesia in critically ill patients, it would be essential to operationalize the terms *effects* and *critically ill patients*. Similarly, in a study comparing the quality of inhalation induction with isoflurane and sevoflurane in pediatric patients, it is essential that the researcher operationalize the terms *inhalation induction* and *quality*. Operationalization of terms clearly designates performable and observable acts or procedures in such a way that they can be replicated immutably.

BOX 4-3

Research Scenario: Understanding the Types of Variables

Study Group

A new intravenous drug that may be associated with fewer cardiovascular effects than thiopental during induction in pediatric patients is being studied. Fifty children ages 3 to 6 years undergoing intravenous inductions for hernia repair or eye muscle surgery are randomized to either the thiopental group or the new drug group. Blood pressure, heart rate, and rhythm are measured by a dedicated observer who is unaware of which drug the patients are receiving.

Analysis

The dependent variables are blood pressure, heart rate, and heart rhythm. The independent variable is the drug the child receives—either the thiopental or the new drug. A number of control variables are present, including sex, fluid status, time of day, underlying medical history, and concurrent drug therapy. With randomization, such control variables should be equated or neutralized for the two groups, but even randomization is not an absolute guarantee.

Classifying Research on the Basis of Methodology

Although different authors use a variety of classification schemes, the following example provides a simple way for the researcher to select and classify a design. This scheme attends to the study's purpose and scope and to the nature of the problem at hand. Table 4-1 offers a simplified approach to classifying research design.

Quasi-experimental research differs from experimental research in that it is missing one or more of the key elements required for the experimental design. Either a control group or a randomization procedure may be absent from the design. For example, at an institution, outpatients may routinely receive ondansetron from a particular practitioner, whereas they routinely do not receive the drug from another practitioner. A prospective trial in which both practitioners use a standard anesthetic technique could be initiated. For example, isoflurane, an opioid, and cisatracurium could be administered; this would allow the two practitioners to use or not use ondansetron as they normally would. Outcome, measured in terms of the incidence of nausea and vomiting in the first 6 postoperative hours, is quantified, and the groups are compared. Although randomization is not achieved, a study that may not otherwise have been possible because of the inflexibility of the clinicians involved is successfully accomplished. Quasi-experiments, by yielding to one or more of the rigid criteria of the experimental design, offer an attractive alternative in certain circumstances.

Qualitative Research: An Alternative Paradigm

Up to this point, the traditional approach to a problem has been characterized by deductive reasoning, objectivity, manipulation, and control. An alternative approach involves a group of methods characterized by inductive reasoning, subjectivity, exploration, and process orientation. These methods fall under the rubric of qualitative research techniques.

Qualitative techniques include philosophic inquiry, historiography, phenomenology, grounded theory, and ethnography. Generally speaking, *qualitative research* refers to systematic modes of

TABLE 4-1 Classifying Research by Method

Type	Qualities and Purpose	Example
Experimental	At least one variable manipulated Random assignment to groups Dependent variable is measured Good for determining cause and effect Prospective in nature	Is there more or less pain on injection of one or the other drug? What did the manipulation do?
Ex post facto	Independent variable has already occurred Examines relationships by observing a consequence and looking back for associations Retrospective in nature (Latin for "from a thing done after")	Looking back over 5 years, did a relationship exist between the rate of myocardial infarction and the inhaled anesthetic that was administered?
Descriptive	Describes something as it occurred Incidence, relationships, and distributions are studied Deals more with "what-is?" than "why-is-it-so?" questions	What are the attitudes of CRNAs regarding the care of patients who have AIDS?
Historical	Describes "what was" rather than what effect variables had on others Events are described as accurately as possible through a process of critical inquiry	A test of the hypothesis is that Sister M. Bernard was the first nurse anesthetist
Qualitative Phenomenology Grounded theory Ethnography	Experiences lived by people Perception is viewed as our access to that experience Discovers and conceptualizes the essence of complex processes	What is the nature of the relationship of CRNAs and surgeons in private and in academic settings?

inquiry directed principally at observing, describing, analyzing, interpreting, and understanding the patterns, themes, qualities, and meanings of specific contextual phenomena. Qualitative research seeks to gain insight by discovering the meanings associated with a given phenomenon and exploring the depth, richness, and complexity inherent in it.

For example, exploring how male and female CRNAs differ in the manner in which they deal with parental and child separation when a child is readied for induction of anesthesia might best be achieved through the use of a qualitative design. The actual experiences might be observed or videotaped. Those involved—anesthetists, parents, and children—might be interviewed immediately and at some time after the procedure. This study would be artificially constrained and disjointed if it were conducted in any setting other than the original one or if too many controls were brought to bear on the experiment.

The qualitative paradigm seems especially appropriate when the researcher does not want to artificially distance a study from its contextual richness or when there is not enough information available on a particular subject for the adequate development of sound and testable hypotheses. The treatise on qualitative approaches by Marshall and Rossman[2] is recommended to interested readers.

Sampling

Under most circumstances, studying everyone who might be affected by a particular study is impractical, if not impossible. For example, if we want to know how effective intravenous nitroglycerin is in minimizing the rise in blood pressure associated with laryngoscopy in hypertensive patients, we cannot realistically study all hypertensive patients who undergo laryngoscopy. Rather, we would hope to find a smaller group of subjects who are representative of the relevant population at large. By accessing certain information in the sample, we can credibly make inferences or generalizations regarding the population at large.

Similarly, if we want to know how often anesthesia machines in small community hospitals receive preventive maintenance, we cannot visit all the community hospitals in the nation. Instead, we might randomly select a number of hospitals in a number of different states, visit those locations, and inspect the maintenance records. By studying this representative sample, we can make some reasonable and safe generalizations regarding the phenomenon of preventive maintenance at large.

Consider the anecdote about the four blind people who encountered an elephant during one of their daily walks. Each person felt a different part of the elephant. When asked to describe what they had encountered, the first person replied, "a tree trunk" (the elephant's leg). The second reported feeling "a large snake" (the elephant's trunk). The third reported that it was "most definitely a wall" (the elephant's torso). The last person reported that it was "a large, frayed rope" (the elephant's tail). This analogy illustrates that a few discrete sampling points may not be adequate for describing a complex phenomenon. Not only is a random sample best, it also should be large enough and sample a sufficient number of points in the population that a truly representative perspective is gained.

Different sampling techniques can be used, depending on the research design used. In a true random sample (also known as *probability sampling*), all members of the population at large have a similar chance of being included in the study. This is rarely the case in clinical research, in which we are confined to dealing with those individuals who present themselves. In this situation, the sample is called a *convenience sample*. When a convenience sample is used in an experimental study, it is important to ensure that the subjects selected for the study are at least randomized when assigned to treatments or groups. In the ideal situation, the researcher aims for both random selection (from the population at large) and random assignment (to the different groups in the study).

For example, in a study designed to quantify the rate of arterial desaturation in pediatric patients who are transported to the postanesthesia care unit with and without supplemental oxygen, the researcher is limited to those patients who are undergoing surgery. It is difficult to obtain a sample from the pediatric population at large and subject them to anesthesia and surgery. Rather, a convenience sample of patients who are having an operation is used. However, the researcher should randomly assign the study participants to one of the two treatment groups—those who receive supplemental oxygen or those who do not receive supplemental oxygen.

Obtaining a random sample, especially in clinical research, is often a complicated process. Most important is the realization that the concept of randomness is essential to minimizing human biases associated with both selection and assignment.

Instrumentation and Measurement

Two important concepts essential to measurement are validity and reliability. Instrument validity is the degree to which an instrument, such as a blood pressure cuff or a personality inventory, measures what one believes it is measuring. *Instrument reliability* refers to the degree of consistency with which an instrument measures whatever it is measuring—that is, whether the same result is obtained on repeated trials.

Validity and reliability are often easily established for measures of certain physiologic phenomena but may be troublesome in behavioral or psychological evaluations. Imagine trying to determine reliability and validity for a thermometer. Contrast this to trying to establish validity and reliability for a psychological tool that professes to measure a CRNA's attitude toward euthanasia; obviously, the latter is a much more difficult undertaking. Although a measure must be reliable to be valid, it can be reliable without being valid. For example, a skin temperature probe might reliably (consistently) measure temperature even in a variety of extreme settings, although it would not be viewed as a valid indicator of core temperature. Both reliability and validity are discussed in degrees rather than in "all-or-nothing" terms.

Many published instruments have reliability and validity testing reported. When choosing an instrument for a study, it is critical to consider whether the instrument's reliability and validity have been established. For example, if an instrument measures evoked responses in the esophagus as an indicator of depth of anesthesia, it must be determined whether the reliability and validity of the instrument have been established under the conditions of the anesthetic protocol being used in the proposed study. Coefficients of reliability and validity are presented on a scale of 0 to 1, with 1 being perfect.

Occasionally the researcher may encounter no reasonable measures to use for a study. For example, instruments for measuring such phenomena as arterial oxygen tension, end-tidal anesthetic concentration, and opioid metabolic by-products are well established. A researcher may need to develop a totally new instrument (questionnaire) to determine perceptions regarding the propriety of a given manufacturer's high-pressure promotional campaigns for newly released pharmaceutical products. In developing such a tool, it is helpful to have an expert in the discipline look over the instrument and provide feedback to ensure that the instrument is appropriate.

Researchers have a variety of instruments for measuring phenomena. These include the following:

- Written tests
- Rating scales
- Questionnaires
- Chemical tests
- Physical tests
- Electrical tests
- Visual observation
- Auditory observation
- Psychological inventories

Levels of Measurement. In designing a study, the researcher must decide how to measure a phenomenon such as anxiety level, blood pressure, attitude toward health care, or rate of complications. There are four levels or degrees of measurement: nominal, ordinal, interval, and ratio. The type of data measured determines the kind of statistical analysis that can be done. Table 4-2 characterizes the four levels of measurement.

TABLE 4-2 Characteristics of the Four Categories of Measurement

Category	Characteristics	Examples
Nominal	Identifies	Male or female Diagnosis
Ordinal	Identifies	American Society of Anesthesiologists (ASA) class
	Orders	Order of race finish
Interval	Identifies	Intelligence
	Orders	Calendar years
	Equal intervals	Degrees Fahrenheit or Celsius
Ratio	Identifies	Blood pressure
	Orders	Reaction time
	Equal intervals	Weight
	Has a true zero	Distance Degrees Kelvin

Nominal level measurement allows categorization of data, but the only numeric data obtained are frequencies. For example, in a study assessing the educational level of CRNAs in the profession, only the frequency of each category (certificates, bachelor's degrees, master's degrees, doctorates) can be reported. No statement can be made concerning the amount of the characteristic.

Ordinal level measurement allows for data to be ordered or ranked. In a sense, numbers are used to indicate the magnitude of the observations. For instance, the American Society of Anesthesiologists' Physical Status system provides for a relative ranking system for patients on the basis of their pathophysiologic status.

Interval level measurement uses numeric data that are ordered and spaced equally, such as temperature on the Fahrenheit or centigrade scale, calendar years, or intelligence quotients derived from an intelligence performance test. Here, the distance between adjacent scores is highly meaningful.

Ratio level measurement uses numeric data that can be ordered and equally spaced. It is based on a scale with an absolute zero point, such as temperature on the Kelvin scale, reaction time, height, and blood pressure. Both interval and ratio level measures can be referred to as *continuous* in nature.

Measurement can also be defined in terms of four broad categories: cognitive, affective, psychomotor, and physiologic. Each can manifest as one of the levels noted earlier. *Cognitive measurement* addresses the test subjects' knowledge or achievement. For example, what actions should be taken in the face of unexplained bradycardia? *Affective measurements* determine interests, values, and attitudes, thereby providing behavioral insights. For example, how do CRNAs in different locations feel about anesthetizing patients with AIDS? *Psychomotor measurements* test the subjects' ability or skill in performing specific tasks, such as evaluating performance with a new laryngoscopic design. *Physiologic measurements* look at the biologic functioning of the organism—for example, heart rate differences in men and women at basal conditions.

Although researchers sometimes develop unique instruments, which must be tested for reliability and validity, many published and acceptable instruments can be located in any number of sources.[3,4]

The Pilot Study

A pilot study is the implementation of a study on a small scale. It includes only a few subjects, who generally will not be included in the formal study. Its purpose is to troubleshoot the methodology for any anticipated design problems. The pilot study allows the researcher the opportunity to perform a dry run, ultimately facilitating the progression of the study.

Common Mistakes

At this point in the process, mistakes include failure to adequately operationalize definitions, failure to define the population or sample adequately, unrealistic expectations for subject recruitment and participation, underestimation of the difficulty of design execution, failure to establish instrument reliability and validity, and failure to appreciate the ethical dimensions of the investigation.

Stage 5: Execution of the Research Plan

Up to this point, the research process has involved the acquisition of knowledge regarding the subject, planning the project, and critical thinking about what is to occur. The next stage of the process involves actual data collection and the organization of the data into a format that allows data analysis.

The data collection must precisely follow the procedure the researcher specified previously. The real payoff in research comes with the drawing of useful and bona fide conclusions once the data have been collected and precisely analyzed within the framework of the research design. The goal of the previous step—namely, maximization of both internal and external validity—would not be achieved if the researcher were to deviate from the plan.

Maintaining careful records of what was done and what results were recorded is essential. The labeling and sorting of data into the respective categories or chronologies should be extremely precise. No data should be discarded until the researcher knows that they are absolutely unnecessary. Many researchers "stockpile" raw data and their notes, because additional uses for the information may not manifest for months or even years after the initial project's completion and publication.

Common Mistakes

The mistakes associated with this stage include drifting from the stated methodology for convenience or administrative purposes, placing excessive demands on subjects, allowing personal bias to creep into the research plan, using observers or research assistants who are improperly trained, failing to obtain a sufficient sample size, and improperly using measurement instruments.

Stage 6: Analysis and Interpretation of the Data

A few words on statistics are in order. Not only is proper analysis essential to the design, analysis, and interpretation of the investigation, it also is necessary for understanding and evaluating research studies conducted by other investigators. Analysis has three general phases: the initial mechanical manipulation of the data, the analysis itself, and the thoughtful formulation of conclusions on the basis of the analysis.

For the purposes of this discussion, the following two questions are posed:

1. What is the rationale for the use of statistical analysis in research?
2. What are the more common statistical procedures used, and under what circumstances are they appropriate?

Descriptive Statistical Techniques

Once the data on the phenomenon under study have been collected, they often are categorized and described. For example, if the goal of a study is the determination of the incidence of headache and the change noted in blood pressure in 50 patients undergoing spinal anesthesia, the researcher would describe the demographics of the sample of patients in terms of sex, height, weight, or any other relevant variable.

The group or set of all the observations of the variable is called a *distribution*. The distribution yields information about the overall dispersion of the phenomenon within the sample, as well as the exact location of a given measure relative to the group as a whole. In the case of an interval- or ratio-level measurement, such as blood pressure, the distribution of values is probably Gaussian or bell shaped in nature (i.e., some pressures are low, most are intermediate, and some are high). By studying the distribution, the researcher can compare a particular measured value with all the values obtained for the phenomenon.

TABLE 4-3 Frequency Distribution for Initial Systolic Blood Pressure

Interval (mmHg)*	Frequency†
0-60	1
60-90	8
91-120	15
121-150	15
151-180	8
>180	3

*Interval equals the range or band into which a given measure is placed.
†Frequency equals the number of observations falling into that interval.

Alternatively, the researcher might use a technique that clusters data into rational blocks or intervals. For example, in the spinal anesthesia study, instead of listing all 50 initial blood pressures individually, the researcher could tabulate them according to frequency relative to a given interval. In this case, each measured blood pressure falls within a range, and the frequency of presentation in the sample is tabulated as shown in Table 4-3. Instead of using the tabular form, the researcher could arrange the same data in graphic form, indicating the frequency of the phenomenon on the vertical (*y*) axis and the blood pressure values on the horizontal (*x*) axis. In histograms and bar graphs, the width of each bar corresponds to the limits of the interval, and the height of the bar corresponds to the frequency or percent of the cases occurring in a specific interval. A frequency polygram also is a commonly used tool for displaying data. Points are plotted directly over the midpoint of each of the intervals. The data given in Table 4-3 are presented in Figure 4-1 as a frequency polygram.

Other descriptive statistics include the *mean* (the arithmetic average of the sample); the *median* (the point below which one half of the measurements lie); and the *mode* (the value occurring most frequently). The range shows the dispersion data from the highest to the lowest value. *Variance* and *standard deviation* (SD) must be computed and are based on the concept of deviation (the difference between an observed score and the mean value in the distribution). Variance is the square of the sum of all of the deviations divided by the number of scores, and the SD is the positive square root of the variance. Because of variation, investigators describe the data not only in terms of the typical or average value but also the amount of variation that is present. With respect to quantitative data such as blood pressure, number of attempts at intubation, or amount of blood loss, this task is generally a matter of characterizing the distribution of the attribute in terms of its central tendency and dispersion. This is achieved by providing the mean and the SD. The SD is a tool for describing the variation of individual observations around the mean. *Standard error of the mean* (SEM) is linked to the SD by the following simple mathematical formula:

$$SEM = SD/\sqrt{n}$$

where $\sqrt{n}$ is the square root of the number of observations in the sample.

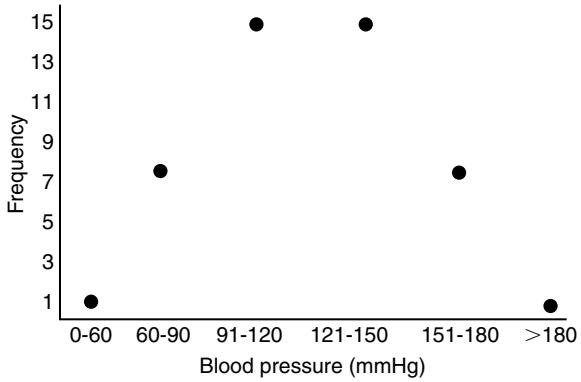

FIGURE **4-1** The frequency polygram. Note the bell-shaped configuration the plotted data have assumed; this typically is the "normal" distribution of biologic data (e.g., blood pressure, weight, heart rate, minimum alveolar concentration, intelligence).

The SEM describes the variation of the sample mean (that for the actual data collected) around the true, but unknown, population mean (that for all possible observations). The difficulty with using the SEM is that as the number of subjects or observations increases, the standard error of the mean decreases. In theoretic terms, as *n* approaches infinity, SEM approaches 0. Researchers are urged to consult with a biostatistician and to develop a rationale before deciding to use the SEM or SD.

In general, the higher the level of measurement used (i.e., ratio > interval > ordinal > nominal), the greater the flexibility in selecting a descriptive statistic. Using the data from the spinal anesthesia study noted earlier, it would be appropriate to compute the SD for initial systolic blood pressure (ratio-level data). However, such a computation would be meaningless for nominal-level information, such as whether subjects are male or female.

Correlational Statistical Techniques

The correlation coefficient is generally used for describing the extent to which two variables are related to each other or for quantifying the degree of that relationship. For example, it would be useful if one were studying the extent to which the level of carbon monoxide in the blood is related to cigarette smoking. Calculated correlations vary from +1.0 (a perfect direct correlation) to −1.0 (a perfect inverse correlation). A correlation of 0 indicates no relationship. Researchers often display the correlations visually in the form of a scattergram, which shows the shape of a relationship between two variables. There are many types of correlational techniques (Table 4-4).

In the hypothetic study of carbon monoxide level and cigarette smoking, a researcher might decide to use the product-moment correlation technique. The numeric value for carbon monoxide in the blood has a true 0 (ratio-level data) and a numeric value (ratio-level data) for daily cigarette smoking. The correlation between these variables would probably be positive and very high (e.g., 0.8 or even higher), which suggests that heavy use of cigarettes is associated with a high carbon monoxide level in the blood.

Conversely, assume a study examines the relationship between gender (a nominal-level variable) and anesthetic minimum alveolar concentration (a ratio-level variable). In this example, the researcher using the point biserial correlation technique would expect to see a very low correlation, because gender has been found to not be associated in any meaningful way with anesthetic requirements.

TABLE 4-4 Correlation Techniques Appropriate to Data Type

Correlation	Variable No. 1	Variable No. 2
Product-moment	Interval or ratio	Interval or ratio
Spearman's rank	Ordinal	Ordinal
Point biserial	Nominal or ordinal	Interval or ratio
Phi	Dichotomy	Dichotomy
Contingency	Nominal	Nominal

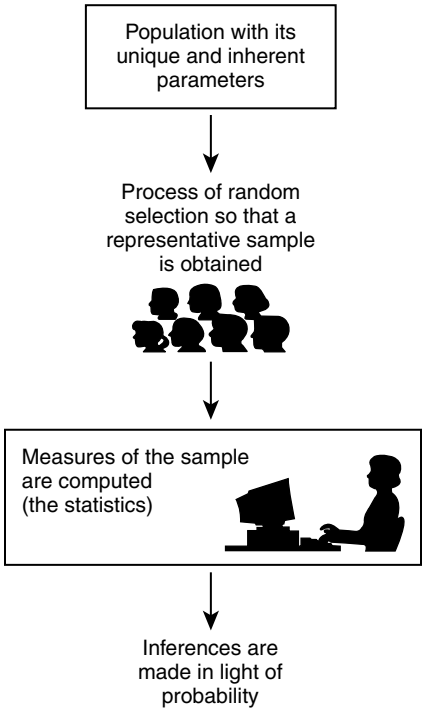

FIGURE **4-2** Conceptual model of inferential statistics.

Inferential Statistical Techniques

Inferential statistical procedures provide a set of techniques that allow the researcher to infer that the events observed in the sample will also occur in the larger unobserved population from which the sample was obtained. There are two basic reasons for using inferential techniques. First, they can assist the researcher who is testing a hypothesis and must decide whether to accept or reject it. For example, a researcher, having a particular value in mind, poses the question, "Is this value reasonable in light of the evidence from the sample?" Second, inferential techniques can be used for estimation. For example, a researcher may have no particular value in mind but wants to know what the population value is. The researcher draws a sample, studies it, and makes an inference about the population characteristic (Figure 4-2). These two classic situations as addressed by inferential techniques are as follows:

1. *Testing a hypothesis* (Table 4-5). Is there a significant difference in the incidence of nausea between those patients given thiopental and those who receive propofol?
2. *Making an estimation*. What percentage of CRNAs perform a thorough machine check at the start of each day?

Researchers are seemingly preoccupied with the concept of significance. The level of significance (also designated as *alpha level* or P *value*) is a criterion used in making decisions regarding a hypothesis. For example, if *P* is less than 0.05, the probability that the difference

TABLE 4-5 Statistical Methods Used for Testing Hypotheses

	TYPE OF EXPERIMENT				
Scale of Measurement	**Two Treatment Groups Consisting of Different Individuals**	**Three or More Treatment Groups Consisting of Different Individuals**	**Before and After a Single Treatment in the Same Individual**	**Multiple Treatments in the Same Individual**	**Association Between Two Variables**
Interval (and drawn from normally distributed populations)*	Unpaired *t*-test	Analysis of variance	Paired *t*-test	Repeated-measures analysis of variance	Linear regression and Pearson product-moment correlation
Nominal	Chi-squared analysis of contingency table	Chi-squared analysis of contingency table	McNemar test	Cochrane Q	Contingency coefficient
Ordinal	Mann-Whitney rank sum test	Kruskal-Wallis statistic	Wilcoxon signed rank test	Friedman's statistic	Spearman rank correlation

Adapted from Glantz SA: *Primer of Biostatistics*. 3rd ed. New York: McGraw-Hill, 1992; Biddle C: *Evidence Trumps Belief: Nurse Anesthetists and Evidence-Based Decision Making in Nurse Anesthesia*. Chicago: AANA Publishing, 2010.
*If the assumption of normally distributed populations is not met, the observations should be ranked, and the methods for data measured on the ordinal scale should be used.

TABLE 4-6 Choice of Statistical Test Based on Assumptions

	Parametric Procedures	**Nonparametric Procedures**
Nature of the assumptions	Data are interval or ratio level	Data are nominal or ordinal level
	Each value is independent of the other values	Not necessarily distributed "normally" (i.e., data do not "fit" a bell-shaped curve)
	Value is normally distributed	
	Groups have similar variance	
	Usually work best with large population	
Examples of tests	*t*-Test for independent groups*	Chi-squared test
	t-Test for dependent samples†	Mann-Whitney test
	Analysis of variance	Kruskal-Wallis test

*For example, two totally unrelated groups are compared.
†For example, a pretest and posttest comparison on one group of people.

observed between the samples was the result of chance alone is less than 5%. Accordingly, if *P* is less than 0.05, the probability that the difference between the samples was real (i.e., it resulted from the treatment) and not just the result of chance is greater than 95%. It is conventional to establish the alpha level before the data analysis is begun; however, there seems to be an increasing trend toward reporting calculated *P* values after hypotheses have been tested. Commonly used levels in research are *P* is less than 0.05 and *P* is less than 0.01; *P* is less than 0.10 is sometimes used in preliminary or descriptive studies. There is also a trend to simply report the calculated *P* value and leave the interpretations up to the reader.

In recent years, there has been growing resistance to exclusive use of the *P* value in interpreting research findings, despite the still widespread use of the *P* value in interpreting hypotheses. *Effect size* is a measure of the magnitude of the observed relationship(s) under consideration. The *P* value is a dimensionless value that is, in the best case, only an indicator of the direction of the effect and in no way speaks to the clinical meaningfulness of the relationship.

A number of standardized effect-size measures are in use, and all have their unique place in the settings of reporting research findings. Although explanation and application illustrations are beyond the scope of this chapter, examples of these include but are not limited to Pearson's *r*, odds ratio, confidence intervals, and Cohen's *d*. The number needed to treat (NNT) is yet another example of a metric that provides clinically applicable "magnitude of effect" information. With these limitations involved, brief descriptions of some common statistical manipulations follow.

Selecting the Appropriate Statistical Procedure

There are two major categories of inferential procedures: parametric analyses and nonparametric analyses. The major factors that dictate which category should be selected involve the assumptions the investigator makes regarding the data. Tables 4-6 and 4-7 provide some guidelines for selecting a statistical procedure.

Power

The sensitivity of the planned experiment and analysis is known as its *power*. The concept of power is important to anyone planning a research project or evaluating a published paper. The estimate of an experiment's ability to accurately test the hypothesis under question should be computed before the research is begun. A researcher should ask the following two critical questions:

1. What is the chance I will incorrectly determine that my treatment had an effect when it really did not (type I error)?
2. What is the chance I will miss an effect that is actually present (type II error)?

Power estimates obtained during a study's design stage encourage investigators to thoughtfully enhance the study's sensitivity.

TABLE 4-7 Choice of Statistical Test Based on Purpose

Test	Goal
t-Test, independent groups	To test the difference between the means of two independent groups
t-Test, dependent samples	To test for the difference between dependent, paired samples (e.g., pretreatment and posttreatment) outcome
Analysis of variance	To test the difference among the means of more than two independent groups or more than one independent variable
Chi-squared	To evaluate the difference between observed and expected frequencies
Correlation coefficient	To test whether a relationship exists between two variables (e.g., product-moment)
Simple linear regression	Used when one independent variable *(x)* is used to predict a dependent variable *(y)*
Multiple linear regression	To understand the effects of two or more independent variables on a dependent measure
Analysis of covariance	To test for differences between group means after adjustment of the scores on the dependent variable to eliminate the effects of the covariate
Factor analysis	To reduce a large set of variables into a smaller, more manageable set of measures
Canonical correlation	To analyze the relationship between two or more independent variables and two or more dependent variables
Discriminant analysis	To make predictions regarding membership in categories or groups, in contrast to using interval- or ratio-level measures

Making such estimates forces the posing of questions regarding effect size (e.g., how potent is the effect of the independent variable on the dependent variable?) and sample size, both of which are essential in a study. Many adverse outcomes that occur as a result of anesthetic management are rare (e.g., death, postspinal hematoma, blindness, stroke), and studies proposing to measure such outcomes as a function of a particular interventional approach must be "powered" by a large sample size and other methodologic controls.

Established procedures and techniques can assist the researcher in determining what sample size must be used if a study is to have an acceptable chance of achieving its purpose (the testing of a given hypothesis). What is at stake is the issue of a trial's having sufficient rigor to detect whether a true difference between treatment groups exists. Other issues should be considered as well, and the reader is referred to the definitive text by Cohen[5] for further treatment of these issues. Careful attention to these issues may help prevent the commission of a type III error (conducting the wrong experiment). Most human subject committees and scientific journals require that study reports contain some discussion of power before they are seriously considered.

Data analysis allows the researcher to organize this information in a focused manner so the research question can be answered. Selecting the appropriate method of data analysis is essential to the proper execution of the research plan. Experienced and beginning researchers alike may need assistance when choosing an appropriate method for data analysis. Expert researchers, statisticians, and clinical nurse specialists may prove to be valuable resources for the beginning researcher.

Once the data collection and analysis have been completed, the researcher must interpret the results. These results are directly related to and should answer the research question or hypothesis. Researchers may find that the answers are different from those they were expecting. The answers, results, and outcomes should be interpreted and their implication for clinical practice described. The researcher also should discuss how the findings relate to other research studies and should present ideas for future practice.

Propensity Score

Mention should be made here of an increasingly common analysis, the *propensity score*. This is particularly important in observational studies where bias may be a powerful confounder. Many factors influence the decision of how to treat a patient. In the randomized control trial, the bias inherent in assigning a particular patient to a particular treatment arm in the study is minimized by the study design itself. However, in an observational study, it is important to know the conditional probability of a particular subject receiving the intervention (treatment), given observed or measured covariates. The propensity score affords us the opportunity to do just that. If there is no hidden bias and treatment assignment is thus "random," the propensity score should reveal that. There is some movement, using the propensity score, to elevate the "power" of observational studies to near that of the randomized trial. However, this is a somewhat contentious issue.

Nonetheless, propensity analysis has been used recently to illuminate clinical judgments associated with beta blockers, antifibrinolytics and other agents with important perioperative implications. Being an increasingly common methodologic and analytic approach to complex clinical questions, we are likely to see its use continue to grow.

Recursive Partitioning

A now commonly used tool that has both statistical and methodologic attributes and implications is recursive partitioning (RP). Its roots are in the word *recursive*, meaning to use a rule or procedure that can be applied repeatedly, and *partitioning*, indicating a division into or distribution into portions or shares. This type of approach creates a rule such as "if a patient has finding *a, b* or *c*……, then he or she likely has condition *x or* should be treated with *z*." Examples where this kind of rule application has been used include the Goldman Cardiac Risk Stratification, obstructive sleep apnea scales such as STOP-BANG, and the ASA (American Society of Anesthesiologists) Difficult Airway Algorithm.

RP tends to work best with dichotomous (e.g., 'yes/no') variables, and a "mistake" make early on is likely to have significant downstream consequences. Nonetheless, when applied appropriately, RP can provide clinical information and decision making that is grounded in supportive evidentiary decision making and can be used when there are multiple variables even in the presence of complex interactions—circumstances that are very often present in the real world of clinical anesthesia care.

Common Mistakes

At this step in the research process, mistakes include selecting an inappropriate statistical procedure, using only one statistical procedure when several should be used, overstating the importance of small differences that are statistically significant but of little clinical importance, interpreting correlational research as evidence of cause-and-effect relationships, and overgeneralizing the findings of the investigation. Some common errors in statistical usage are noted in Box 4-4.

BOX **4-4**

Top 10 Common Errors in Statistical Usage

1. No justification for reporting statistical results
   - No control group (when one is possible)
   - Random sampling or random group assignment not performed (or reported)
   - Statistical test not specified
   - Obvious biases or threats to validity
   - No documentation of consent or institutional review board approval
2. Errors in use of the *t*-test
   - Multiple application without correction
   - Use of independent groups form for paired data and vice versa
   - Use for ordinal data
3. Negative conclusions when statistical test results are not significant
4. Use of a test for independent samples for paired data or repeated measures
5. Inappropriate or no follow-up to analysis of variance
6. Hypotheses generated by the data
7. Use of one-sided tests without justification (or disclosure)
8. Inadequate number for chi-squared analysis
9. Standard error of the mean used for specifying variability
10. Misinterpretation or misrepresentation of *P* value
    - Small *P* value called "highly significant"
    - No confidence intervals stated
    - Different interpretation of $P = 0.04$ and $P = 0.06$

Stage 7: Dissemination of the Findings to Interested Colleagues

The research process is not complete until the results, conclusions, and implications have been adequately communicated to those likely to be interested in the study. Clearly, a study that has been completed but whose results have not been disseminated is of little value. Communication of the research findings can be done through a variety of routes, including publication in journals or newsletters, oral and poster presentations at formal symposia, or even simply discussion with others interested in the phenomenon.

Researchers fail to publish the results of their work for many reasons. These include such claims as "my findings were not significant," "my results were negative," and "the sample size was small." Negative or insignificant results can be as valuable as positive ones. For example, it has been found that in most circumstances, the by-product of atracurium breakdown, laudanosine, is unlikely to have significant clinical effects.[6] This is an important negative finding that has contributed substantively to clinical understanding.

Similarly, small sample sizes may provide an element of control over variables not present in larger studies or may indicate some preliminary direction as to how to approach a problem. An example is the finding that epidural anesthesia or analgesia in conjunction with light general anesthesia may be preferable to a purely general anesthesia technique and may be associated with lower mortality rates in critically ill patients.[7] Although the sample size in this particular investigation is relatively small, the overall design is acceptable and contributes to our understanding of the issue by stimulating other investigators to pursue answers to the questions raised.

Because the goal of nurse anesthesia research is the improvement of practice, the dissemination of research findings to clinicians is a major challenge faced by nurse anesthesia researchers. In a report directed at a highly research-oriented audience, the introduction is usually somewhat detailed, emphasizing the theoretic basis for the research. The introduction is followed by an extensive methodologic section that focuses on establishing the reliability and validity of the instruments used. The findings of the study are presented next, with emphasis on the statistical procedures employed. Finally, the conclusion focuses on the limitations and implications of the study's results.

Writing for a Clinically Oriented Audience

Generally, clinicians find research literature difficult to understand and its clinical application cumbersome. Both authors and journal editors can do much to make research more palatable to the clinical reader, thereby improving the chance that the research findings will be broadly disseminated and integrated into clinical situations. A recipe for successful clinical writing follows.

Clinical readers of research want to extract information applicable to clinical practice as quickly as possible. Therefore, the introduction of the research report should be brief, should establish the practical importance of the study, and should present a clear statement of the study's purpose. A deliberate effort should be made to connect the study with the realities of clinical practice.

With respect to the methods section, writing that "a quasi-experimental, Solomon three-group crossover design yielded data that were subjected to canonical and discriminant analysis" does little to satisfy the needs of the average clinical reader. Instead, stating how the subjects were obtained, what manipulations were made, how the measurements were taken, and how the statistical analysis was performed provides the reader with clear straightforward information, allowing him or her to put the study into a clinical context. The methods section should completely describe both the research design and the statistical procedures used, and it should indicate why this approach was selected.

The results of the study should focus on the relevant findings and describe them clearly and fully. Tables or figures, explicitly labeled and simple in design, should be used for representing the findings visually. Admittedly, the more complex the findings, the more difficult it is to avoid a statistical or technical focus.

In the discussion section, the implications of the investigation for theory and future research are somewhat less important to the clinical reader than are the implications for practice. For example, assume that a study demonstrates that the proposed intervention is not ready to be implemented in practice. In this situation, the discussion section should emphasize why this is so and what can be done about it. Encyclopedic comparisons of the results with those of other investigators at this point probably will not contribute materially to the report and may, paradoxically, deter the reader. Alternatively, if a researcher finds that a particular intervention, strategy, or assessment is ready to be introduced into clinical practice, the discussion section should emphasize how and for whom it should be used. It should include considerations such as efficiency and cost, as well as suggestions for clinical implementation.

This recipe for making research reports more palatable to primarily clinically oriented readers is not meant to diminish the importance of highly theoretic research-oriented writing. Many CRNAs continue to generate and publish valuable theoretic papers that contribute materially to a scientific basis for practice. Researchers and writers must keep the CRNA audience in mind as they develop and disseminate their findings.

All researchers must understand that the results of their studies, once published, become part of the general knowledge of the scientific community at large. However, the use of this knowledge requires acknowledgment of the original researchers; also, published results may be subject to copyright protection laws (i.e., their use may require permission from the publisher). It is not until

the information becomes common knowledge that others may use it freely without acknowledgment.

Common Mistakes

At this stage of the research process, common mistakes include not keeping the study focused on the original problem, overwriting, generalizing the findings too broadly, and failing to address the clinical significance of the study.

Stage 8: Evaluation of the Research Report

Both clinicians (in their reading for application) and researchers (in their writing and analysis) are called on to evaluate research reports, despite the fact that many may not have received formal training in reading and interpreting professional literature. Evaluation is the process of appraising the quality of a phenomenon—in this case, the findings of research as they bear on the art and science of nurse anesthesia. Outside of the practice settings, humans evaluate hundreds of things every day: Are the apples on the grocery shelves to our liking? Does the description of the program in the television guide entice us to tune in? Is the weather too warm to wear a jacket? Have we cooked the eggs sufficiently? These seem trivial and informal compared with the clinical evaluations the CRNA must perform daily: Is the patient's anesthesia too deep, too light, or about right? Should I administer more opioid? Is the patient dehydrated, or is the hematocrit level misleading me? Should I perform a rapid-sequence induction? What dose of which sleep agent do I use in this 80-year-old patient with a fractured hip? Both sets of questions, nonprofessional and professional, are highly evaluative and parallel the evaluative decision making that occurs when anesthesia research literature is read.

Systematic evaluation of the research, which influences the practice of nurse anesthesia, consists of a formal appraisal of the quality and value of the research. This essential step in the research process is multidimensional and can be approached in many ways. The approach outlined in the following subsections involves asking carefully orchestrated, critical questions. The answers to the suggested questions are not necessarily a dichotomous yes or no, but rather are qualitative in nature. An overview of this approach is detailed in Box 4-5.

Gaining Experience at Evaluation: the Journal Club

Most clinicians and researchers are familiar with the concept of the journal club, a common curricular component of many programs in the anesthesia community. A journal club offers a planned, periodic, and critical reading of anesthesia-oriented research and clinical articles pertaining directly to practice. Participants in a journal club are assigned to read selected articles; later, a discussion of the articles can proceed under the direction of an informed leader. Questions that should be asked during discussion and critique include the following:

- What are the purposes and the research questions or hypotheses, and how does the related literature review bear on the purpose or problem?
- What methods did the authors use to study or evaluate the problem?
- How are the data presented, and in what manner are they analyzed?
- What are the conclusions of the study, and what are the implications for practice?

Participation in a journal club can be a rewarding and intellectually stimulating activity that can be used for keeping one's knowledge of the field current and for gaining experience in evaluating the anesthesia-related literature.

BOX 4-5

Research Scenario: A Guide for Researchers* and Clinicians† in Evaluating Research for Completeness and Clinical Application

Problem
Is it lucid, researchable, justified, and practical?

Hypothesis
Is it clear, with the appropriate variables under consideration correctly identified?

Definitions
Are terms adequately defined and put into context?

Literature
Is it relevant, current, and organized?

Review
Is it logical, and does it justify the study?

Methods
Is the sample representative of the population being considered? Is the sample large enough? If human subjects were used, was institutional approval granted? Is the instrumentation described and valid? Is the design compatible with the problem and the hypothesis or research question? Is there any evidence of drift from established procedure? Are the data-gathering procedures defined? Is there enough information for replication of the study, if desired? Are the statistical procedures described, and are they appropriate?

Results
Are results presented clearly, concisely, and without bias? Are they organized and displayed logically in tables or figures? Are they relevant to the problem or hypothesis?

Discussion
Is the discussion logically based on the results? Is it intimately grounded in the original problem or hypothesis? Is there overgeneralization of the findings? Is the writing impartial and scientific? How can this study be used in the practice setting? How similar is the study's environment to the real world? What are the risks associated with implementation of the recommendations?

*Researchers should benefit from this by critically asking themselves whether they have included answers to these questions in their report.
†Clinicians should benefit from this by judging the report on the basis of completeness and utility and by finding out whether it contains answers to these questions.

Evaluating a Study: the Bottom Line

Ultimately, the nurse anesthetist evaluating a study is faced with the following three questions:

1. Do I disregard the study and its findings entirely, not applying them to either clinical practice or future analysis in any fashion?
2. Do I apply the study only in the sense of expanding my cognitive approach to anesthetic management? (In this scenario, although one may not materially or directly apply the study or its findings to practice, some intellectual growth or understanding is gained from the study, which subsequently is incorporated into one's repertoire.)
3. Do I make a direct application of the study to my practice?

Some questions to ask when one reads a study are listed in Box 4-6.

BOX **4-6**

Questions to Ask in the Reading of a Study

Object or Hypothesis

What are the objectives of the study or the questions to be answered?

What is the population to which the investigators intend to refer their findings?

Design of the Investigation

Was the study an experiment, planned observations, or an analysis of records?

How was the sample selected? Do possible sources of selection exist that would make the sample atypical or nonrepresentative? If so, what provision was made for dealing with this bias?

What is the nature of the control group or standard of comparison?

Observations

Are there clear definitions of the terms used, including diagnostic criteria, measurements made, and criteria of outcome?

Was the method of classification or of measurement consistent for all the subjects and relevant to the objectives of the investigation? Do possible biases in measurement exist, and, if so, what provisions were made to deal with them?

Are the observations reliable and reproducible?

Presentation of Findings

Are the findings presented clearly, objectively, and in sufficient detail to enable the reader to judge them for herself or himself?

Are the findings internally consistent? That is, do the numbers add up properly, can different tables be reconciled, and so on?

Analysis

Are the data worthy of statistical analysis? If so, are the methods of statistical analysis appropriate to the source and nature of the data, and is the analysis correctly performed and interpreted?

Is analysis sufficient for determining whether "significant difference" may be the result of lack of comparability of the group in gender or age distribution, in clinical characteristics, or in other relevant variables?

Conclusions

Which conclusions are justified by the findings? Which are not?

Are the conclusions relevant to the questions posed by the investigators?

Constructive Suggestions

Assume you are planning an investigation to answer the questions put forth in this study. If they have not been clearly asked by the authors, frame them in an appropriate manner. Suggest a practical design, criteria for observations, and type of analysis that would provide reliable and valid information relevant to the questions under study.

Adapted from Colton T: *Statistics in Medicine*. Boston: Little, Brown, 1974.

Common Mistakes

At this stage of the research process, mistakes include failing to adequately evaluate a study's methods and findings and in the process, uncritically accepting into practice information that may be misleading or incorrect. Although articles in professional journals should undergo critical review by peers who can detect mistakes, omissions, and alternative explanations, the ultimate responsibility for evaluating a study and determining the pros and cons of the implementation of its recommendations rests with the clinical reader.

FRAUD, DECEIT, AND HUMAN ERROR IN SCIENTIFIC RESEARCH

Scientists are human and suffer from the inherent frailties of the human condition. Even the most scrupulous and compulsive scientist can make an honest mistake, and such mistakes are tolerated by the community at large. Errors are costly in a variety of ways. Not only might an error result in months or years of wasted effort if it is not identified and rectified, but it also can mislead others who attempt to use or build on the original, flawed work.

Unfortunately, not all errors are honest. Scientific and academic misconduct occurs in a variety of forms. Although the motives of the involved parties are not always identifiable, some researchers feel pressure to publish, whereas others simply are intent on gaining attention by compiling a long list of publications or presentations. The bottom line is that scientific misconduct ultimately erodes the foundation on which science is built and may result in the administration of inappropriate therapy to those in need of treatment. Common examples of scientific and academic misconduct include the following:

- Plagiarism
- Alteration of data so they conform to expectations
- Outright fabrication of data
- Intentional sloppiness in scientific work
- Selective publication of data with intent to support one's beliefs
- Coercing subordinates to acknowledge oneself unreasonably
- Unapproved use or misuse of human or animal subjects
- Not giving appropriate credit in collaborative research

Recently there have been dramatic examples of research fraud and misconduct in the anesthesia literature by prominent (not so much as of this writing!) anesthesiologists in the domains of pain relief and perioperative fluid therapy. Drs. Scot Reuben and Joachim Boldt are dramatic recent examples of incredible misconduct leading to the retraction of dozens of papers by the authors and even the imprisonment of the former physician.

Guidelines for Dealing with Errors or Suspected Misconduct

The nurse anesthetist who is personally involved with or suspects scientific or academic misconduct on the part of a colleague is morally and professionally compelled to take action as soon as possible. Box 4-7 lists guidelines to adhere to if such a situation occurs.

STUDIES INVOLVING HUMAN SUBJECTS

The process of making a research project a reality involves coordination between patients' needs and rights and the study's parameters and goals. This process is controlled in some respects by criteria set up by various governing agencies. The 1947 Nuremberg Code, the 1964 Helsinki Declaration, and the 1971 guidelines of the U.S. Department of Health, Education, and Welfare were drafted to reflect the concern for individuals participating in research. In 1979 the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research was established to continue work in this area. The culmination of that work, the Belmont report, defines the limits between research and practice and outlines the ethical guidelines to be considered for patient participation in research projects. According to the report,

BOX **4-7**

Dealing with Errors and Misconduct

If the Situation Has Resulted from Your Own Actions

Immediately acknowledge the error to your colleagues. If the error is in print, write to the journal editor or source in which the mistaken information was published.

If You Discover an Error in a Publication

Write a letter to the editor of the publication stating your case and supply any supportive materials you have.

If You Believe a Colleague Has Engaged in Misconduct

1. Discuss the situation with a trusted and experienced colleague, maintaining the anonymity of the accused. This will help you judge the motives of your own suspicions and establish the veracity of your charges.
2. Once the facts have been established, contact the colleague privately to determine whether the concern can be satisfactorily explained or rectified.
3. If resolution is not at hand, discuss the situation with the department director, chairperson, or dean, as indicated by the hierarchic administrative arrangement. Many institutions and universities have written procedures that carefully outline the process to be followed in such situations.
4. In situations in which resolution is still not achieved or if a definable administrative structure is not in place, consider contacting the National Academy of Sciences, Sigma Xi, the American Association for the Advancement of Science, the American Association of University Professors, or other scientific or professional organizations.

Adapted from Colton T: *Statistics in Medicine*. Boston: Little, Brown, 1974.

the difference between standard practice and research is defined in terms of design and outcomes. The phrase *medical practice* refers to diagnosis, treatment, and preventive health care whose purpose is the enhancement of the well-being of an individual. The term *research* refers to procedures whose purpose is the examination of a question or the testing of a hypothesis to expand the existing body of knowledge.

Institutional Review of Research That Involves Humans and Animals

All protocols involving the living must be submitted to a local institutional review board (IRB). The IRB is charged with the protection of each subject participating in the study. It is the responsibility of the IRB to ensure that informed consent is adequate, that no coercion is used in the recruitment of subjects, and that the risks to the subjects are minimal or no greater than necessary. To accomplish this, the IRB carefully reviews the study's protocol and consent forms, considering the study's design and patient selection.

A number of factors must be considered when a study calls for the involvement of human participants. The risk-benefit assessment compares the benefits of participating in a study with the potential risks generated by the study. Vulnerable populations (e.g., children, pregnant women) require special considerations. Risks can involve the patient, the family, or the community. The risk-benefit balance should be justified by an analysis of information to be gained from the research, a description of the available treatment alternatives, and the measures to be taken to minimize risks and discomfort.

Providing a patient with the information necessary for making an informed decision about participation is fundamental. Informed consent should be easy to understand and include a description of the research and plan of treatment, the risks and benefits, the alternatives to participation in the study, confidentiality, costs, and compensation. Informed consent also must include an assertion of the voluntary nature of the study, a statement that the patient may withdraw at any time without penalty, and a commitment that during the course of the study, the discovery of any new findings that may affect the subject's participation will be disclosed. In most instances, a signed consent form from a participant is necessary; ultimately, however, the IRB decides whether such a form is necessary.

Virtually all institutions and funding agencies have model consent forms whose format researchers must follow when developing a study. Consent forms (written in lay terminology) should include a brief description of the study, a summary of the anticipated risks and benefits of participation in the study, a statement regarding the maintenance of the participant's confidentiality, a disclaimer obviating the host institution of financial responsibility for damages that might occur, and the names and telephone numbers of the researchers. Under most circumstances, the individual who has agreed to participate in the study signs the consent form in the presence of the researcher and a witness who cosigns the consent. A copy of the consent form is given to the participant for his or her records.

CONTROVERSIES IN ANIMAL RESEARCH

Biomedical institutions now operate under guidelines that mandate the humane treatment of animals used in research. The use of animals for research is a subject of controversy fueled by disagreements between people who are highly supportive of the use of animals and those who strongly oppose it, such as supporters of the People for the Ethical Treatment of Animals (PETA) and the Animal Liberation Front (ALF). Researchers contemplating the use of animals in their research should carefully consult with their local IRB for guidance in this area.

EVIDENCE-BASED PRACTICE: EMPOWERING DECISION MAKING THROUGH RESEARCH

Evidence-based practice (EBP) is an approach to patient care founded on the belief that clinical decisions must be based on results obtained from rigorously controlled investigations. It cautions against using studies with low external validity (e.g., animal studies) or those based on uncontrolled observations (e.g., case reports, retrospective studies) in rendering decisions that influence or dictate patient care interventions.

Although many recipes for and approaches to EBP exist, the essential ingredients common to all include the following:

- Defining the patient's problem
- Proficiently searching the relevant literature
- Critically appraising the discovered literature
- Rationally applying the relevant literature in the context unique to the patient

At the core of EBP is the notion of critical thinking (appraisal) of the applicable literature. Here, intellectual rigor is balanced with clinical experience as the clinician determines whether the evidence is applicable to a particular patient's situation.

The dizzying array of studies in the anesthesiology field coupled with the complexities and vagaries of this patient population produce an informational tidal wave both frustrating and daunting to clinicians who endeavor to remain on the cutting edge with respect to patient care decisions. We all rely to one extent or another on

reviews of primary research to assist us in coming to understand and apply clinical research findings. Whenever possible, we should endeavor to use systematic reviews. Systematic reviews are those that incorporate (1) a comprehensive study retrieval process that minimizes publication bias, (2) selection criteria that identify only relevant studies, (3) a critical appraisal of the emergent literature accomplished by knowledgeable and sophisticated clinicians and researchers, and (4) reproducible decisions regarding the relevance and methodologic rigor of the selected primary research.

Recently the meta-analysis has begun to appear in the anesthesia literature. A meta-analysis is a systematic review that includes a quantitative statistical analysis of the findings that have emerged from several (or many) discrete studies examining a similar phenomenon. Examples of anesthesia-based meta-analyses include those by Tramer, who examined ondansetron as an antiemetic; Ballantyne et al., who studied pulmonary outcomes in patients who had epidural analgesia; Lee et al., who looked at acupuncture and acupressure as alternative approaches in the management of postoperative emetic symptoms; and Biddle, who evaluated the use of nonsteroidal anti-inflammatory drugs in the treatment of acute postoperative pain.[8-11]

When solid evidence evolves into sound clinical decision making, patients receive the best possible care; EBP helps us choose scientific evidence over confusing (or even unsound) opinion. In addition, EBP complements other foundational approaches to patient care and teaching. Some researchers argue that there is a crucial final step in the EBP model—namely, that clinicians self-evaluate their own EBP. In doing so, clinicians provide an ongoing process of evaluation and sensitivity testing for practice-based decisions.

Clinical research seeks to resolve, refine, and clarify the issues involved in the care and management of patients. Each day, we are faced with a host of common and uncommon patient scenarios that demand thoughtful, efficient decision making and resultant interventions. How we come to decide what course of action to take is in many cases as important as the action itself. Decisions involving the care of patients should be evidence based, a process of considerable complexity involving judging sources of information, evaluating the quality and relevance of information, recognizing the contextual elements that may alter the application of that information in a particular setting, and assessing its impact on the patient(s).

The Process of Evidence-Based Clinical Practice

What we do in a given circumstance is often more a matter of entrenched belief than a course of action firmly grounded in research. The published series *Clinical Evidence*, the international source of best available evidence related to common clinical interventions in various disease states, reveals that of 2500 treatments reviewed, 325 (13%) were rated "beneficial," 575 (23%) "likely to be beneficial," 200 (8%) as "a tradeoff between benefit and harm," 150 (6%) "unlikely to be beneficial," 100 (4%) "likely to be ineffective or harmful," and 1150 (46%) as having "unknown effectiveness." One might interpret this in many ways, but clearly it points to the theme that many treatment decisions are inadequately grounded in firm scientific rationale.[12]

The fundamentals of medicine and nursing have evolved from a time when the teaching and practice of authoritative figures (sages) were simply passed down and uncritically applied to patients. Advances came with clinical evolution, but primarily in the form of case reports, case series, editorials, and other publications that were too often based on preconceived notions, and deliberate or unintentional bias. The advent of the randomized controlled clinical trial (RCT) some six decades ago set the stage for a new era in patient care. In the RCT, patients are randomized to treatment strategies, the effect of outside influences on outcome are considered, and there is methodologic precision, not only with regard to the interventions applied to patients but also to how outcomes are measured. A brief overview/checklist is noted in Box 4-8 to help in judging the value of a particular RCT. Despite advances, practitioners, and nurses in particular, are often resistant in regard to bringing research advances to the bedside.

BOX 4-8

Checklist for Evaluation of the Randomized Controlled Trial

- Is a clear objective for the study stated?
- Is the sample size adequate?
- Is the study population well described?
- Are the interventions clearly described?
- Are randomization and blinding procedures adequate?
- Are valid and reliable outcome measures used?
- Is attrition (dropouts) considered in the analysis?
- Are the statistical methods appropriate?
- Are both clinical and statistical significance reported?
- Are the results generalizable to clinical practice?

Evidence-based practice (EBP) involves a series of consecutive, somewhat overlapping steps that follow.

Step 1: Asking a Question That Deserves an Answer

Should we anesthetize and perform elective surgery on a child who presents with an upper respiratory infection on the day of the scheduled procedure? What fluid and glucose management strategy should be used in the diabetic patient recovering from a major peripheral vascular procedure? Is it safe to use ketorolac in the patient just now recovering from tonsillectomy? What can be done to minimize the risk of ventilator-acquired pneumonia in the postoperative patient receiving mechanical ventilation? Should all patients recovering from general anesthesia receive supplemental oxygen in the PACU (postanesthesia care unit)? Should obstructive sleep apnea patients recovering from general anesthesia receive CPAP (continuous positive airway pressure) throughout their hospital stay if significant pulmonary hypertension is present? Such questions are common in practice and merit careful consideration in terms of intervention-related outcome, but relevant questions also apply to diagnosis, prognosis, and the potential for harm. It may seem like word play, but the answers to our questions are more likely to be important and valid if the questions posed are good. Questions should be focused to the extent that they are both applicable to the patients who are cared for and can be researched.

Steps 2 and 3: Searching for Relevant Evidence and Judging Its Worth

Once a question is at hand, the search for information begins, a process that can be both time consuming and challenging. Seeking evidence to address the question "What is the best antiemetic for the postoperative patient?" is much different than asking "Is isopropyl alcohol inhalation more effective than ondansetron in managing post–general-anesthesia nausea in the postpartum tubal ligation patient?"

Although providers usually have an opinion about care-related questions, EBP demands that we critically evaluate researchable and meaningful information sources to best address a particular

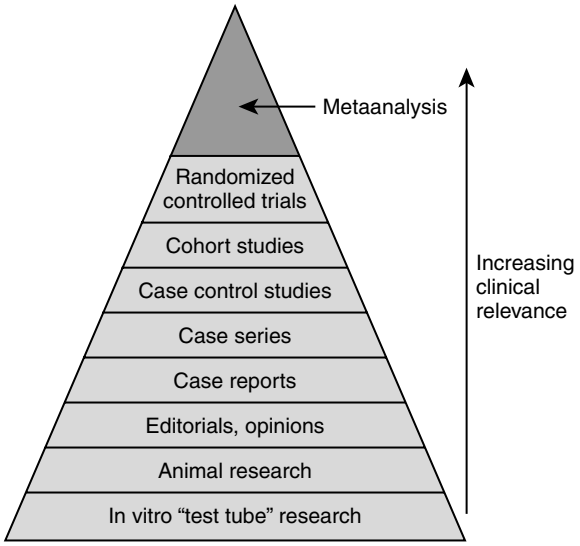

FIGURE **4-3** The pyramid of evidence.

patient's care. *Index Medicus* and *MEDLINE* are familiar and excellent sources but are not applicable in all circumstances, especially if time is of the essence. A particularly valuable database specifically related to EBP is the Cochrane Collaboration, a collection of well-conducted clinical trials organized into specific topics. Established websites, well-regarded (peer reviewed, authoritative) textbooks, or even colleagues with a more robust knowledge base than yours may suffice. But crucial to this is your level of confidence that your colleague, the database, or the book chapter is evidence based. The phrase "garbage in, garbage out" has particular application here.

A particularly powerful, and underused search tool that readers should investigate is CINAHL, the Cumulative Index of Nursing and Allied Health Literature. This tool has exceptional utility to the anesthesia domain and should be a part of any broad or focused research that one performs.

Definitions of EBP abound; for its practicality and relevance, consider the following description: EBP is the conscientious and critical use of quality published evidence in making decisions related to the care of a particular patient, considering the caregiver's unique expertise and the setting in which the patient presents. It is important to recognize that not all evidence that is retrieved or brought to bear on a question has the same value. Figure 4-3, the pyramid of evidence, demonstrates that the randomized, double-blind, controlled clinical trial has greater worth than the editorial or case report. This hierarchy of value is case and issue sensitive, because not all questions have relevant or applicable RCTs. On the other hand, when a number of RCTs are directed toward a similar issue, these can sometimes be combined, using rigorous methodology and a common set of statistical proceduring, to produce a meta-analysis (or quantitative systematic review).

Step 4: Determining Whether the Evidence Applies to Your Particular Patient

Translating knowledge into practice is the next critical step. If you have determined the evidence is valid and important, you must now decide whether you should apply it to the care of your patient. EBP then becomes an ongoing process of inquiry, asking "Why am I doing it this way?" and "Are there compelling reasons for me to do it differently to achieve a better outcome?" The factors influencing these decisions are complex. Ultimately the decision to implement an intervention is a blend of experience and science (evidence) as you carefully assess what value the evidence has in the context and setting of a particular patient. What is meant by *context?* Box 4-9 illustrates just a few of the contextual factors that we must consider in the process of EBP.

BOX 4-9

Some Contextual Considerations in the Process of Evidence-Based Clinical Practice*

Considerations in Weighing the Application of a Therapy in a Particular Patient

- Age and gender
- Hydration status
- Smoking history
- Current drug therapy
- Duration of illness
- Severity of symptoms
- Cost of therapy
- Side effects
- Inpatient or outpatient
- Coexisting conditions
- Physician and staff familiarity and experience with intervention
- The degree of technical mastery necessary to perform the intervention
- Staff makeup (specialists, generalists)
- Type of hospital (community, medical center, urban, rural)
- Support personnel
- Is reasonable follow-up available to assess the intervention's outcome?

*The list is partial and meant only to stimulate thinking regarding how factors may influence the application and outcome of a particular intervention.

Step 5: Evaluating the Effect (Outcome) of the Evidence-Based Intervention

Absolutely vital to the process of EBP is evaluation. Here one determines whether the evidence has altered the "usual" practice pattern. If so, has it been associated with improved efficiency and health outcome, and has it maintained the quality of care? Evaluation allows not only for deciding whether the intervention "works" but also for determining whether variations arise (e.g., dosing, timing, duration, complications, unexpected occurrences, etc.). In doing so, a kind of living, evolving document arises that can be used for purposes of assessing efficacy, quality assurance, and risk.

The "PICO" Approach

A common model used in developing an appropriate clinical question is the so-called *PICO* approach. PICO is a mnemonic that describes key components of good question construction, that is, **P**atient, **I**ntervention (or cause), **C**omparison (if appropriate), and **O**utcome. Because clinical circumstances, and their associated questions, vary considerably, not all questions will have a "comparison" group, although many will. Examples of PICO-derived questions follow:

Patient	Intervention	Comparison	Outcome
61-year-old male, infarction	Streptokinase	Plasminogen activator	Death
31-year-old female, laparoscopy	Ondansetron 4 mg	Droperidol 1.25 mg	Nausea
17-year-old male, arthroscopy	Spinal anesthesia	—	Time in PACU

Using the PICO approach, a clinically focused, relevant question emerges from each of the scenarios established earlier. For example, with respect to the second, a comparison scenario, the following question might emerge:

- In young women undergoing diagnostic laparoscopy for nonspecific pelvic pain and receiving anesthesia with sevoflurane, atracurium, and fentanyl, is there a difference in the rate of postoperative nausea when either ondansetron 4 mg or droperidol 1.25 mg is given 30 minutes prior to emergence?

With respect to the third, noncomparison question, the following question might emerge:

- In adolescents undergoing knee arthroscopy under spinal anesthesia with lidocaine 75 mg and sufentanil 10 mcg, what is the anticipated length of stay in the PACU before they are street fit?

SUMMARY

Although CRNAs are only now becoming prepared to assume the role of primary researchers, all CRNAs are in a position to read about the latest advances in nurse anesthesia practice and incorporate validated interventions into their clinical practice. Nurse anesthesia research is grounded fundamentally in solving patient-care problems during the preoperative, intraoperative, and postoperative periods. Although much behavioral, educational, and product evaluation–oriented research has been conducted by nurse anesthesia researchers, all nurse anesthesia research is wedded inextricably to patient care. Research is essential to the professional evolution of nurse anesthesia as CRNAs become increasingly accountable for their own independent basis for practice.

A number of antiscience movements are operative in the world today. At the heart of all of these movements is the sophisticated use of the concept of proof by proclamation rather than proof by experimentation. As active consumers and producers of scientific knowledge, nurse anesthetists can do their part by resisting the integration of aberrant and ill-founded thinking into their discipline. This can be achieved if each CRNA understands the need to maintain a critical dialogue regarding what can be incorporated into nurse anesthesia practice.

All CRNAs are mandated to understand and use research in their practices. The American Nurses Association strongly urges even undergraduate nursing students to learn how to read, interpret, and evaluate published research for applicability to nursing practice. Although the evolution of nursing research—and that of nurse anesthesia research in particular—has lagged behind that of many other disciplines, tremendous strides are being made as greater numbers of nurse anesthetists are prepared at both the master's and doctoral levels. It is essential that nurse anesthetists recognize the need to promote nurse anesthesia as a science-based profession. There is no better way to achieve this end than to continue emphasizing the importance of the research process.

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General Principles, Pharmacodynamics, and Drug Receptor Concepts

CHAPTER 5

◆ *John J. Nagelhout*

The practice of anesthesia requires a full spectrum of drugs from which an anesthetic plan can be implemented to achieve the desired level of surgical anesthesia, analgesia, amnesia, and muscle relaxation. In addition to surgical anesthesia, pain medicine has evolved as a significant clinical practice component.[1,2] Now that the human genome has been mapped and the field of molecular and cellular proteomics is exploring new concepts, specific receptor-targeted drugs are envisioned, as is a revolution in the way health care is delivered. Likewise, the methods used to provide anesthesia care will undergo a profound change based on this new knowledge. Already, studies are challenging long-held concepts of pharmacodynamics and pharmacokinetics that guide the clinical use of anesthetic agents. Target-controlled drug administration that factors in clinical pharmacodynamic and pharmacokinetic information is already being applied.[3,4]

Although the mechanism of action of the general anesthetics remains unknown, the primary site of anesthetic action is now considered to be membrane receptors and not the lipid bilayer surrounding the nerve cells.[5-7] Spinal cord receptors are being differentiated from receptors in the brain and targeted with specific drugs. A more in-depth knowledge of the concept of minimum alveolar concentration, which is used to define inhalation anesthetic dosing, is now coming to light.[8,9] Receptor super families with definable amino acid subunits are the targets of new classes of anesthetic drugs such as α_2-agonists and analgesics.[10] The potentiation of the inhibitory γ-aminobutyric acid (GABA) receptors is considered a primary mechanism of action of inhalation and intravenous anesthetics.[11] The recovery from intravenous anesthesia is described in terms of context-sensitive half-time, which in addition to the usual concept of drug half-life takes into consideration the duration of anesthetic administration rather than just drug redistribution and elimination profiles.[12-14]

The importance of the individual, with his or her unique genetic profile, is surfacing as a major determinant of anesthesia outcome.[15,16] The number of patients who now make up the portion of the population classified as elderly—those age 60 years and above—is ever increasing. Clinical experience has shown that the response to anesthetic drugs in elderly patients differs from that in younger patients. Age-related changes in drug pharmacokinetics do not totally explain the differences in drug dosing necessary to achieve anesthetic end-points in elderly patients. Studies to date in elderly patients, although limited, demonstrate an age-related decline in most receptor populations and an overall decrease in pharmacodynamic responses.[17-20] Preoperative assessment may soon take on an entirely different meaning as patient information becomes more genetically oriented. The choice of anesthetic agents will be based on age-related receptor profiles and the patient's genetic ability to rapidly clear and recover from anesthetic drugs once their administration has been terminated.[21-24] Until that time, anesthetists will continue to administer anesthesia based on age-indexed population drug profiles adjusted for individual pathologies (i.e., general principles of pharmacology).

The current medical economic climate necessitates the optimum selection and use of anesthetic drugs based on their pharmacologic profiles. The term *pharmacology* refers to the study of processes by which a drug produces one or more measured physiologic responses. The concept of a drug-induced tissue response has changed little since Ehrlich first proposed it (circa 1905). What has changed, and continues to change, is our understanding of the processes involved in drug-receptor interactions.[25-27] Recent attention has focused on the biosphere, or the protein receptor site, as not only the locus of drug binding but also a primary regulator of the measured pharmacologic response. Secondary processes, including drug absorption, distribution, biotransformation, and excretion, also influence the pharmacologic response.[28]

RECEPTOR STRUCTURE

A *receptor* is a protein or other substance that binds to an endogenous chemical or a drug. This coupling causes a chain of events leading to an effect. Receptors have three common properties: sensitivity, selectivity, and specificity. These properties are characterized by the fact that a drug response occurs from a low concentration (sensitivity) produced by structurally similar chemicals (selectivity), and the response from a given set of receptors is always the same because the cells themselves determine the response (specificity). The bonds that form between drugs and receptors typically fall into these categories from weakest to strongest: van der Waals, hydrophobic, hydrogen, ionic, and covalent.

Drug Receptors

The historic concept of a drug receptor complex considered the receptor to be a single protein to which the drug aligned and attached itself. We now have identified multiple mechanisms by which an endogenous substance or drug may complex with a receptor and transmit a signal. There are seven classes of drug receptor proteins based on genetic characterization and similarity of structure and functions.[29] Some examples of different types of receptors are given in Box 5-1.

Drug receptor proteins may be located within the luminal membrane and at the surface of the ionic channel. They also occupy intracellular sites. The drug lidocaine and other amide and ester local anesthetics, for example, act at intracellular receptor sites near the sodium channel. Studies of acetylcholine and its receptor at the neuromuscular junction indicate that less than 1% of the cell surface binds drug to receptor protein to achieve the tissue response.[30] Complete saturation of available receptors with drug molecules is not necessary for a desired tissue response to be elicited. With recent advances in molecular biology, many receptors have been extensively characterized, amino acid sequenced,

BOX 5-1

Receptor Classification

- 7-Transmembrane receptors
- Ligand-gated ion channels
- Ion channels
- Catalytic receptors
- Nuclear receptors
- Transporters
- Enzymes

Data from: Guide to receptors and channels (GRAC), 4th ed. *Br J Pharmacol* 2009; 158(Suppl 1):S1-S254.

and cloned. This is leading to new and better understanding of receptor pharmacology and new approaches to drug discovery.[31-34]

For intravenously administered drugs, sufficient drug for a maximal tissue response is delivered to the receptor site within the time required for a single complete circulation (approximately 1 minute), provided an adequate drug dose was administered initially. Current understanding of molecular pharmacology suggests that the delay recorded from initial drug administration to the onset of the tissue response reflects the time required for molecular orientation and attachment to the receptor—that is, the time course of the receptor protein conformational change and the tissue response time.[35] As long as both the drug and the receptor are hydrophobic, bonding occurs.[36] Intravenous anesthetics act by binding to membrane receptor channel proteins. The $GABA_A$ (ionotropic receptor family A) inhibitory receptor has been implicated and suggested as a primary site of intravenous anesthetic action, except in the case of ketamine.[37-39] Inhalation anesthetics have long been thought to produce their anesthetic action by dissolving in the lipid bilayer surrounding membrane ion channels and interfering with their ability to open and close. Recent electrophysiologic evidence, however, indicates that inhalation anesthetics, like intravenous anesthetics, bind to $GABA_A$ receptor proteins and cause inhibition of signal transduction by increasing the influx of chloride ions through membrane channels.[11,37-39]

Individual agonist drugs have at least three configuration points for attachment to their receptors. With more points of attachment, a more perfect drug-receptor fit occurs. Agonist drugs can induce receptor proteins to alter their topography to achieve a more exacting fit with the drug. The alignment of a drug with its receptor is aided by various bonding forces, of which van der Waals forces and ionic bonding are prominent. Volatile anesthetics (e.g., desflurane, sevoflurane, isoflurane, and nitrous oxide) bond to cell receptors by means of a nonspecific hydrophobic bonding mechanism.

Some endogenous proteins provide alternative drug-binding sites. These sites are more correctly termed *acceptors;* the acceptor reduces the amount of unbound drug available for receptor complexing. Albumin contains numerous acceptor sites and generally binds to acidic drugs. $Alpha_1$ acid glycoprotein and β-globulin favor basic drugs. Drugs bound to these proteins are unavailable to interact with receptors, therefore reducing the available active drug concentration.

Types of Receptors

As noted earlier, a variety of receptor types have been isolated and investigated, including GABA, opioid, alpha, beta, acetylcholine, histamine subtypes, and the pain-related capsaicin receptor, as well as numerous others.[39-43] The nicotinic and muscarinic

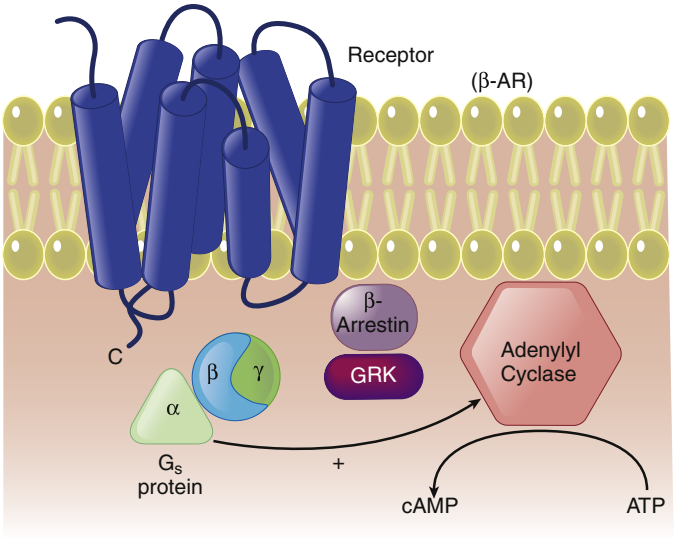

FIGURE **5-1** G Protein–coupled receptors. Upon ligand binding, β-adrenergic receptors (β-AR) bind to the heterotrimeric guanine nucleotide–binding protein Gs, inducing the exchange of GTP for GDP on the Gα subunit. Guanine nucleotide exchange induces dissociation of the α subunits from βγ subunits, the former of which activates adenylyl cyclase and the production of the second messenger cyclic AMP (cAMP). Signaling is terminated by GTP hydrolysis by the Gα subunit, resulting in its occupation by GDP, promoting reassociation of the heterotrimeric αβγ complex and inactivation of adenylyl cyclase. Moreover, receptors are inactivated by phosphorylation by G protein–coupled receptor kinase (GRK) resulting in the binding of β-arrestin, producing receptor desensitization by preventing productive interaction with G proteins and inducing internalization. (From: Waldman SA, Terzic A: *Pharmacology and Therapeutics: Principles to Practice*. Philadelphia: WB Saunders, 2009:55.)

cholinergic receptors that bind acetylcholine have been extensively studied.[44-46] The acetylcholine receptor protein is a pentamer of five peptide subunits conceptually forming a five-sided ring, with the central portion serving as the transduction ion channel. Only two of the five subunits are involved in acetylcholine binding. The remaining three peptide subunits participate in the signal transduction process that involves a protein conformational shift, allowing inward movement of sodium ions through the opened ion channel. It is interesting to note that the $GABA_A$ receptor also has been shown to be composed of five peptide subunits arranged to form a pentameric ring.[43,47-49]

Signal Transduction

In biology, *signal transduction* refers to processes by which a cell converts one kind of signal or stimulus into another. Most often, these involve ordered sequences or cascades of biochemical reactions inside the cell. They are commonly referred to as *second messenger pathways*. An example of a G protein–coupled receptor (GPCR) and its second messenger system is shown in Figure 5-1.

Many of the actions of the common anesthetic drugs are transduced through cell-surface receptors that are linked to GPCRs. Receptor signaling translates changes to G proteins that are then linked to a second messenger such as cyclic AMP (adenosine monophosphate) or cyclic GMP (guanosine monophosphate). These second messengers regulate enzymes such as protein kinases and phosphatases, which drive their ultimate intracellular actions.

Signal transduction for the $GABA_A$ receptor, for example, involves inward chloride ion movement through the opened central channel. The protein compositions of acetylcholine and GABA receptors are remarkably similar, despite their functional differences—specifically, acetylcholine and sodium ion transduce an excitatory signal, and GABA and chloride ion transduce an inhibitory signal.[50,51]

For many drugs, the composition of the receptor protein and the signal transduction process may be identical, even though the drug-induced tissue response is not. The primary difference among drug receptor proteins may be only the selective binding subunits and the ion species moving through the channel.[37,39,41,52,53] The specific peptide subunits are ultimately responsible for the pharmacologic properties of specificity, affinity, and potency.

In addition, specific isomers that have fewer side effects than the racemic mixture have been marketed. Drugs such as dexmedetomidine, ropivacaine, and cisatracurium are selective in their receptor binding and thus achieve a better clinical side effect profile.[54,55]

DRUG RESPONSE EQUATION

The drug response equation is fundamental to pharmacologic principles.[35] It is derived from the law of mass action and is shown in the following equation, where drug (D) combines with receptor (R) to form a drug receptor complex (DRC) that elicits a tissue response (TR).

$$D + R \rightleftharpoons (DRC) \rightleftharpoons TR$$

What remains unique about this equation is that in most cases, the drug receptor complex represents a highly selective process. Yet the resultant tissue response tends to vary from individual to individual, reflecting each individual's receptor and genetic profile and physiologic state. The basic drug response relationship conceptually depends on a common pharmacologic theory of drug action. This is the *occupancy theory*. Simply stated, the magnitude of a drug's effect is proportional to the number of receptors occupied. Although it is understood that drug receptor interactions have more complexity than this theory accounts for, it serves as a useful background for many pharmacologic concepts.

POPULATION VARIABILITY

Because the objective of pharmacologic intervention is to achieve a desired therapeutic response, anesthetists recognize that a range of responses to a given drug and dosage is possible within a patient population. Therapeutic drug doses reflect average doses of a "normal" population of individuals. Specific therapeutic doses for population subsets (e.g., pediatric, neonatal, geriatric, patients with cardiac or other chronic diseases) are available, thereby narrowing the degree of response variability for a given drug and clinical population. The age, sex, body weight, body surface area, basal metabolic rate, pathologic state, and genetic profile of an individual directly influence the pharmacologic response.

Given the increasing median age of the population in the United States, studies of the influence of age on the responses to anesthetic drugs have increased. Steady-state plasma concentrations of hypnotic drugs such as midazolam and propofol and minimum alveolar concentrations (MAC) for inhaled anesthetics (e.g., desflurane, isoflurane, or sevoflurane) required to achieve desired anesthetic end-points decrease as age increases, independent of any age effect on drug pharmacokinetics.[56,57-59] In addition, the effective plasma concentration 50 (median effective concentration [EC_{50}]) needed to achieve sedation with midazolam infusion is reported to be decreased by 50% in elderly volunteers.[57,60] Unfortunately, the specifics responsible for the observed age-related decrease in effective dose of anesthetic drugs is not presently known. Receptor changes associated with aging and kinetic differences in the elderly are in part responsible for the variation in response. Until a better understanding of the age-related changes exists, empirical dose reduction or the use of dosing algorithms for the elderly patient population is indicated.

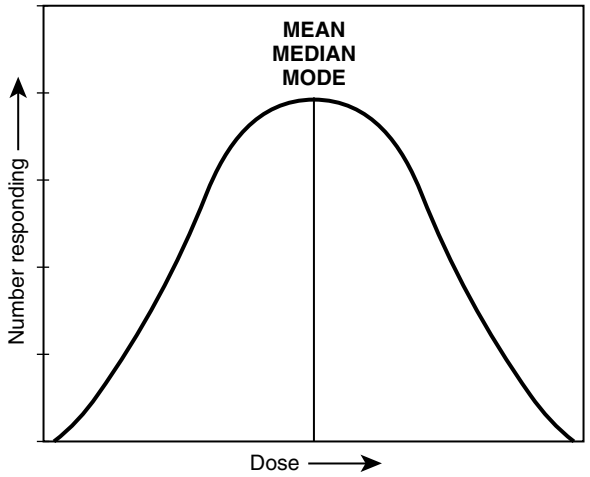

FIGURE **5-2** The theoretic normal frequency distribution of a drug response in a normal population.

Mean, Median, and Mode

A graphic description of the dose-response relationship is displayed in Figure 5-2. The theoretic normal distribution of quantal (desired) responses to increasing drug dose takes the shape of a Gaussian curve. Theoretically, the numbers of respondents on both sides of the mean (average dose) are equal, with the greatest percentage of individuals responding near the center of the curve. In a Gaussian distribution curve, the mean, median, and mode are equidistant from the two extremes.[61] Atypical responders fall at each end of the curve.

On the curve, the mean dose is the arithmetic average of the range of doses that produce a given response. The median dose is that dose on either side of which half of the responses occur. The mode dose is the dose representing the greatest percentage of responses. The mean, median, and mode doses are often close but are rarely the same in actual dose-response curves.

Standard Deviation

The terms *standard deviation* (SD) and *standard error of the mean* (SEM) describe population response variability.[62] The SD provides information regarding the actual responses measured and their difference from the calculated mean. In Figure 5-3, 1 SD makes up 68% of the responses (34% to the left and 34% to the right of the mean value); 2 and 3 SDs constitute 95% and 99.7% of the responses, respectively. The greater the SD, the less the mean reflects the central tendency of responses.

Standard Error of the Mean

The SEM describes the variance of the mean. It is equivalent to the SD of the mean. By repeating the dose-response measurements on different, normally distributed populations, a slightly different mean dose value is obtained each time because the mean value is only an arithmetic average of the responses obtained. In Figure 5-4, 1 SEM represents the range within which the mean value would occur on repeat testing 68% of the time, and 2 and 3 SEMs (not shown) represent the range within which the mean value

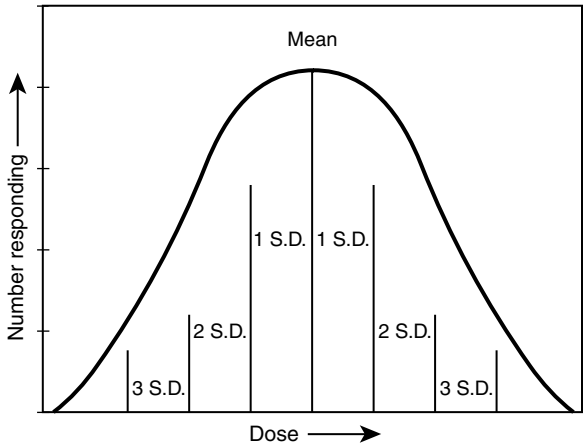

FIGURE **5-3** A normal distribution curve showing the standard deviation (SD) in relation to the mean (average) dose value.

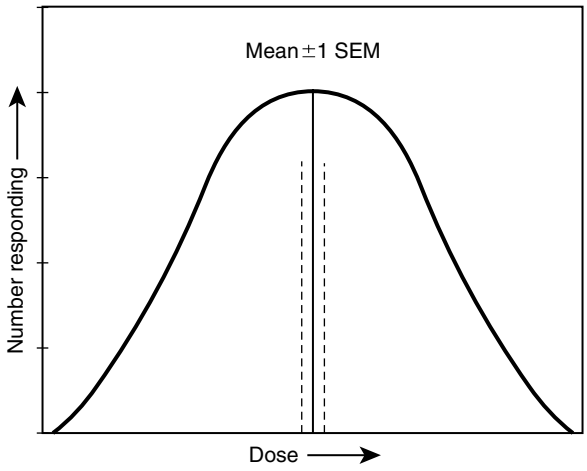

FIGURE **5-4** A normal distribution curve showing the relationship of the standard error of the mean (SEM) to the mean (average) value.

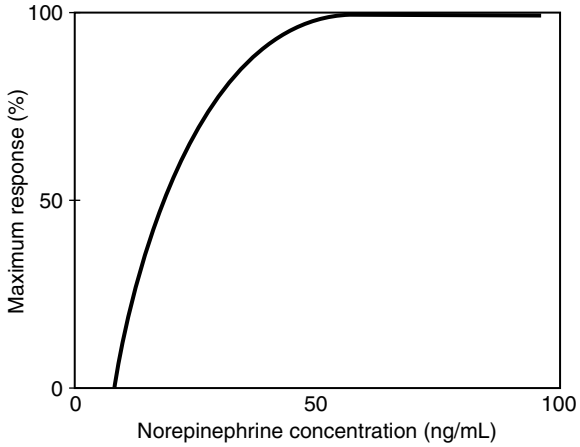

FIGURE **5-5** A linear arithmetic-graded response curve showing blood vessel constriction to increasing norepinephrine concentrations.

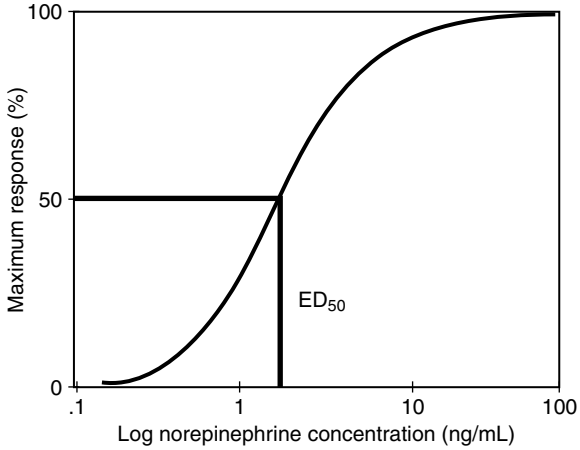

FIGURE **5-6** A logarithmic plot of the data from Figure 5-5 showing blood vessel constriction to increasing concentrations of norepinephrine. The median effective dose (ED_{50}) is identified.

would occur 95% and 99.7% of the time, respectively. Both the SD and the SEM are important statistical descriptors of observed drug responses in patient care and in research and reflect pharmacologic principles of population variance.[62]

DRUG DOSE RESPONSE

The administration of drugs is largely determined by a mean therapeutic dose per kilogram of body weight or body surface area calculated from a previously determined average dose for the normal population. This approach may be responsible for underdosing and overdosing of patients, because population variability is not considered in the calculation. The individual therapeutic response to a fixed mean dose is frequently less than optimal.

Studies that used sensitive quantitative measurement techniques identified a response variability to given drug doses in the normal population that was far greater than previously demonstrated.[25] Clearly, the optimal dosing approach for patients when drugs are administered by the intravenous route is by titration until the desired therapeutic response is attained. This is particularly true in critical care and anesthesia patients, in whom drug onset and offset responses are relatively rapid.

Two types of dose-response curves—graded and quantal—describe average drug response and subject variability within a given population.

Graded Dose Response

The graded dose-response curve, which is plotted in linear fashion, characterizes the change in measured response as an administered dose is increased (Figure 5-5). The response curve has a hyperbolic shape, with the greatest change in response occurring to the left on a small portion of the x-axis. When plotted on a logarithmic scale, the graded dose-response curve takes an S shape; at the lowest dose, the measured response (e.g., vascular response to norepinephrine) is small or even nonexistent. At the highest doses, the response is maximal and approaches a plateau (Figure 5-6). Typically, at some point between 20% and 80% of the maximal response, the curve approaches a straight line because changes in dose and response reflect a proportional relationship.

Plotting on a semilogarithmic scale, with the dose in log units, provides a more detailed representation of the entire graded dose-response curve, especially at the two extremes.[25] From a semilogarithmic plot of graded dose responses, the potency of different agonist drugs with similar mechanisms of action (i.e., action through the same receptor) can be compared, or the ability of an antagonist drug to reduce the response to an agonist (e.g., in the alpha receptor blocker, phenoxybenzamine antagonism of norepinephrine-induced vasoconstriction) can be observed. It should be noted that "antagonist" drugs that do not bind to the agonist receptor are actually not antagonists. For example, neostigmine

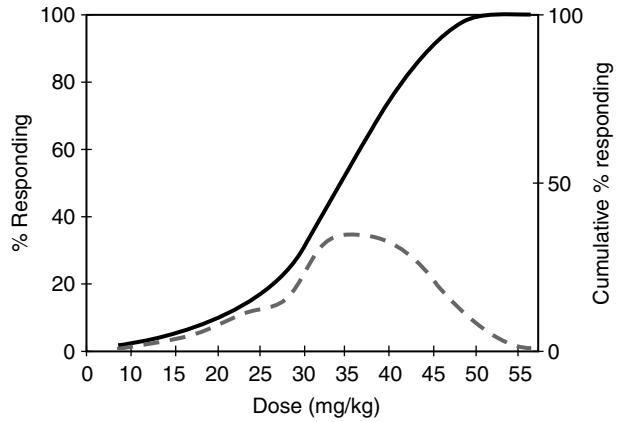

FIGURE **5-7** A quantal dose-response curve indicating the frequency of all-or-nothing dose responses. The *dashed line* represents a histogram of the number of responses measured at each dose. The *solid line* represents the cumulative response curve of the total number of responses up to and including each dose.

is not an antagonist of rocuronium, because it does not compete with rocuronium for the muscle end-plate receptor site. Neostigmine inhibits acetylcholinesterase, which allows acetylcholine to compete effectively with rocuronium and other nondepolarizing muscle relaxants for the receptor, leading to a recovery of muscle tone. Therefore, its effect is at least a partial form of indirect antagonism. Sugammadex is the first and so far only drug in a new class of muscle relaxant reversal drugs. Known as a *selective relaxant binding agent* (SRBA), sugammadex offers a unique mechanism in that it encapsulates the muscle-relaxant molecule, rendering it inactive. The complex formed is eliminated. This is a form of chemical antagonism, because no direct receptor action is evident.[63]

Quantal Dose Response

Clinically, a quantal dose-response curve provides information on the frequency with which a given drug dose produces a desired therapeutic response in a patient population. The response is measured in an all-or-nothing fashion. The quantal response curve describes the variation in response to the threshold dose within a population of seemingly similar individuals (Figure 5-7). For example, with propofol induction of anesthesia, a small number of patients become unconscious after administration of 0.5 mg/kg, more after administration of 1 mg/kg, and virtually all after administration of 2 to 3 mg/kg. Plotting the cumulative number of patients with all-or-nothing responses over a range of doses produces an S-shaped response curve. However, the quantal dose S-shaped curve differs from the graded dose-response S-shaped curve because it reflects population variation for the threshold dose needed to produce a given all-or-nothing desired response.

Descriptive information about population dose-response characteristics can be obtained from quantal dose-response curves.[25] Descriptors such as effective dose, toxic dose, and lethal dose can be identified. The effective dose 99% (ED_{99}) and lethal dose 1% (LD_1) identify the therapeutic safety margin of a drug, as shown in the following equation.

$$\text{Safety margin} = LD_1 - ED_{99} / ED_{99} \times 100$$

When the therapeutic safety margin is great, the risk of drug-induced death is small, and the margin of therapeutic safety is wide. The opposite is true when the therapeutic safety margin is small.

The term *therapeutic index* (LD_{50}/ED_{50}) describes a drug's median therapeutic safety margin for a particular therapeutic effect.[25] For example, chemotherapeutic drugs have a very narrow margin of safety. Drugs that produce surgical depths of anesthesia, such as sevoflurane and other halogenated anesthetics, also have a relatively narrow margin of safety. Sevoflurane is administered clinically in an amount that is 1.3- to 1.4-fold the MAC (minimum alveolar concentration), or the dose at which 50% of the patients do not move on surgical stimulation. The MAC can be lethal if the volume percentage delivered is increased to 1.7- to 2.0-fold and maintained for a prolonged period of time.

Another descriptor obtained from the quantal dose-response curve is the median effective dose (ED_{50})—the dose at which 50% of a population responds as desired. The ED_{50} is often used for comparing the potency of drugs within a class. Because the ED_{50} is derived from the linear portion of the quantal dose-response curve (20% to 80% of the responders), relatively accurate comparisons of drugs that cause similar responses can be made (see Figure 5-6). Important in each of these descriptions is the word *median*. Median ED_{50} dose values are derived average response doses from a population of patients.[25] Each individual within the population responds, more or less, to a median dose on the basis of his or her biologic variation or, specifically, genetic variations in drug-receptor protein. Confidence limits for a given median dose and its therapeutic response can be calculated. Typically, the proportion of subjects responding to an ED_{50} dose ranges from 45% to 55%. Derived median population dose values provide a point of reference for achieving an individual's optimum therapeutic dose.

For intravenously administered drugs used in anesthesia, the trend is toward drugs that have brief onset-offset times and can be administered by infusion, often with the use of a computer-controlled pump.[64,65] For example, the desired anesthetic response to propofol and remifentanil can be effectively titrated after an initial loading dose.

Future developments related to drugs will include the availability of indwelling drug-analyzing probes similar to the continuous mass spectrometers currently used for analysis of end-tidal anesthetic gas concentrations. Real-time analysis of drug concentration can incorporate feedback control to drug-infusion devices. These target-controlled infusions allow the dose to be set to patient response and automatically maintained with minimal fluctuations in blood and effect site drug concentrations and the tissue response.[66,67] Currently, computer-controlled infusion pumps use programs based on pharmacokinetic modeling studies in an attempt to approximate the required effect site drug concentration to achieve and maintain a desired level of anesthesia in patients. The continuing development of ultrafast onset-offset anesthetic drugs such as remifentanil and propofol will simplify titration of the anesthetic end-point by the anesthetist and minimize undesired effects.

DRUG RECEPTOR INTERACTIONS

Advances in molecular receptor pharmacology have provided a new understanding of patient drug responses.[26] The *drug receptor interaction* describes the formation of a single drug receptor complex, which leads to a fractional tissue response (FTR):

$$D + R \underset{k_2}{\overset{k_1}{\rightleftharpoons}} DR \overset{k_3}{\rightarrow} FT$$

The desired tissue response is observed when sufficient receptors have been occupied and activated by free drug. This process obeys the law of mass action: At steady state, equilibrium exists between bound and unbound drug receptors and the concentration of free unbound drug at the site. Specific characteristics of the drug and the receptor determine the association and dissociation of a drug with regard to its receptor and the kinetic, *k*, rates, which are constants.[35]

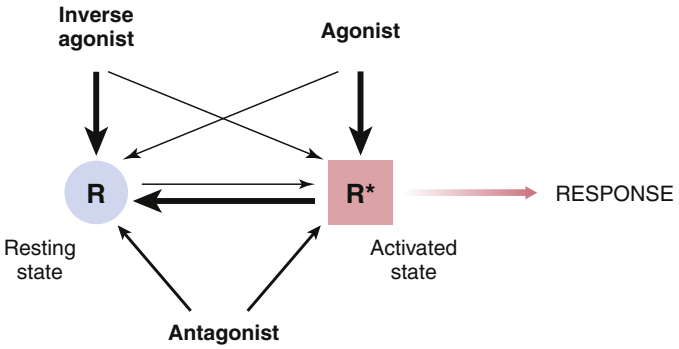

FIGURE **5-8** The two-state model. The receptor is shown in two conformational states, 'resting' (R) and 'activated' (R*), which exist in equilibrium. Normally, when no ligand is present, the equilibrium lies far to the left, and few receptors are found in the R* state. For constitutively active receptors, an appreciable proportion of receptors adopt the R* conformation in the absence of any ligand. Agonists have higher affinity for R* than for R, and so shift the equilibrium toward R*. The greater the relative affinity for R* with respect to R, the greater the efficacy of the agonist. An inverse agonist has higher affinity for R than for R*, and so shifts the equilibrium to the left. A 'neutral' antagonist has equal affinity for R and R*, and so does not by itself affect the conformational equilibrium but reduces by competition the binding of other ligands. (From Rang HP, et al. *Rang and Dale's pharmacology,* 7th ed. Edinburgh: Churchill Livingstone, 2012:14.)

Drug Affinity and Efficacy

The terms *affinity* and *efficacy* (intrinsic activity) describe the degree of drug receptor interaction for a given drug and receptor protein population (e.g., $GABA_A$ and propofol). The observed tissue response reflects the quantity of drug receptor complexes intact at any given moment. Each drug receptor interaction elicits a quantum of excitation, and the summation of many individual quanta produces the tissue response.[62]

The time constant that describes the fractional tissue response after the drug receptor complex formation typically has been considered to be near zero or instantaneous. Until recently, the primary time constant thought to influence the onset of tissue response was the duration of the delay in the delivery of drug to the receptor sites. The phrase *pharmacokinetic analysis* of drug absorption and distribution describes onset time and magnitude of drug response. *Drug elimination kinetic analysis* describes the duration of the tissue response.

Drug-Receptor-Response Triad

Current understanding of receptor dynamics has added an additional and possibly the most descriptive component of the drug-receptor-response triad. When a drug combines with its receptor, a conformational change occurs in the receptor protein itself. No tissue response can occur without the structural shift. Evidence does suggest that events within the biosphere after drug association with the receptor are the principal regulatory variables of the response onset-offset time course.[62] An additional theory of drug action is referred to as the *two-state model*. In this model, the receptor is thought to exist in equilibrium between either an activated or inactivated state. Constitutively active receptors can exist and are shifted toward the activated state, even though no agonist or ligand is present. Receptors for benzodiazepines, cannabinoids, and serotonin are examples. Agonists shift the equilibrium toward activation. Antagonists freeze the equilibrium, and inverse agonists shift the equilibrium toward inactivation.[68,69] The two-state model is shown in Figure 5-8.

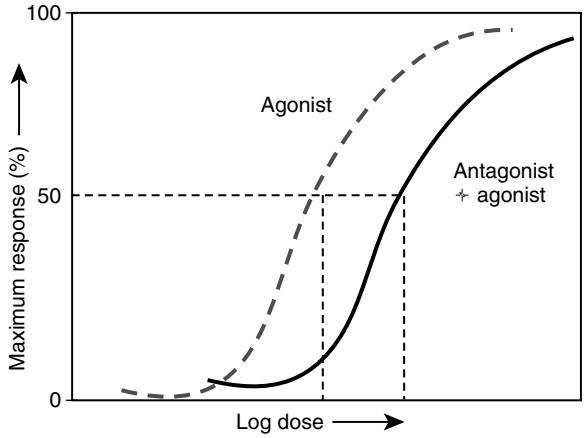

FIGURE **5-9** A logarithmic dose-response curve that shows an agonist drug response alone *(dashed line)* and in the presence of an antagonist drug *(solid line)*.

Until recently, the terms *drug absorption*, *distribution*, and *elimination* were used solely to describe the tissue-response time course.[70] However, the response may be more complex than was originally thought. It is now known that drug delivery sufficient to occupy 1% of the receptors is in many instances all that is required for a maximum tissue response to occur. Furthermore, the synthesis and destruction of receptor proteins occur at a much more rapid rate than was previously believed—within minutes rather than days. Receptor up-regulation and down-regulation can occur during drug infusion, with new receptor protein being synthesized in response to availability of free unbound drug.[25,26,71,72]

DRUG ANTAGONISM

Pure Antagonists

Pure pharmacologic antagonist drugs are similar in molecular structure to their corresponding agonist drugs. However, owing to the addition or subtraction of one or more chemical moieties, they are unable to initiate the receptor protein conformational shift necessary for eliciting a tissue response. Such antagonist drugs have receptor affinity but lack intrinsic activity or efficacy.

Antagonists that possess the property of weak affinity for the same receptor protein (e.g., atropine, esmolol) are competitive and may be displaced by an agonist. Noncompetitive antagonists, such as phenoxybenzamine and aspirin, have a strong affinity for the receptor protein, usually via covalent bonds, and cannot be displaced by the agonist.[73] New receptor protein must be synthesized if agonist receptor complexing is to occur.[72,73] As with agonist drugs, not all receptors are bound by antagonists. Antagonists cause a rightward shift in the drug dose-response curve. The extent of rightward shift reflects the number of available receptors occupied by the antagonist drug (Figure 5-9). Comparison of the ED_{50} in Figure 5-9 shows a reduced affinity of the agonist for its receptor when the antagonist is present.

Agonist-Antagonists

Agonist-antagonists are the second major type of antagonist drugs.[25] As the name implies, agonist-antagonist drugs have receptor protein affinity and intrinsic activity, but often only a fraction of the potency of the pure agonist. Narcotic antagonists often are of the nonpure, agonist-antagonist type, such as nalbuphine. The mechanism by which agonist-antagonist drugs elicit less of a tissue response is not fully understood. An incomplete receptor protein conformational shift has been suggested.

TABLE 5-1 Drug Interaction Terminology

Drug Interaction	Explanation	Viewed as an Equation
Addition	The combined effect of two drugs acting via the same mechanism is equal to that expected by simple addition of their individual actions.	1 + 1 = 2
Synergism	The combined effect of two drugs is greater than the algebraic sum of their individual effects.	1 + 1 = 3
Potentiation	The enhancement of the action of one drug by a second drug that has no detectable action of its own.	1 + 0 = 3
Antagonism	The action of one drug opposes the action of another.	1 + 1 = 0

Physiologic Antagonism

Physiologic antagonism, another form of antagonism, involves two agonist drugs that bind to different receptors.[25] For competitive antagonism, the agonist and antagonist have affinity for the same receptor protein; in contrast, in physiologic antagonism, both drugs bind to specific unrelated receptor proteins, initiate a protein conformational shift, and elicit individual tissue responses. The responses, however, generate opposing forces such as are observed with isoproterenol-induced vasodilation and norepinephrine-induced vasoconstriction. The net effect on blood pressure is less than it would be if either drug were used by itself. The drug response that predominates depends on the intrinsic activity of each and on the extent of the tissue response that can be elicited.

Chemical Antagonism

Chemical antagonism occurs when a drug's action is blocked and no receptor activity is involved. For example, protamine is a positively charged protein that forms an ionic bond with heparin, thus rendering it inactive. Sugammadex, mentioned previously, is another example.

Receptor Regulation and Adaptation

Receptors not only initiate regulation of physiologic and biochemical functions but also are themselves subject to many regulatory and homeostatic controls. These controls include regulation of the synthesis and degradation of the receptor by multiple mechanisms, covalent modification, association with other regulatory proteins, and/or relocation within the cell. Modulating inputs may come from other receptors, directly or indirectly, and receptors are almost always subject to feedback regulation by their own signaling outputs.

Continued stimulation of cells with agonists generally results in a state of desensitization, also referred to as *refractoriness* or *down-regulation*, such that the effect that follows continued or subsequent exposure to the same concentration of drug is diminished. This phenomenon is very important in therapeutic situations; an example is attenuated response to the repeated use of β-adrenergic agonists as bronchodilators for the treatment of asthma. Clinically the patient experiences tolerance; increasing doses are required to achieve the same effect.

Chronic administration of an antagonist results in up-regulation as the number and sensitivity of the receptors increase as a response to chronic blockade. Again the patient develops tolerance, requiring higher doses of the antagonist to counteract the increasing receptor number.

Drug Interaction Terminology

A drug interaction is an alteration in the therapeutic action of a drug by concurrent administration of other drugs or exogenous substances. The common classification is given in Table 5-1.

SUMMARY

The pharmacologic principles described in this chapter are essential to understanding drug responses in patients. The drug receptor subunit site is the primary regulator of onset-offset drug response. More and more evidence suggests that individual genetic variation in receptor proteins accounts for drug-response variation within seemingly normal populations. In clinical anesthesia, the range of patient responses to a given drug dose reflects this variation. The trend toward dosing by titration with rapid onset and offset anesthetic drugs minimizes the response variability factor by optimizing the use of available receptor proteins. The age-related decline in anesthetic drug dose needed to achieve a desired anesthetic end-point is related to a change in both pharmacodynamics and pharmacokinetics.

The anesthetist uses pharmacologic intervention to elicit a desired patient response. The site of the intervention is the biosphere, or the protein drug receptor, which is the primary regulator of the therapeutic response. Observed variation in patient drug response reflects the functionality of the biosphere and genetics, as well as physiologic variability.

The mean, median, and mode typically describe the dose-response relationship of a "normally distributed" population. In anesthesia, the patient population is rarely "normal." The drug response of population subsets can be expected to vary around the mean dosage. The trend toward dose titration by infusion allows individualization of the desired drug response, with fewer resultant overresponses and underresponses. The SD, SEM, and median effective dose provide a description of a population's response to a drug. Such descriptors provide only an approximate dosage; the anesthetist must adjust this dosage for each patient to achieve the desired physiologic response. Viewed at the molecular level, the observed response to a drug represents countless individual drug responses at the biosphere. Each drug-receptor interaction at the protein receptor elicits a fractional tissue response, and the sum of the fractional responses provides the observed response. In accordance with the law of mass action, when free drug binds to a receptor, a conformational shift occurs in the receptor protein. This shift causes a central space or channel to open, allowing specific ions to enter or leave the cell or a G protein to be activated, resulting in a biochemical cascade yielding pharmacologic effects. The resultant tissue response continues until the drug dissociates from the receptor. Antagonist drugs also bind to the receptor but lack the ability to initiate the required protein conformational shift. The sum of fractional tissue responses elicited when an antagonist is present is inadequate for maintaining the desired tissue response. Some common pharmacodynamic concepts are given in Box 5-2.

Molecular pharmacology is identifying site-specific and age-related causes for the observed variation in patient drug response. The fact that we can now sequence and clone many of the receptors and other proteins responsible for a drug's action is rapidly increasing our understanding of pharmacologic events.

BOX **5-2**

Pharmacodynamic Concepts

- **Agonist:** An agonist is a substance that binds to a specific receptor and triggers a response in the cell. It mimics the action of an endogenous ligand (such as hormone or neurotransmitter) that binds to the same receptor. In adequate concentrations, it can cause maximal activation of all receptors (a full agonist).
- **Antagonists:** An antagonist is a drug that has affinity for the receptor but no efficacy. It does not activate the receptor to produce a physiologic action. By occupying the receptor, it may block an endogenous chemical response, thereby producing a physiologic consequence. Antagonists commonly have a higher affinity for a given receptor than do agonists. Types of antagonism include pharmacologic, in which competitive is reversible and noncompetitive is irreversible, requiring syntheses of new receptors to reestablish homeostasis. Pharmacokinetic, chemical, and physiologic antagonism may also occur.
- **Affinity or potency:** When considering agonists, the term *potency* is used to differentiate between different agonists that activate the same receptor and can all produce the same maximal response (efficacy) but at differing concentrations. The most potent drug of a series requires the lowest dose.
- **Efficacy or intrinsic activity:** The efficacy of a drug is its ability to produce the desired response expected by stimulation of a given receptor population. It refers to the maximum possible effect that can be achieved with the drug. The term *intrinsic activity* is often used instead of efficacy, although this more accurately describes the relative maximum effect obtained when comparing compounds in a series.
- **Partial agonist:** A partial agonist activates a receptor but cannot produce a maximum response. It may also be able to partially block the effects of full agonists. It is postulated that partial agonists possess both agonist and antagonist properties, thus the term *agonist-antagonist* has been used. A partial agonist has a lower efficacy than a full agonist.
- **Inverse agonist:** A drug or endogenous chemical that binds to a receptor, resulting in the opposite action of an agonist. Using the two-state model, they appear to bind preferentially to the inactivated receptor. They may have a theoretic advantage over antagonists in situations in which a disease state is partly due to an up-regulation* of receptor activity.
- **Spare receptor concept:** The relationship between the number of receptors stimulated and the response is usually nonlinear. A maximal or almost maximal response can often be produced by activation of only a fraction of the receptors present. A good example can be found in the neuromuscular junction. Occupation of more than 70% of the nicotinic cholinergic muscle receptors by an antagonist is necessary before there is a reduction in response, implying that a maximal response is obtained by activation of only 30% of the total number of receptors.
- **Tolerance:** Individual variation can result in a situation in which an increasing concentration of drug is required to produce a given response. This usually results from its chronic exposure to the agonist. Very rapid development of tolerance, frequently with acute drug administration, is referred to as *tachyphylaxis.* The underlying mechanism may not be clear. Common causes include up- or down-regulation, enzyme induction, depleted neurotransmitter, protein conformational changes, and changes in gene expression.
- **Ligand:** In biochemistry, a ligand is a molecule that is able to bind and form a complex with a receptor to produce a biologic response. Ligands are endogenous chemicals such as neurotransmitters and hormones that are exogenously administered drugs.
- **Quantal drug response:** Using dose response curves, the actions of drug can be quantified and expressed as the effective dose ED_{50}, toxic dose TD_{50}, and lethal dose LD_{50}. The therapeutic index is the LD_{50}/ED_{50}.
- **Receptor adaptation or homeostasis:** The number and activity of a receptor population may increase or decrease in response to (usually) chronic drug administration.

**Up-regulation* is the process by which a cell increases the number of receptors to a given drug. *Down-regulation* is the process by which a cell decreases the number of receptors for a given drug in response to chronic stimulation. β-adrenergic receptors, for example, up-regulate in the presence of antagonists and down-regulate in the presence of agonists.

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CHAPTER 6

Pharmacokinetics

◆ *Ladan Eshkevari and Donna Jasinski*

Pharmacokinetics is a term used to describe the study of the changes in the concentration of a drug during the processes of absorption, distribution, metabolism or biotransformation, and elimination from the body. Essentially, it is the study of what the body does to a drug once the agent has been introduced into the system. The knowledge of this discipline is important to understanding the time course and disposition of the anesthetic drugs and the variability of responses from patient to patient. Knowledge of pharmacokinetic concepts is vital for the delivery of serum concentrations that will result in desired effects while minimizing side effects.

Regardless of the route of administration, the vascular system delivers the drug to various tissues. Therefore most kinetic concepts revolve around assessment of blood level over time, even if the correlation with the amount of drug at the effector site is poor. Once in the blood, the drug can either remain within the vascular system and body water, bound to proteins, or cross membranes to enter tissues. The unbound drug enters organs, muscles, fat, and of greatest importance, the site of activity—the receptors. This transfer of drug to various sites depends on several intrinsic properties of the agent, such as molecular size, degree of ionization, lipid solubility, and protein binding. In addition to these drug properties, uptake also depends on the amount of blood flow to the tissue and the concentration gradient of the drug across membranes.

PROPERTIES THAT INFLUENCE PHARMACOKINETIC ACTIVITY

Molecular Size

The smaller the molecular size of an agent, the better it crosses the lipid barriers and membranes of tissues. When a drug is administered, it must be absorbed across biologic membranes that have very small openings or pores. Generally, molecules with molecular weights greater than 100 to 200 do not cross the cell membranes. Transport across the membranes can occur passively or actively. Passive transport does not require energy and involves transfer of a drug from an area of high concentration to an area of lower concentration. Active transport mechanisms are generally faster and require energy. This transport system uses carriers that form complexes with drug molecules on the membrane surface and can involve movement of the drug molecule against a concentration gradient from an area of low concentration to an area of high concentration.[1] Figure 6-1 depicts the movement of a drug across cell membranes.

Drug Transporters

Many cell membranes possess specialized transport mechanisms that control entry and exit molecules, such as sugars, amino acids, neurotransmitters, and metal ions. They are broadly divided into *solute carrier (SLC) transporters* and *adenosine triphosphate (ATP)–binding cassette (ABC) transporters*. The SLCs control passive movement of solutes down their electrochemical gradient. The ABCs are active pumps requiring energy derived from adenosine triphosphate. Over 300 human genes are believed to code these transporters, most of which act on endogenous substrates; however, some drugs are also transported. Other SLCs are coupled to ATP-dependent ion pumps and transport can occur against an electrochemical gradient. It may involve exchange of one molecule for another called *antiport* or transport of two molecules together in the same direction referred to as *symport*. The main sites where SLCs, including organic cation transporters (OCTs) and organic anion transporters (OATs), are important are the blood-brain barrier, gastrointestinal tract, renal tubule, biliary tract, and placenta. Drug transporters are recognized as key players in the pharmacokinetic processes. Transporter proteins have a unique gatekeeper function in controlling drug access to metabolizing enzymes and excretory pathways. This can affect bioavailability, clearance, volume of distribution, and half-life for orally dosed drugs. A classification model referred to as the Biopharmaceutics Drug Disposition Classification System (BDDCS) categorizes drug transporter effects.[2,3]

Degree of Ionization and Lipid Solubility

Most drugs are salts of either weak acids or weak bases. When introduced into the body, they behave as a chemical in solution. As acids or bases they exist in solutions in both ionized and nonionized forms. The charged (ionized) form is water soluble, and the uncharged (nonionized) form is lipophilic. Because the nonionized molecules are lipid soluble, they can diffuse across cell membranes such as the blood-brain, gastric, and placental barriers to reach the effect site. On the other hand, the ionized molecules are usually unable to penetrate lipid cell membranes easily because of their low lipid solubility. This results from the electric charges exerted by the ionized drug molecules. These charged drugs are repelled by those sections of the cell membranes with similar charges, preventing their diffusion across the membrane.[1] The higher the degree of ionization, the less access the drug has across tissues such as the gastrointestinal tract, the blood-brain and placental barriers, and liver hepatocytes. This is important in that ionized drugs are not absorbed well when taken orally and may not be metabolized by the liver to a significant extent. Instead, they commonly are excreted via the renal system.[4]

Whether acidic or basic, the degree of ionization of an agent at a particular site is determined by the dissociation constant (pK_a) of the agent and its pH gradient across the membrane. The pK_a is the negative log of the equilibrium constant for the dissociation of the acid or base. The relationship between the pK_a of the drug and the pH of the solution may be expressed by two equations. The first equation applies to drugs that are basic in nature:

$$pK_a = pH = \log \frac{(HA^+)}{(A^-)}$$

The second equation applies to acidic drugs:

$$pK_a = pH = \log \frac{(A^-)}{(HA^+)}$$

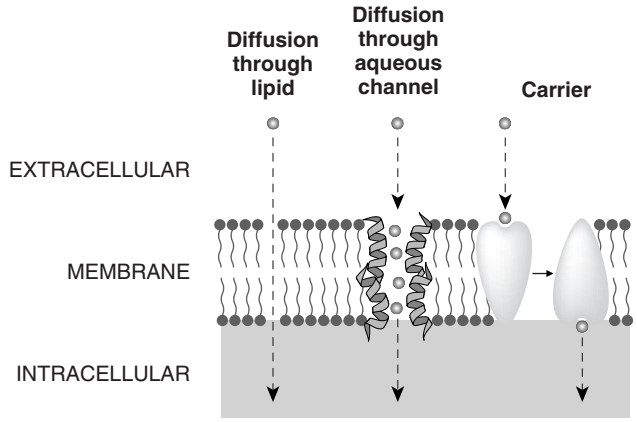

FIGURE **6-1** Routes by which solutes can traverse cell membranes. (From Rang HP, et al. *Rang and Dale's Pharmacology*. 7th ed. Edinburgh: Churchill Livingstone; 2012:100.)

From these equations an estimate of the degree of drug absorption can be developed.[4,5] Acids are usually defined as proton donors, whereas bases are made up of molecules that can accept a proton. When the pH is equal to the pK_a, the two species exist in equal amounts; for example, because phenobarbital has a pK_a of 7.4 and blood has a pH of 7.4, in the bloodstream the drug is present in equal proportions of charged and uncharged forms.

It is of importance to note that relatively modest changes in the pH of the environment, when it is close to the pK_a, are more significant in changing the ratio of charged to uncharged forms than the same change in pH at some value far removed from the pK_a. For example, phenobarbital, with a pK_a of 7.4, is for the most part nondissociated and therefore is nonionized at a pH of 1.4. This results from the fact that the pH is well below the pK_a, and when phenobarbital is in a relatively strongly acidic environment with an abundance of protons, it does not give up its protons readily. If a drug is a weak acid and if the pH of the fluid environment is below the pK_a, most of the drug's protons are associated with the drug molecule, and the predominant species is uncharged and therefore lipid soluble (Figure 6-2). Conversely, if the pH is below the pK_a for a drug that is a weak base, an abundance of protons exists, and most of the drug tends to ionize as the proton is donated by the drug molecule, which results in a species that is highly charged and therefore lipid insoluble[4] (Figure 6-3). The effects of pK_a and pH on ionization are summarized in Box 6-1.[6]

Ion Trapping

Ion trapping has several anesthesia-related applications. Influences on oral absorption of drugs, maternal-fetal transfer, and central nervous system toxicity of local anesthetics are commonly cited. The degree of ionization for a specific agent can vary across a membrane that separates fluids with different pH values. For example, morphine sulfate, a base with a pK_a of 7.9 when present in the blood (pH 7.4), exists in appreciable amounts in both ionized and nonionized forms. The uncharged drug fraction moves freely across tissue membranes, and the charged fraction does not. As the drug enters the stomach, a very acidic environment with a pH of 1.9, morphine accepts protons and becomes ionized, and ion trapping occurs[4] (Figure 6-4 illustrates this phenomenon using diazepam as an example). The drug, however, will be absorbed later, as stomach contents move farther down the gastrointestinal tract to the more basic and favorable environment of the small intestine.

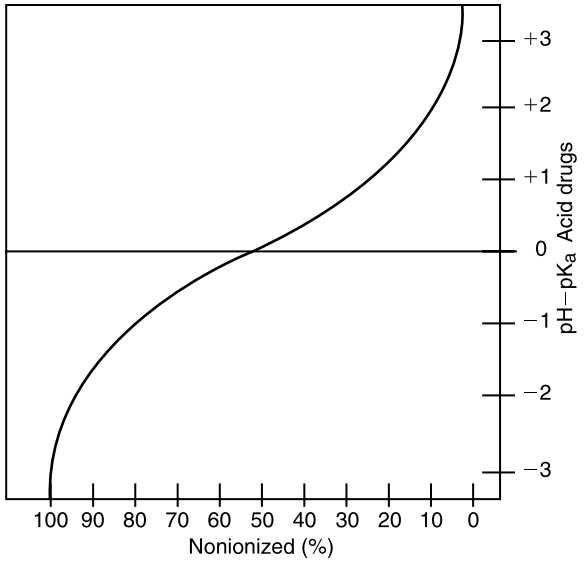

FIGURE **6-2** When acidic drugs are placed in physiologic solutions, the degree of nonionization is greater if the pH of the solution minus the pK_a of the drug (pH − pK_a) is less than zero. Conversely, when the pH − pK_a is greater than zero, more of the drug exists in an ionized, less absorbable form.

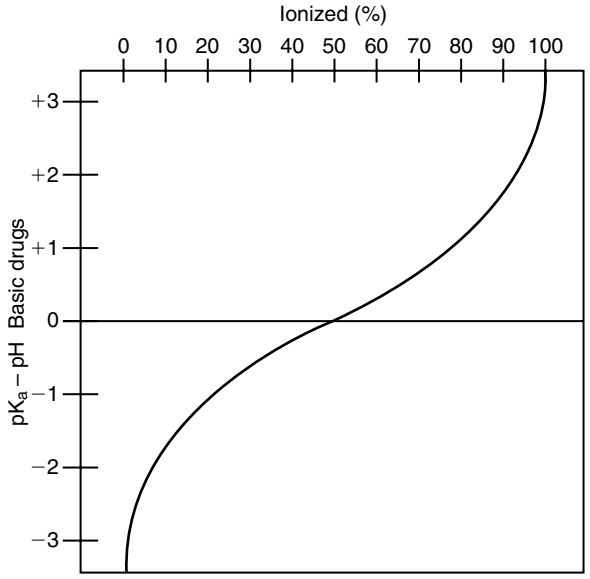

FIGURE **6-3** pK_a − pH versus the percent ionized. The degree to which a basic drug remains in its nonionized state depends on the medium in which it is placed. pK_a is the dissociation constant (see text for further explanation).

A similar scenario occurs when agents are transferred between a mother and a fetus, where the placenta is the membrane separating fluids with varying pH values—that of the fetus is more acidic than that of the mother. Again, the lipid-soluble fraction of basic agents such as lidocaine (pK_a 7.9) crosses to the placenta easily. However, once there, because of the lower pH of the fetus, the drug becomes more ionized and cannot easily cross the lipid bilayer of placenta, resulting in accumulation of drug in the fetus. Finally, ion trapping may occur in a local anesthetic overdose situation in which high concentrations of a basic local anesthetic agent have entered the central nervous system and caused toxicity. If the patient experiences respiratory arrest and hypoxia, the resulting

BOX 6-1

Relationship Between pH, pK_a, and Ionization for Weak Acids and Weak Bases*

Weak Acids

- If the pK_a – pH is 1 or higher and the pH is lower than the pK_a, then the drug is essentially 100% nonionized and in a lipid-soluble form. It will easily cross biologic membranes.
- If the pH – pK_a is 1 or higher and the pH is higher than the pK_a, then the drug is essentially 100% ionized and in a water-soluble form. It will not cross biologic membranes.

Weak Bases

- If the pK_a – pH is 1 or higher and the pH is lower than the pK_a, then the drug is essentially 100% ionized and in a water-soluble form. It will not cross biologic membranes.
- If the pH – pK_a is 1 or higher and the pH is higher than the pK_a, then the drug is essentially 100% nonionized and in a lipid-soluble form. It will easily cross biologic membranes.

For Both Weak Acids and Weak Bases

- If the pK_a – pH is less than 1 regardless of whether the pH is lower or higher than the pK_a, the drug will be partially ionized (water soluble) and partially nonionized (lipid soluble), and if the dose is adequate, the nonionized fraction can cross biologic membranes.

**Rule of thumb for determining ionization: Use absolute values for all calculations.*

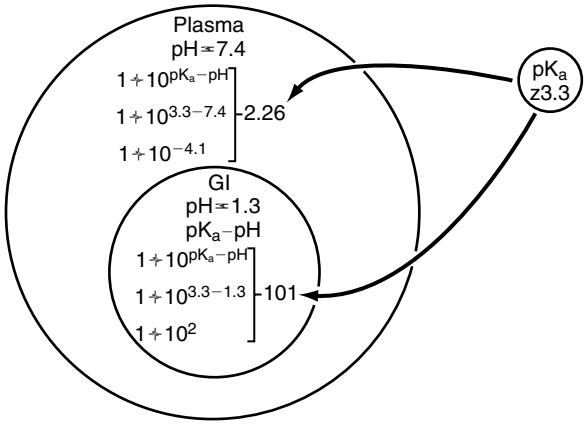

FIGURE **6-4** For both weak acids and weak bases, the total concentration of a drug is greater on the side of the membrane where it is more highly ionized. Diazepam, a basic drug with a pK_a of 3.3, is more ionized at gastric pH than it is in plasma. Consequently, it has a greater total concentration in the gastrointestinal compartment than it does in the plasma.

acidosis may trap the drug in the brain, resulting in prolonged and possibly more intense toxicity. Ion trapping also plays a role in the use of bicarbonate solutions and carbonated local anesthetics. A discussion of the effects of ion trapping on local anesthetics can be found in Chapter 10, Box 10-3.[7,8]

Protein Binding

Changes in protein binding have long been theorized to influence a drug's clinical effect. Two situations are commonly cited. The first involves a patient with a reduction in proteins, such as occurs with severe liver or kidney disease, with protein deficiencies caused by poor nutrition, and during the last trimester of pregnancy, when fluid shifts alter distribution volume. The second situation involves a drug interaction between two or more highly protein-bound drugs.

BOX 6-2

Binding of Drugs to Plasma Proteins

- Plasma albumin is most important; β-globulin and α_1-acid glycoprotein also bind some drugs.
- Plasma albumin binds, for the most part, acidic drugs (approximately two molecules per albumin molecule). Basic drugs may be bound by β-globulin and α_1-acid glycoprotein.
- Saturable binding sometimes leads to a nonlinear relationship between dose and free (active) drug concentration.
- Extensive protein binding slows drug elimination (metabolism and excretion by glomerular filtration).
- Competition between drugs for protein binding rarely leads to clinically important drug interactions.

Modified from Rang HP, et al. *Rang and Dale's Pharmacology.* 7th ed. Edinburgh: Churchill Livingstone; 2012:106.

Potential clinical changes are conceptualized by the following phenomena. Some drugs are bound extensively to proteins in the plasma because of their innate affinity for circulating and tissue proteins. The drug-protein molecule is too large to diffuse through blood vessel membranes and is therefore trapped within the circulatory system. Albumin is quantitatively the most abundant plasma protein, and although it is capable of binding basic, neutral, or acidic drugs, it favors acidic compounds. Two other proteins, α_1-acid glycoprotein (AAG) and β-globulin, favor binding to basic drugs.[9] Lipoproteins bind cyclosporine, and transcortin binds corticosteroids. Protein binding influences how a drug is distributed, because protein-bound drug is not free to act on receptors. High protein binding prevents the drug from leaving the blood to enter into tissue, which results in high plasma concentrations. The degree of protein binding for a drug is proportional to its lipid solubility such that the more lipid soluble an agent, the more highly protein bound it tends to be (Box 6-2).[10]

The number of potential binding sites on plasma proteins for drugs is finite; therefore the kinetics for binding behaves like any saturable process, in that protein binding can be overcome by adding more agent.[4] The bond between drug and protein is usually weak, and they can dissociate when the plasma concentration of the drug declines or a second drug that binds to the same protein is introduced. For example, when a drug has been in chronic use and is at steady state, an equilibrium will be reached between free and protein-bound drug. If a new drug with a high affinity for the same protein sites is introduced, the new drug competes with the chronic drug for binding sites. This leads to displacement of the first drug with an increase in free fraction of that agent. It is important to note that the displaced free drug does become available for biotransformation and elimination, so unless these clearance mechanisms are at capacity, a rise in free fraction will lead to a small change in free plasma concentrations.

Protein binding is expressed in terms of the percentage of total drug bound. Drugs with protein binding greater than 90%, such as warfarin, phenytoin, propranolol, propofol, fentanyl and its analogs, and diazepam, are conceptualized to have an unexpected intensification of their effect if they are displaced from plasma proteins.[11] Drugs that exhibit less than 90% binding have so little change in free active fractions that they are not a concern. The anticoagulant warfarin is commonly used as an example.

TABLE 6-1 Routes of Administration

Route	Bioavailability (%)	Comments
Intravenous	100 (by definition)	Most rapid onset; allows for titration of doses; suitable for large volumes
Intramuscular	75 to 100	Moderate volumes feasible; may be painful
Subcutaneous	75 to 100	Smaller volumes than intramuscular; may be painful; suitable for implantation of pellets
Oral	5 to 100	Most convenient and economical; first-pass effect may be significant; requires patient cooperation
Rectal	30 to 100	Less first-pass effect than oral; useful in pediatric patients
Inhalation	5 to 100	Common anesthetic use for inhalation drugs, steroids, bronchodilators, and occasionally resuscitative drugs; very rapid onset (parallels intravenous administration)
Sublingual	60 to 100	Lack of first-pass effect; absorbed directly into systemic circulation
Intrathecal	Low (intentionally)	Specialized application, as with local anesthetics and analgesics, chemotherapy, and antibiotic administration; circumvents blood-brain barrier
Topical	80 to 100	Includes skin, cornea, buccal, vaginal, and nasal mucosa; dermal application results in slow absorption; used for lack of first-pass effect; prolonged duration of action

Because warfarin is approximately 98% bound to plasma proteins, a reduction in bound fraction to 96% causes an increase in the free active fraction of the drug. Furthermore, when hypoalbuminemia exists, decreased albumin levels result in the availability of a greater amount of free drug. These theoretic concerns are rarely clinically relevant, as explained subsequently.

No clinically relevant examples of changes in drug disposition or effects can be clearly ascribed to changes in plasma protein binding. The idea that a drug displaced from plasma proteins increases the unbound drug concentration, increases the drug effect, and perhaps produces toxicity seems a simple and obvious mechanism. Unfortunately this simple theory, which is appropriate for a test tube, does not work in the body, which is an open system capable of eliminating unbound drug.[12]

First, a seemingly dramatic change in the unbound fraction from 1% to 10% releases less than 5% of the total amount of drug in the body into the unbound pool because less than one third of the drug in the body is bound to plasma proteins, even in the most extreme cases (e.g., when warfarin is used). Drug displaced from plasma protein, of course, distributes throughout the volume of distribution, so a 5% increase in the amount of unbound drug in the body produces at most a 5% increase in pharmacologically active unbound drug at the site of action.

Second, when the amount of unbound drug in plasma increases, the rate of elimination increases (if unbound clearance is unchanged), and after four half-lives, the unbound concentration returns to its previous steady-state value. When drug interactions associated with protein binding displacement and clinically important effects have been studied, it has been found that the displacing drug is also an inhibitor of clearance, and it is the change in *clearance* of the *unbound* drug that is the relevant mechanism explaining the interaction.

The clinical application of plasma protein binding is only to help interpretation of measured drug concentrations. When plasma proteins are lower than normal, total drug concentrations are lowered, but unbound concentrations are not affected.[1]

Absorption

Routes of Drug Administration

An important variable in the bioavailability of a drug at its effect site is the route by which the agent is administered. The route of administration determines how much of the drug is delivered to the systemic circulation. When the entire amount of drug given is delivered, the drug is said to have *100% bioavailability*. Many routes of drug administration are used; each has advantages and disadvantages (Table 6-1). The routes of drug administration are enteral (involves the gastrointestinal tract); parenteral (injected subcutaneously, intramuscularly, intravenously, intrathecally, or epidermally); pulmonary; and topical.[13] Absorption mechanisms of relevance to anesthesia are discussed in the following sections.

Enteral Administration. The oral route is the most common and convenient method for administration of drugs. It is relatively inexpensive, does not require sterile technique, and can be carried out with little skill. However, several disadvantages exist because many conditions—such as emotions, physical activity, and food intake—change the gastrointestinal environment. Therefore orally administered drugs tend to have a lower bioavailability. The stomach has a large surface area, and the length of time a drug remains there is a significant factor in absorption. Because of the low pH in the stomach (1.5 to 2.5), drugs that are highly acidic, such as barbiturates, tend to remain nonionized and are highly absorbed. Basic drugs that remain intact in the stomach acids can pass through and are more readily absorbed in the intestine. The small intestine is highly vascular and has an alkaline environment (pH 7 to 8).[13]

The enteral route often results in failure of the drug to be absorbed into the systemic circulation. Alternatively, chemical alteration may occur before entry into the intestines. *Presystemic elimination* refers to the elimination of drug by the gastrointestinal system before the drug reaches the systemic circulation. This occurs by means of three mechanisms: the stomach acids hydrolyze the drug (e.g., penicillin); enzymes in the gastrointestinal wall deactivate the drug; or the liver biotransforms ingested drug before it reaches the effect site.[4] This liver activity is called *first-pass* hepatic effect. Drugs absorbed from the gastrointestinal tract after oral ingestion enter the portal venous blood and pass through the liver first, with subsequent delivery to the tissue receptors. In the liver they may undergo extensive hepatic extraction and metabolism before they have a chance to enter the systemic circulation (Box 6-3). Agents such as these exhibit large differences between oral and intravenous dosages. To have the desired effect, oral dosages must be exaggerated to compensate for the initial metabolism that occurs before the drug reaches the effect site.

The role transporters play in drug absorption and distribution should be further clarified. P-glycoprotein transporter is part of a larger family of efflux transporters found in the intestine, liver cells, renal proximal tubular cells, and capillary endothelial cells comprising the blood-brain barrier. Using ATP as an energy

BOX **6-3**

Examples of Drugs That Undergo Substantial First-Pass Elimination

- Aspirin
- Glyceryl trinitrate
- Isosorbide dinitrate
- Levodopa
- Lidocaine
- Metoprolol
- Morphine
- Propranolol
- Salbutamol
- Verapamil

Modified from Rang HP, et al. *Rang and Dale's Pharmacology.* 7th ed. Edinburgh: Churchill Livingstone; 2012:118.

source, they transport substances against their concentration gradients. They appear to have developed as a mechanism to protect the body from harmful substances and can influence the ability of a drug to traverse barriers.

The sublingual and buccal routes of administration of drugs bypass the presystemic, portal system first-pass effect and are delivered rapidly to the superior vena cava for transport to the effect site.[1] Nitroglycerin is an example of a sublingual drug that is put under the tongue and absorbed by the rich blood supply there. If ingested, the drug would be hydrolyzed by the stomach; therefore sublingual administration is the ideal route for this agent. Protein hormones that would also be digested by the stomach are instead placed between the gum and cheek (buccal administration) and enter venous drainage without undergoing hepatic, presystemic elimination.[14,15]

Occasionally the rectal route of drug administration is the ideal route for prevention of emesis caused by irritation of the gastrointestinal mucosa by the drug. It is also a preferred method of drug delivery for patients in whom oral ingestion poses difficulty. For example, rectal acetaminophen is administered to infants and young children undergoing general anesthesia for postoperative pain control. Drugs placed in the proximal rectum are absorbed into the portal system via the superior hemorrhoidal vein. They will therefore undergo significant first-pass effect in the liver before entering the systemic circulation, leading to unpredictable responses.[1] Conversely, agents placed in the distal rectum do not undergo presystemic elimination and therefore have more predictable circulatory levels. The disadvantage historically associated with this route was the unpredictability of drug retention and absorption because of rectal contents. However, more recent studies have demonstrated that regardless of enema volume, agents are absorbed with consistent plasma concentrations within subjects.[16]

Parenteral Administration. *Parenteral administration* refers to administration by injection. The most rapid and predictable route to the systemic circulation is the parenteral route. With intramuscular injections, the drug is instilled deep into the muscle among the muscle fascicles.[4] Subcutaneous agents are placed under the skin. With both intramuscular and subcutaneous injections, the systemic absorption of the drug is dependent on the capillary blood flow to the area and the lipid solubility of the agent.[1] Conversely, intravenous injections allow for rapid and accurate delivery of drug into the systemic circulation. Parenteral administration is the route of choice for anesthetists, because it is an exact method of achieving the desired effect from agents delivered.

Pulmonary Administration. The lungs provide a large surface area for drugs administered by inhalation. Bronchodilators and antibiotics are administered via devices such as nebulizers, used to propel aerosols into the alveolar sacs.[16] Anesthetic gases are also effectively administered through the lungs, as described in detail in Chapter 7.

Transdermal (Topical) Administration. The transdermal route is usually chosen for administration of a sustained release agent, providing the patient with a steady therapeutic plasma concentration. Drugs that are administered via this route must possess several characteristics. They usually exist in a combined form—both water soluble and lipid soluble. The water solubility is necessary so the drug can penetrate the hair follicles and sweat ducts. Once in the system, the drug must be lipid soluble to traverse the skin and exert effect at the receptors. These agents must have a molecular weight of less than 1000, dose requirements less than 10 mg in a 24-hour period, and a pH of 5 to 9.[1] The area to which the drug is applied must have a relatively thin epidermis with a sufficient blood supply (Figure 6-5).

Bioavailability

Bioavailability is the extent to which a drug reaches its effect site after its introduction into the circulatory system. The rate at which systemic absorption occurs establishes a drug's duration of action and intensity. Many factors play a role in the bioavailability of agents, including lipid solubility, solubility in aqueous and organic solvents, molecular weight, pH, pK_a, and blood flow. For example, drugs given in aqueous solution are more rapidly absorbed than those given in oily solution or solid form because they mix more readily with the aqueous phase at the absorptive site.[17,18] A recent study demonstrated that propofol in the form of a water-soluble prodrug is metabolized to propofol with a longer half-life, increased volume of distribution, delayed onset, and greater potency.[19]

The environment into which the drug is introduced also has an impact on its bioavailability. The patient's age, sex, pathology, pH, blood flow, and temperature are all factors to consider. For example, pH plays a role when local anesthetic (a weak base) is injected into an infected wound (an acidic environment). In this instance, the local anesthetic is highly ionized (basic agent in acidic environment) and therefore cannot enter the lipid nerve membrane to reach the site of action. Some important concepts influencing absorption are listed in Box 6-4.

Distribution

Compartment Models

Compartment models depict the body as composed of distinct sections that represent theoretic spaces with calculated volumes and are used to describe the pharmacokinetics of agents. These models are useful for prediction of serum concentrations and changes in drug concentrations in other tissues. A single-compartment model represents the entire body, through which homogeneous distribution occurs (Figure 6-6, *A*). Although a one-compartment model is sufficient to describe the action of many drugs, it is generally insufficient to explain the kinetics of lipid-soluble anesthetic drugs. A two-compartment model is typically used to simplify and explain pharmacokinetic concepts that can be extrapolated to more complex models.[20]

In the two-compartment model, the first compartment is termed the *central compartment* and is composed of intravascular fluid and the highly perfused tissues such as the heart, lungs, brain, liver, and kidneys (see Figure 6-6, *B*). The central compartment represents only approximately 10% of body mass in an adult; however, it receives approximately 75% of the cardiac output and is also referred to as the *vessel-rich group*. The peripheral compartment (vessel-poor group) is composed of muscle, fat, and bone and

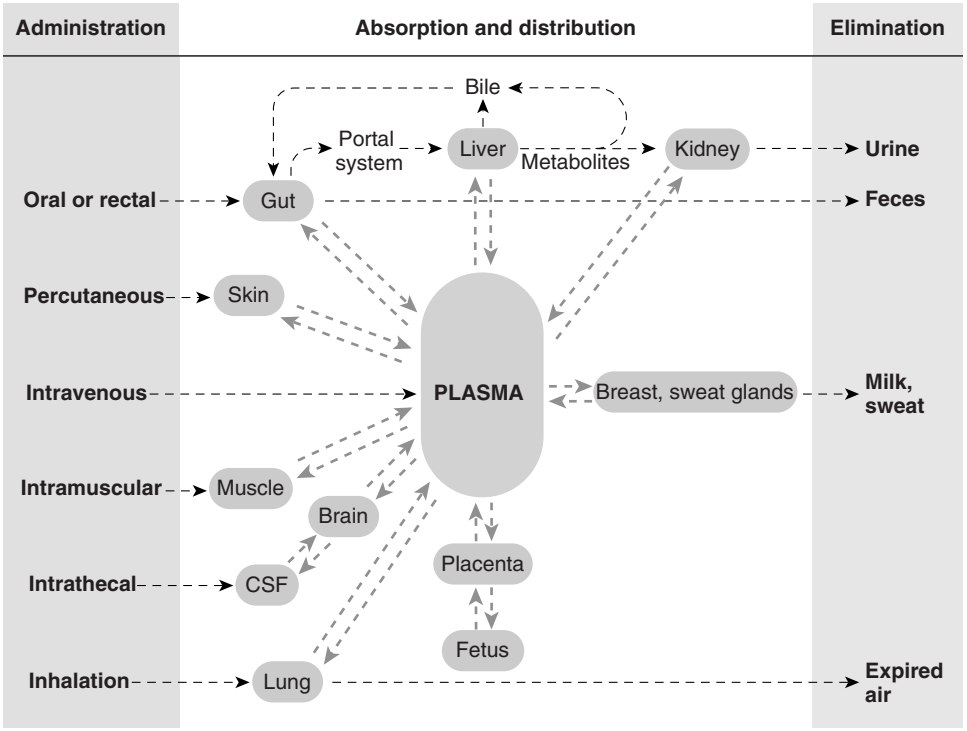

FIGURE **6-5** The main routes of drug administration and elimination. *(From Rang HP, et al:* Rang and Dale's Pharmacology, *7th ed. Edinburgh: Churchill Livingstone, 2012, p 107.)*

BOX **6-4**

Movement of Drugs Across Cellular Barriers

- To traverse cellular barriers (e.g., gastrointestinal mucosa, renal tubule, blood-brain barrier, placenta), drugs must cross lipid membranes.
- Drugs cross lipid membranes mainly by passive diffusional transfer or by carrier-mediated transfer.
- The main factors that determine the rate of passive diffusional transfer across membranes are a drug's lipid solubility and the concentration gradient. Molecular weight is a less important factor.
- Most drugs are weak acids or weak bases; their state of ionization varies with pH according to the Henderson-Hasselbalch equation.
- With weak acids or bases, only the uncharged species (the protonated form for a weak acid; the unprotonated form for a weak base) can diffuse across lipid membranes; this gives rise to pH partition or ion trapping.
- The term *pH partition* refers to the fact that weak acids tend to accumulate in compartments of relatively high pH, whereas weak bases tend to leave compartments of high pH.
- Carrier-mediated transport involves solute carriers (SLCs), including organic cation transporters (OCTs) and organic anion transporters (OATs), and P-glycoproteins or P-gp (P for permeability, also referred to as ABC [ATP-binding cassette] transporters) in the renal tubule, blood-brain barrier, and gastrointestinal epithelium, which are important for the distribution of some drugs. Many are chemically related to endogenous substances.
- Drugs of very low lipid solubility, including those that are strong acids or bases, are generally poorly absorbed from the gut.
- A few drugs (e.g., levodopa) are absorbed by carrier-mediated transfer.
- Absorption from the gut depends on many factors, including the following:
  - Gastrointestinal motility
  - Gastrointestinal pH
  - Particle size
  - Physicochemical interaction with gut contents (e.g., chemical interaction between calcium and tetracycline antibiotics)
- Bioavailability is the fraction of an ingested dose of a drug that gains access to the systemic circulation. It may be low because absorption is incomplete or because the drug is metabolized in the gut wall or liver before reaching the systemic circulation.
- Bioequivalence implies that if one formulation of a drug is substituted for another, no clinically untoward consequences will ensue.

Modified from Rang HP, et al. *Rang and Dale's Pharmacology.* 7th ed. Edinburgh: Churchill Livingstone; 2012:99-114.

represents 90% of body mass. This second compartment receives approximately 25% of the cardiac output.[20] The terms *central* and *peripheral compartments* refer to differences in the size of the compartments and the rate at which a drug is distributed to them. In reality, the compartments are not true anatomic areas but instead are conceptual representations of two separate volumes in which a quantitative change in drug concentration occurs.[21]

Drugs leave the central compartment in two phases. Drugs leave by distribution into the tissues or via metabolism and excretion. In the initial phase, after an intravenous bolus dose, those organs with the highest blood flow have the largest amount of drug delivered to them. These highly perfused tissues equilibrate with the initial high serum concentration and attain a high concentration of drug (Table 6-2). As blood flows through the less perfused organs, the

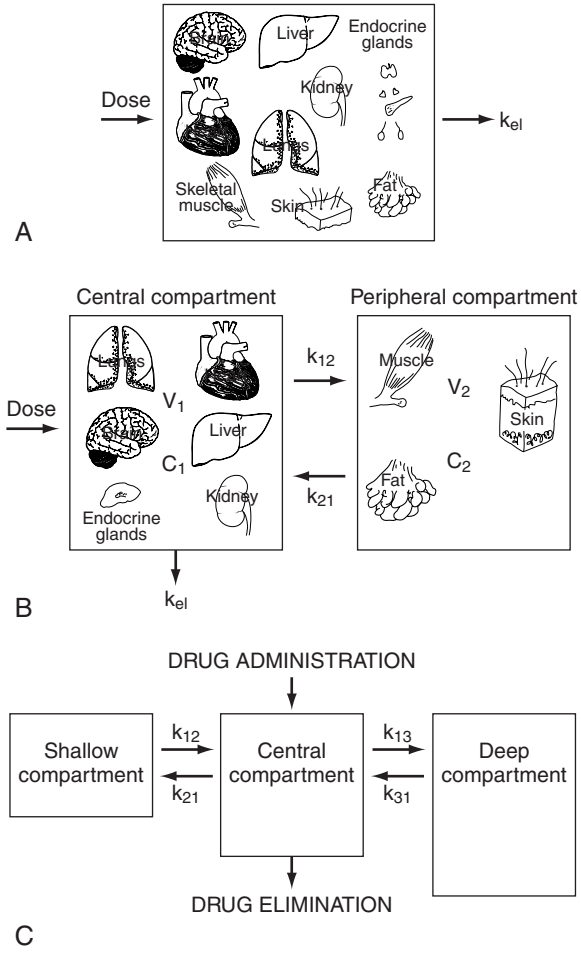

FIGURE **6-6** **A,** In the one-compartment model, a drug instantaneously and homogeneously is distributed throughout the fluids and tissues that constitute the compartment. When changes in drug concentration occur in any of these tissues, a corresponding quantitative change occurs in drug concentration in all the other tissues. **B,** In the two-compartment model, the body is assumed to be made up of two compartments: a central compartment (C_1) made up of a small apparent volume (V_1) and a peripheral compartment (C_2) made up of a larger apparent volume (V_2). **C,** The three-compartment model is depicted as having a central compartment into which the drug is administered and two peripheral compartments to which reversible drug distribution occurs. k_{12}, Rate of distribution of drugs to the peripheral compartment; k_{21}, rate of redistribution of drugs back to the central compartment; k_{el}, rate of drug removal or elimination from the body; k_{13}, rate of distribution of drugs from the central compartment to a shallow peripheral compartment; k_{31}, rate of distribution of drugs from the shallow peripheral compartment back to the central compartment (see text for further explanation).

drug begins to be deposited in those tissues as well.[17] However, the tissue levels rise more slowly and do not reach as high a concentration as in the vessel-rich group or central compartment, with extraction occurring to a lesser degree. As blood flows through the tissues, serum concentrations drop because of this distribution, and the fall in plasma concentration is described mathematically via the alpha half-life.[22] When the plasma concentration falls below the tissue concentration, the drug reemerges from the highly perfused tissue, enters the plasma serum, and is again redistributed. The drug enters the central compartment for clearance from the body. The degree to which drugs distribute and redistribute from the central compartment to the peripheral compartment, and the resultant concentration of the drug established before elimination occurs, allow for the calculation of the volume of distribution.

TABLE 6-2 Tissue Groups Based on Perfusion*

Characteristic	Vessel Rich	Muscle	Fat	Vessel Poor
Percentage of body weight	10	50	20	20
Percentage of cardiac output	75	19	6	0
Perfusion (mL/min/100 g)	75	3	3	0

*The vessel-rich group represents the central compartment, and the muscle, fat, and vessel-poor groups are peripheral compartments.

Volume of Distribution

The volume of distribution (Vd) is a proportional expression that relates the amount of drug in the body to the serum concentration. It is the apparent volume in which the drug is distributed after it has been introduced into the system.[1] Essentially it is calculated by dividing the dose of the drug administered intravenously by the plasma concentration before elimination occurs. The volume of distribution is used to calculate the loading dose of a drug that will achieve a steady-state concentration.[20] In practice, a patient's volume of distribution is unknown, and an average volume of distribution is assumed and used to calculate a loading dose that will attain a therapeutic concentration rather than a steady-state concentration.

$$\text{Volume of distribution} = \frac{\text{Dose of drug}}{\text{Plasma concentration of drug}}$$

The theoretical compartments and volumes are envisioned as follows. The plasma compartment contains 4 liters (L). The interstitial fluid (IF) volume contains 10 liters. The extracellular fluid (ECF) volume combines the plasma and IF and therefore contains (4+10) or 14 liters. The intracellular fluid (ICF) volume is 28 L. Total body water is equal to plasma (4L) + IF (10L) + ICF (28L) = 42 liters. The typical Vd, normalized for the body weight of a 70 KG adult, would be 42L/70KG or 0.6L/kg. The Vd gives one the sense of how extensively a drug distributes throughout the body. A drug with a large Vd (> 0.6L/KG) implies that it is widely distributed in the body and likely lipid soluble. A drug with a small Vd (< 0.4 L/ KG) is largely contained in the plasma and likely water soluble. Other factors such as size, carrier molecules, disease states, and fluid shifts associated with burn injuries or pregnancy may also alter expected distribution volumes.

The volume of distribution of a drug is affected by the physiochemical properties of that drug, such as lipid solubility, plasma protein binding, and molecular size.[4] Drugs that are free, unbound to plasma proteins, and lipid soluble easily cross membranes to tissues and therefore have large calculated volumes of distribution with low plasma concentrations. An example of a drug with a large volume of distribution is propofol.[1] On injection of an induction dose, this highly lipid-soluble drug is distributed quickly to peripheral tissue, thereby ending its action much more rapidly than its elimination half-life would predict. The patient wakes up in just a few minutes because of redistribution from the brain (central compartment) to the peripheral compartment; however, the patient may feel sleepy for hours because of the long elimination half-life of the drug from the whole body (11.6 hours).[4]

The volume of distribution of a drug administered by bolus is also calculated by dividing the total dose administered by the area under the plasma concentration curve. The greater the area under the curve, the longer the drug acts and the drug intensity increases.[4] However, if the drug is infused or given in multiple

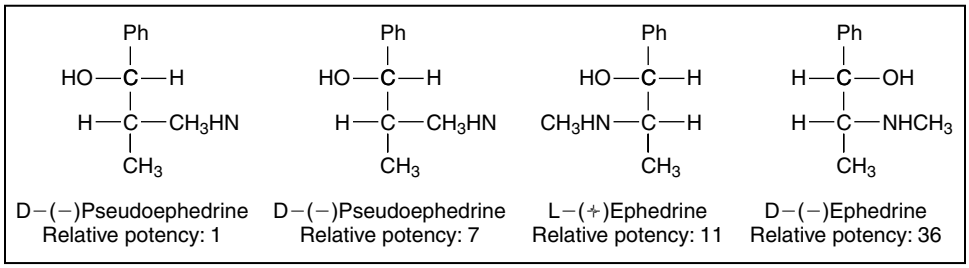

FIGURE **6-7** Ephedrine has two chiral centers and four isomers with varying potencies.

doses and the amount given equals the amount eliminated, the central and peripheral compartments are in equilibrium. Therefore the volume of distribution at this steady state would differ if the agent were given as a bolus injection.[5]

Structure-Activity Relationship

The affinity of a drug for a specific macromolecular component of the cell and its intrinsic activity are intimately related to its chemical structure.[23] The relationship is frequently quite a rigid one, in that relatively minor modifications in the drug structure may result in major changes in pharmacologic properties. In fact, manipulation of structure-activity relationships often leads to the synthesis of therapeutic agents quite varied in their therapeutic effects, as well as their side effects. Changes in molecular configuration must occur in a manner that leads to alterations of all actions and effects of a drug equally. Therefore it is sometimes possible to develop a congener with a more favorable ratio of therapeutic to toxic effects, enhanced selectivity among different cells or tissues, or more acceptable secondary characteristics than those of the parent drug.[23] Additionally, effective therapeutic agents have been developed by cultivating structurally related competitive antagonists of other drugs or of endogenous substances known to be important in biochemical or physiologic function. Minor modifications of structure can also have profound effects on the pharmacokinetic properties of drugs. The structure of a drug can therefore occasionally supersede all of the above properties discussed, and this structure is of great importance in how a drug behaves in vivo. Important considerations in structure-activity relationships are enantiomerism and isomerism.

Stereochemistry

A carbon-containing compound usually exists as stereoisomers-molecules with the same chemical bonds but different configurations in their fixed spatial arrangements. A specific configuration is achieved by either the presence of double bonds, where there is no freedom of rotation, or by chiral centers, around which varying groups are arranged in a specific sequence.[24] Chiral centers are therefore formed by a carbon atom with four different asymmetric substituents. A molecule with one chiral carbon can have two stereoisomers; however, as the number of carbons in a molecule increases, so does the number of its potential stereoisomers. Some stereoisomers are non-superimposable mirror images of each other called *enantiomers*. Free rotation about a chiral carbon is not possible, resulting in the existence of two stable forms of the molecule. These concepts become important in that interactions between biomolecules are stereospecific, and interface with biologic receptors can differ greatly between two enantiomers, even to the point of no binding. There are numerous examples among drug molecules in which only one isomer exhibits the desired pharmacology. Some isomers may even cause side effects or entirely different effects than their mirror image.[23] For instance, D(−) ephedrine, with a relative potency of 36, is used to a large extent as an antiasthmatic and, by an anesthesia professional, as a pressor amine to restore low blood pressure in the operating arena, whereas L(+) pseudoephedrine, with a relative potency of 7, is used primarily as a nasal decongestant (Figure 6-7). These drugs therefore have varying activities as well as potencies, rendering them ideal for varying situations. Cisatracurium, levobupivacaine, and ropivacaine are additional examples of select isomers with improved clinical properties.

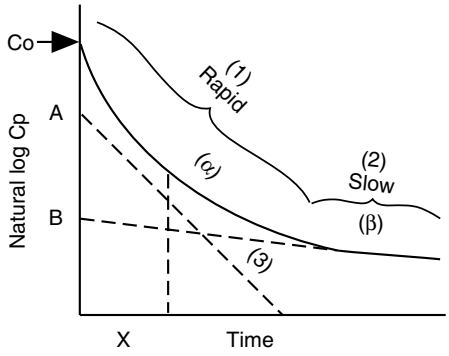

FIGURE **6-8** The plot of the natural log of drug concentration. For drugs that conform to the two-compartment model, the plot of the natural log of the drug concentration is not linear along its entire length. Rather, it is curvilinear. The initial segment *(1)*, which represents the decline in drug concentration, is parabolic, then linear *(2)*. This decline in the drug concentration is also described as *biphasic*—a rapid phase, representing distribution *(3)*, and a slow phase, representing elimination. The slope of the slow phase *(2)* is determined in a manner similar to that used for the elimination rate constant, k_{el}, in the one-compartment model.

Plasma Concentration Curve

A schematic depiction of the decline in plasma concentration of a drug with time after rapid intravenous injection into the central compartment is plotted on a logarithmic graph in Figure 6-8. The y-axis of the graph represents the plasma concentration, and the x-axis reflects the time after the dose is injected. The first phase of the curve is the α phase, or the distribution phase, which represents the initial dispersal of drug into the tissue compartments from the central compartment. This slope is usually steep with drugs that are highly lipid soluble, which demonstrates the ability of these agents to cross membrane lipid bilayers and be distributed to the peripheral compartment rapidly, leading to a rapid fall in plasma levels.[1]

The second phase of the curve is a logarithmic plot of the slower elimination, or β, phase of the plasma concentration curve. Once equilibrium has been reached, the concentration falls exponentially because of elimination. This portion of the graph is much less steep and has a plateau shape, illustrating the more gradual decline in the drug's plasma concentration. The slope is flatter because it reflects the elimination of the drug from

the circulation by the hepatic, renal, and other systems, which is a more gradual process. The plasma concentration curve is an example of a biexponential decay curve, because two distinct components of decay exist—a steep slope that describes distribution and a second, less steep slope that depicts the elimination phase.[4]

The elimination phase of the plot is used to determine the elimination half-life of drugs, which becomes important with regard to dosing intervals.

Steady State

Theoretically, a steady state occurs when a stable plasma concentration of a drug is achieved. In this instance, all body compartments will have had ample opportunity to equilibrate with the circulating agent, and although tissue concentrations of the drug vary from organ to organ, they are not changing. At this point, drug elimination is equal to the rate at which the drug is made available, so the amount being eliminated in a given time equals the amount being added to the system at the same time.[25] This state is typically reached with chronic administration of a drug or by continuous intravenous administration. Some important distribution concepts are listed in Box 6-5.

Metabolism

Drug *metabolism* is synonymous with drug *biotransformation*. Metabolism is an enzyme-catalyzed change in the chemical structure of agents, and it usually involves more than one pathway. The main organ for drug metabolism is the liver, although metabolism can occur in the plasma, lungs, gastrointestinal tract, kidneys, heart, brain, and skin. The goal of metabolism is to change lipid-soluble agents into more water-soluble forms so the kidneys can then eliminate them from the body. Metabolism usually leads to transformation of active drugs into inactive metabolites; however, numerous consequences can occur. For example, a drug can be metabolized to an active drug with the same or new activity, or an agent can be converted from an inactive prodrug to its active form, as occurs with the metabolism of inactive enalapril to active enalaprilat. A new formulation of propofol, fospropofol, (Lusedra), is a prodrug that is converted by hydrolysis in the plasma by alkaline phosphatases to free active propofol.[21]

For most drugs administered in therapeutic doses, metabolism occurs as a first-order process, in that the drug is cleared at a rate proportional to the amount of drug present in the plasma. Thus a constant fraction of total drug is metabolized in a set time period. The greatest amount of drug eliminated per unit time occurs when the concentration is highest.[26]

Drugs such as alcohol undergo zero-order kinetics at therapeutic doses. This means that even at therapeutic levels, they exceed the body's ability to excrete or metabolize them. In zero-order kinetics, the available enzyme systems for elimination of drugs are saturated. For these agents, a constant amount of drug is cleared regardless of the plasma concentration, as opposed to a constant percentage as occurs with first-order kinetics. The amount of agent cleared per unit time during zero-order kinetics is the same amount, independent of its plasma concentration.

Drug metabolism occurs in two phases. Phase I reactions are oxidation, reduction, and hydrolysis reactions and generally result in increased polarity of the molecule, transforming a lipid-soluble compound to a water-soluble one. Phase II reactions involve conjugation reactions, in which a drug or metabolite is conjugated with endogenous substrate such as glucuronic, sulfonic, or acetic acid.[27]

BOX 6-5

Drug Distribution

The major compartments are as follows:

- Plasma (5% of body weight)
- Interstitial fluid (16%)
- Intracellular fluid (35%)
- Transcellular fluid (2%)
- Fat (20%)
- Volume of distribution (V_d) is defined as the volume of plasma that would contain the total body content of the drug at a concentration equal to that in the plasma.
- Water-soluble drugs are mainly confined to plasma and interstitial fluids; most do not enter the brain after acute dosing.
- Lipid-soluble drugs reach all compartments and may accumulate in fat.
- For drugs that accumulate outside the plasma compartment (e.g., in fat, or by being bound to tissues), V_d may exceed total body volume.
- For many drugs, disappearance from the plasma follows an exponential time course characterized by the plasma half-life.
- Plasma half-life, in the simple case, is directly proportional to the volume of distribution and inversely proportional to the overall rate of clearance.
- With repeated dosage or sustained delivery of a drug, the plasma concentration approaches a steady value within 4 or 5 plasma half-lives. Elimination of a drug also takes 4 or 5 half-lives.
- A two-compartment model is often needed. In this case the kinetics are biexponential. The two components roughly represent the processes of transfer between plasma and tissues or distribution (α phase) and elimination from the plasma (β phase).
- Some drugs show nonexponental "saturation" kinetics, with important clinical consequences, especially a disproportionate increase in steady-state plasma concentration when the dose is increased.

Modified from Rang HP, et al. *Rang and Dale's Pharmacology.* 7th ed. Edinburgh: Churchill Livingstone; 2012:118.

Phase I Reactions

Oxidation reactions generally are reactions in which oxygen is introduced into the molecule or the oxidative state of a molecule is changed so that its relative oxygen content is increased. The molecule of oxygen is split; one atom oxidizes each molecule of drug, and the other is incorporated into a molecule of water. The loss of electrons results in oxidation. Oxidative metabolism reactions are catalyzed by the enzymes of the cytochrome P-450 system.[27] Reduction pathways of metabolism also use the cytochrome P-450 system. When insufficient amounts of oxygen are present to compete for electrons, these enzymes transfer electrons directly to a substrate rather than to oxygen. Reduction involves the gain of electrons.[28]

Hydrolysis is the addition of water to an ester or amide to break the bond and form two smaller molecules. Adding water to these compounds leads to an acid and alcohol, in the case of esters, and to an acid and an amine, in the case of amides. Amide drugs rarely undergo hydrolysis, even though they are formed by removing water. Steric hindrance limits the ability to add water to a drug (hydrolyze it) once the water has been removed. Examples of drugs that are hydrolyzed are listed in Box 6-6.

The end result of phase I reactions is typically a more polar compound that is easily excreted by the kidneys. It is also important to

BOX 6-6

Common Anesthesia-Related Drugs That Undergo Phase 1 Hydrolysis

Pseudocholinesterase Catalyzed
- Succinylcholine
- Cocaine
- Procaine
- Chloroprocaine
- Tetracaine
- Neostigmine (partial pathway)
- Edrophonium (partial pathway)

Nonspecific Esterase Dependent
- Remifentanil
- Atracurium (partial pathway)
- Cisatracurium (partial pathway)
- Esmolol (RBC esterase)
- Aspirin
- Clevidipine
- MOC-etomidate

Alkaline Phosphatase Hydrolysis
- Lusedra prodrug to active propofol base

MOC, *Methoxycarbonyl*; RBC, *red blood cell*.

BOX 6-7

Drug Metabolism

- Phase I reactions involve oxidation, reduction, and hydrolysis—usually form more chemically reactive products; sometimes pharmacologically active, toxic, or carcinogenic. Phase 1 reactions often involve a monooxygenase system in which cytochrome enzymes play a role.
- Phase II reactions are conjugation (e.g., glucuronidation) of a reactive group (often inserted during phase I reaction) and usually form inactive and polar products that are readily excretable.
- Some conjugated products are excreted via bile, are reactivated in the intestine, and then reabsorbed (e.g., enterohepatic circulation).
- Induction of enzymes by other drugs and chemicals can greatly accelerate hepatic drug metabolism. It can also increase the toxicity of drugs with toxic metabolites.
- Some drugs show rapid "first-pass" hepatic metabolism and therefore poor oral bioavailability due to presystemic metabolism in the liver or intestinal wall.

Modified from Rang HP, et al. *Rang and Dale's Pharmacology*. 7th ed. Edinburgh: Churchill Livingstone; 2012:119.

note that phase I reactions, by placing hydroxy or carboxy groups on drug molecules, enable phase II reactions to occur.[1]

Phase II Reactions

Phase II reactions are also referred to as *synthetic reactions* because the body actually synthesizes a new compound by donating a functional group usually derived from an endogenous acid. The new compound is the conjugate of the drug or the drug product of the phase I reaction with either glucuronic acid, sulfuric acid, glycine, acetic acid, or a methyl group.[25]

The products of phase II reactions almost always have little or no biologic activity. Conjugation always leads to a more polar compound that is more highly ionized at physiologic pH and therefore more easily extractable by the kidney via glomerular filtration. The conjugation proceeds by joining the body's donated group (during phase I reactions) with an OH, COOH, or NH group to form an ester or amide bond. However, many drugs already possess an appropriate functional group for conjugation and therefore do not need to be modified by a prior phase I reaction in order to be conjugated.

Many intracellular sites exist for drug metabolizing enzymes, such as the endoplasmic reticulum, mitochondria, cytosol, lysosomes, and plasma membrane. Hepatic microsomal enzymes, responsible for biotransformation of numerous agents, reside mainly in the smooth hepatic endoplasmic reticulum. They are termed *microsomal enzymes* because microsomes are fragments of the endoplasmic reticulum that are obtained in vitro by physical disruption of the tissue and differential centrifugation. This microsomal fraction includes proteins called *cytochrome* (iron-containing hemoprotein) *P-450*, indicating its peak absorption at 450 nm, when it reacts with carbon monoxide. The cytochrome P-450 is also called the *mixed-function oxidase system* because it includes both oxidation and reduction steps and has low substrate specificity.[4] Some extrahepatic sites of the P-450 system exist, such as the kidneys, lungs, skin, and intestinal mucosa.

Six well-characterized forms, or isozymes, of the cytochrome P-450 system are involved in drug metabolism in humans: CYP1A2, CYP2D6, CYP2C19, CYP2E1, CYP2C9, and CYP3A.[29] The letters *CYP* stand for cytochrome P-450; the first number denotes genetic family, the next letter describes the genetic subfamily, and the second number stands for the specific gene or isozyme.

It is important to note some characteristics of these isozymes. It should be appreciated that small differences in amino acid sequences of the different isozymes lead to differences in drug metabolism and account for genetic variability among individuals' abilities to metabolize agents.[29] Therefore hepatic enzyme activity varies among individuals and is determined genetically. Genetic variability exists in the expression of CYP2C19, CYP2C9, and CYP2D6 and other cytochromes. Genetic variation in CYP2D6 enzyme, for example, leads to changes in metabolism of β-blockers, which may produce toxicity or their ultrarapid degradation decreasing efficacy. These polymorphisms in the adrenergic signaling pathway and CYP2D6 gene may influence efficacy, safety, and toxicity of β-blocker therapy in prevention and treatment of perioperative myocardial infarction.[30,31]

It is possible to increase enzyme activity by stimulating the enzymes over a period of time. This is called *enzyme induction* and is usually produced by exposure to certain drug or chemical compounds. Alcohol is one such compound; when ingested chronically it induces enzymatic activity. The system can more quickly break down agents that use the same enzymatic system for biotransformation. Other drugs capable of enzyme induction include phenobarbital, phenytoin, rifampin, and carbamazepine. This increased capacity to clear drugs leads to reduction in half-lives of agents and is important with regard to dosing intervals.[32,33]

Microsomal enzymes also can be inhibited. This usually occurs through exposure to certain drugs and chemicals, leading to accumulation of the substrate agent, and can cause elevated plasma levels and potentially greater activity and toxicity. For example, erythromycin inhibits the metabolism of theophylline, and cimetidine inhibits metabolism of many drugs.[29] Box 6-7 contains a summary of important metabolic concepts. A list of cytochrome enzymes, metabolites, inducers, and inhibitors is given in Table 6-3.

TABLE 6-3 List of Cytochrome Enzymes, Metabolites, Inducers, and Inhibitors

Isozyme	Metabolic Substrates	Inducers	Inhibitors
CYP1A2	Theophylline—has a narrow therapeutic range, so inhibition of its metabolism can lead to toxic levels Imipramine Propranolol Clozapine	Tobacco smoke—smokers may require higher doses of these drugs because their metabolism is increased	Ciprofloxacin Erythromycin
CYP2C19—absent in 20%-30% of Asians, who therefore need a reduced dose when these drugs are administered	Diazepam Phenytoin Omeprazole (proton pump inhibitor for ulcers)		Omeprazole Ketoconazole (antifungal agent) Isoniazid
CYP2C9—absent in approximately 1% of Caucasians	NSAIDs COX II inhibitors Warfarin Phenytoin		Fluconazole
CYP2D6—absent in approximately 7% of Caucasians; hyperactive in approximately 30% of East Africans (Ethiopians) because they have multiple copies of the gene	Codeine → morphine Some β-blockers Some tricyclic antidepressants		Fluoxetine Haloperidol Paroxetine Quinidine
CYP2E1	Acetaminophen Ethanol Some halogenated hydrocarbons such as halothane	Chronic ethanol Isoniazid	Disulfiram
CYP3A—present in GI tract and liver; responsible for a large amount of first-pass metabolism	Calcium channel blockers Most benzodiazepines HIV protease inhibitors HMG-CoA reductase inhibitors (lipid-lowering agents) Cyclosporine (immunosuppressant) Most nonsedating antihistamines	Carbamazepine Rifampin Rifabutin (to treat TB) Ritonavir (to treat HIV) St. John's wort (herbal product used for depression and menopause)	Azole antifungal agents such as itraconazole Ketoconazole Fluconazole Cimetidine (broad range P-450 inhibitor) Macrolide Antibiotics (but *not* azithromycin) Grapefruit juice

COX, Cyclooxygenase; *GI*, gastrointestinal; *HIV*, human immunodeficiency virus; *HMG-CoA*, 3-hydroxy-3-methylglutaryl coenzyme A; *NSAIDs*, nonsteroidal antiinflammatory drugs; *TB*, tuberculosis.

Drug Elimination

Elimination Half-Life

The elimination half-life (t½) is the time necessary for the plasma content of a drug to drop to half of its prevailing concentration after a rapid bolus injection. It takes the same amount of time to reduce a drug's concentration from 100 to 50 mg/L as it does to decrease the concentration from 10 to 5 mg/L. The amount of drug remaining in the body is related to the number of elimination half-lives that have elapsed (Table 6-4). For practical purposes, a drug is regarded as being fully eliminated when approximately 95% has been eliminated from the body. This usually occurs when four or five half-lives have elapsed and is important with regard to dosing intervals because drug accumulation occurs if dosing intervals are shorter than this. The body has not been able to rid itself of the initial dose, and subsequent doses will lead to overdose and potential adverse effects. Instances can occur in which, although only 5% of the drug amount remains, it is still somewhat active; however, for the majority of agents, four half-lives is considered sufficient time for the drug's action to be terminated and the agent eliminated from the body. As noted earlier, most drugs leave the body at a constant rate or percentage over time. This is referred to as *first-order kinetics* or *dosage independence* and is the reason half-life is constant. Other elimination rate kinetic models include zero-order (e.g., alcohol) elimination, in which a constant amount (not a percentage) is eliminated over time, and Michaelis-Menton models (e.g., phenytoin), which are dose dependent and follow zero order at high doses and first order once drug levels have fallen.[4]

TABLE 6-4 Relationship Between Half-Life and Drug Remaining in the Body

Half-Life	Drug Eliminated (%)	Drug Remaining (%)
0	0	100
1	50	50
2	75	25
3	87.5	12.5
4	93.75	6.25
5	96.875	3.125

Context-Sensitive Half-Time

Deficiencies in the use of standard pharmacokinetic parameters such as half-life when describing anesthetic drug administration have led to a proposal for the introduction of a new model that accounts for continuous infusion or repeated dosing-induced changes in drug behavior.[3,4] *Context-sensitive half-time* was developed through use of computer simulations of typical anesthetic dosing practices to provide a more clinically relevant measure of

Table 6-5 Pharmacokinetic Metrics for Describing Drug Offset

Parameter	Definition	Advantages	Limitations
Terminal half-life	Time taken for drug concentration in the blood to fall by one half of the current value	Easily understood Simple to calculate Useful for describing drug disposition in a one-compartment model	One-compartment models rarely used for describing the kinetics of anesthetic drugs Not "context sensitive" with respect to infusion duration Not informative with respect to actual duration of action
Context-sensitive decrement times	Time required for drug concentration to decrease by a given percentage, after termination of an infusion of a given duration	Can be calculated for the central (plasma) or a peripheral effect compartment Context sensitivity allows rational drug selection based on anticipated infusion duration	Decrement curves are generated by kinetic-dynamic simulation using known models Impractical to attempt clinical validation due to vast numbers of patients required An arbitrary decrement time (particularly if relating to plasma concentration) may not relate to actual recovery time
Mean effect time	Calculation of the average recovery time, based on the probability of drug effect as a function of drug concentration and time	An extension of the context sensitive half-time. For example estimates of C90, the concentration at 90% recovery, which considers the probability of drug effect, in addition to pharmacokinetic parameters	Calculation requires knowledge of the concentration-effect relationship and the variance of drug concentration Useful for quantifying the duration of drug effect when dealing with "response or no response" binary data

Adapted from Rigby-Jones AE, Sneyd JR. Pharmacokinetics and pharmacodynamics—is there anything new? *Anaesth* 2012; 67(1):5-11; Minto CF, Schnider TW. Contributions of PK/PD modeling to intravenous anesthesia. *Clin Pharmacol Ther.* 2008; 84(1):27-38; Bailey JM: Context-sensitive half-times: what are they and how valuable are they in anaesthesiology? *Clin Pharmacokinet.* 2002;41(11):793-799.

drug concentrations, taking into consideration the method and duration of administration.[35] It is defined as the time to halving of the blood concentration after termination of drug administration by an infusion designed to maintain a constant concentration. It is believed that through incorporation of the effect compartment, the context-sensitive half-time of the pharmacodynamic effect can be modeled.[36] A flaw in the concept is that it describes only the time to a 50% decrease in central compartment concentration, which may not be the decrement in drug level required to achieve recovery.[37] Whether context-sensitive half-time is a useful secondary kinetic descriptor may await its more widespread application. Advantages and disadvantages of the various elimination models are summarized in Table 6-5.

Other parameters have been introduced including the *relative decrement times*. This is the time needed for 80% or 90% decreases in inhalation anesthetic concentration. The major differences in the rates at which desflurane, sevoflurane, and isoflurane are eliminated occur in the final 20% of the elimination process.[38,39]

Clearance

The clearance of a drug is an independent value and is governed by the properties of the drug and the body's capacity to eliminate it. It is defined as the volume of plasma completely cleared of drug by metabolism and excretion per unit of time. Clearance is directly proportional to the dose and inversely related to the agent's half-life as well as its concentration in the central compartment. Clearance is a very important pharmacokinetic concept, because it influences the steady-state concentration for a given drug administered at repeated intervals or by infusion.

The two main organs for clearance are the liver and kidneys. The rate of clearance is determined by the blood flow to these organs, as well as by their ability to extract the drug from the bloodstream. Mathematically, clearance is equal to the product of the blood flow (Q) and extraction ratio (E):

$$\text{Clearance} = Q \times E$$

Total clearance is the sum of all organs' clearance values. The changes in clearance occur when blood flow to the liver or kidney is altered or when their extraction ratios are changed.

Hepatic Clearance. Drugs typically go through perfusion-dependent elimination or capacity-dependent elimination in the liver. Drugs that have a high extraction ratio of 0.7 or greater rely heavily on the perfusion of the liver to be cleared. These drugs are referred to as *high-clearance drugs*. Examples of high-clearance drugs are verapamil, morphine, and lidocaine. Hepatic blood flow for these agents far outweighs enzymatic activity in clearing them from the body, so a decrease in hepatic blood flow decreases the rate of clearance, and a high perfusion state leads to faster clearance. This is termed *perfusion-dependent* elimination.[1]

Capacity-dependent elimination occurs with agents that possess a low extraction ratio of 0.3 or less. When a low extraction rate exists, only a small fraction of the agent is removed per unit time, and changes in hepatic perfusion do not have significant effect on hepatic clearance. Clearance of these drugs depends on hepatic enzymes and the degree of protein binding. Therefore alterations such as enzyme induction or suppression cause a change in the elimination of these drugs from the body. An increase in enzyme activity causes faster elimination from the body, and enzyme suppression has the opposite outcome. A decrease in protein binding (increase in availability of drug at hepatocytes) also leads to a greater rate of clearance. Examples of drugs with a low hepatic extraction ratio are diazepam and theophylline.[1]

Renal Clearance. The kidneys excrete water-soluble molecules with great ease. The excretion of drugs involves passive glomerular filtration, active tubular secretion, and some reabsorption. Selected substances that are actively secreted are noted in Box 6-8. The amount of drug made available to the renal tubule for elimination depends on the amount of free, unbound drug and the glomerular filtration rate. Water-soluble metabolites are filtered by the glomeruli and eliminated. The kidneys do not excrete lipid-soluble agents as efficiently as water-soluble compounds. For these agents, elimination depends on the liver for metabolism

BOX 6-8

Important Drugs and Related Substances Secreted into the Proximal Renal Tubule by OAT or OCT Transporters

OAT	OCT
p-Aminohippuric acid	Amiloride
Furosemide	Dopamine
Glucuronic acid conjugates	Histamine
Glycine conjugates	Mepacrine
Indomethacin	Morphine
Methotrexate	Meperidine
Penicillin	Quaternary ammonium compounds
Probenecid	
Sulfate conjugates	Quinine
Thiazide diuretics	5-Hydroxytryptamine (serotonin)
Uric acid	Triamterene

OAT, *Organic anion transporter;* OCT, *organic cation transporter.*
From Rang HP, et al. *Rang and Dale's Pharmacology.* 7th ed. Edinburgh: Churchill Livingstone; 2012:120.

into water-soluble molecules. Indeed, increased water solubility reduces the volume of distribution of agents, leading to their excretion by the kidneys. Conversely, lipid-soluble molecules are reabsorbed from the renal tubules back into the systemic circulation. An example of a lipid-soluble drug that is almost completely reabsorbed (such that little or none of it is excreted unchanged) is propofol.

The pH of the urine can also affect the elimination of drugs. Weak acids are better excreted in alkaline urine; conversely, weak bases are readily excreted in acid urine. The kidneys can use glomerular filtration for elimination of drugs that are highly polar (e.g., aminoglycoside antibiotics). Certain agents (e.g., penicillin) are eliminated via secretion. Some important clearance concepts are noted in Box 6-9.

OTHER FACTORS THAT INFLUENCE PHARMACOKINETICS

Age

Age plays an important role in the manner in which drug disposition occurs. Elderly patients have a decrease in renal function, resulting in impaired excretion of agents that are eliminated in the urine.[6] Creatinine clearance, as an indicator of renal function, parallels the kidneys' ability to excrete drugs and is a useful test in predicting renal pharmacokinetics in the elderly.[4] Liver blood flow decreases with age as well, decreasing the metabolism of agents with moderate to high extraction ratios. The elderly also have an increase in the fat compartment, leading to an increased volume of distribution, which can lead to accumulation of lipid-soluble agents.[15] Liver and renal function are also important in neonates. Elimination of drugs via the kidneys is altered in neonates because of poor renal function in the first year of life. Neonates and premature infants lack the ability to metabolize certain agents because of immature liver enzyme systems.[4] It is therefore important to consider extremes of age when administering any agent that may be highly lipid soluble with a high hepatic extraction ratio or that relies primarily on the kidneys for elimination.

Gender

Gender differences account for some variability in the pharmacokinetics of many agents. In a recent review of the literature, it was found that female patients had a 20% to 30% greater sensitivity to the muscle relaxant effects of vecuronium, pancuronium, and rocuronium.[40,41] It was also found that male patients were more sensitive to propofol than female patients and that it may be necessary to reduce propofol doses in male patients.[42] Gan et al.[43] studied emergence from general anesthesia with propofol, alfentanil, and nitrous oxide. Female patients emerged significantly more quickly than male patients. In fact, female patients were three times more likely than male patients to experience recall under general anesthesia. Females are more sensitive than males to some of the effects of opioid receptor agonists while being more resistant to others.[40-42]

BOX 6-9

Elimination of Drugs by the Kidney

- Most drugs, unless highly bound to plasma protein, cross the glomerular filter freely.
- Many drugs, especially weak acids and weak bases, are actively secreted into the renal tubule and therefore are more rapidly excreted.
- Lipid-soluble drugs are passively reabsorbed by diffusion across the tubule and are not efficiently excreted in the urine.
- Because of pH partition, weak acids are more rapidly excreted in alkaline urine, and vice versa.
- Several important drugs are removed predominantly by renal excretion and are liable to cause toxicity in elderly persons and patients with renal disease.

Modified from Rang HP, et al. *Rang and Dale's Pharmacology.* 7th ed. Edinburgh: Churchill Livingstone; 2012:121.

Temperature

Because temperature affects tissue metabolism and blood flow, it follows that the pharmacokinetics of agents are also affected by varying temperatures. Knibbe et al.[44] examined the pharmacokinetics of long-term propofol sedation in critically ill patients. Temperature was a significant covariate for clearance of propofol. Warmer temperatures led to faster elimination of propofol, regardless of the concentration of the drug in solution.

Disease States

Comorbidities account for some of the variability observed in drug pharmacokinetics. The pharmacokinetics of ropivacaine in patients with and without uremia after axillary brachial plexus block was examined. An enhanced absorption and larger total plasma concentrations of ropivacaine and its main metabolite were noted in the patients with uremia.[45] Conversely, Goyal et al.[46] found a negative correlation of propofol dose with preoperative hemoglobin concentration in patients with renal failure. They concluded that the hyperdynamic state caused by anemia in these patients was responsible for their higher propofol dose requirement.

Other disease states can cause variability, as illustrated by a recent study that found an increase in the volume distribution of ketamine disproportional to increases in clearance in spinal cord injury inpatients in the intensive care unit, leading to a longer than expected half-life for the drug, again placing the patients at risk for overdose.[47] See Box 6-10 for a summary of some pharmacokinetic principles.

PHARMACOGENETICS AND PHARMACOGENOMICS

Definition

Pharmacogenetics is the study of variations in human genes that are responsible for different responses to drug therapy. These

BOX **6-10**

Summary of Pharmacokinetic Principles

- Clinical pharmacokinetics is the discipline that describes the absorption, distribution, metabolism, and elimination of drugs in patients who require drug therapy.
- Clearance is the most important pharmacokinetic parameter, because it determines the steady-state concentration for a given dosage rate. Physiologically, clearance is determined by blood flow to the organ that metabolizes or eliminates the drug and the efficiency of the organ in extracting the drug from the bloodstream.
- The dosage and clearance determine the steady-state concentration.
- The fraction of drug absorbed into the systemic circulation after extravascular administration is defined as its *bioavailability.*
- Pharmacokinetic models are useful for description of data sets, prediction of serum concentrations after several doses or different routes of administration, and calculation of pharmacokinetic constants such as clearance, volume of distribution, and half-life. The simplest case uses a single compartment to represent the entire body.
- The volume of distribution is a proportionality constant that relates the amount of drug in the body to the serum concentration. The volume of distribution is used to calculate the loading dose of a drug that will immediately achieve a desired steady-state concentration. The value of the volume of distribution is determined by the physiologic volume and how the drug binds in blood and tissues. The volume of distribution determines the loading dose.
- Half-life is the time required for serum concentration to decrease by one half after absorption and distribution are complete. Half-life is important because it determines the time required to reach steady state and the dosage interval. Half-life is a dependent kinetic variable because its value depends on the values of clearance and volume of distribution.
- The half-life determines the time to reach steady state and the time for "all" drug to be eliminated from the body.
- If a drug obeys first-order pharmacokinetics, a simple ratio of dosage to steady-state concentration can be used to estimate a new dosage, as long as the clearance has not changed.
- Phenytoin is an example of a drug that obeys the Michaelis-Menton model rather than first-order pharmacokinetics. In this case, as plasma concentration increases, the clearance decreases and the half-life becomes longer.
- *Cytochrome P-450* is a generic term for the group of enzymes responsible for most drug metabolism oxidation reactions. Several P-450 isozymes have been identified, including CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4.
- Factors to be taken into consideration when deciding on the best drug dose for a patient include age, gender, weight, ethnic background, other concurrent disease states, and other drug therapy.
- The importance of transport proteins in drug bioavailability and elimination is now better understood. The principal transport protein involved in the movement of drugs across biologic membranes is P-glycoprotein. P-glycoprotein is present in many organs, including the gastrointestinal tract, liver, and kidney.

Modified from Dipiro JT, et al, eds. *Pharmacotherapy: A Pathophysiological Approach*. 8th ed. New York: McGraw-Hill; 2011; and Helms RA, et al, eds. *Textbook of Therapeutics: Drug and Disease Management*. 8th ed. Philadelphia: Lippincott Williams & Wilkins; 2006; Schnider TW, Minto CF. Principles of Pharmcokinetics. In: Evers AS, eds. Anesthetic Pharmacology: *Basic Principle and Clinical Practice*. 2nd ed. Cambridge, UK: Cambridge University Press; 2011:57-71.

differences are identified in the pharmacodynamic and pharmacokinetic processes.[48] Pharmacogenomics is an evolution of pharmacogenetics research and involves the identification of drug response markers at the level of disease, drug metabolism, or drug target.[49,50]

Pharmacogenetics and pharmacogenomics take into account the genetic basis for the variability in an individual's drug response. Pharmacogenetics studies variations in genes suspected of affecting drug response, whereas pharmacogenomics encompasses the genome (all genes). The discipline of pharmacogenetics integrates biochemical and pharmacologic concepts and seeks to correlate phenotypic biomarkers such as toxicity with genetics via twin studies. Pharmacogenomics involves DNA sequencing and gene mapping to identify the genetic basis for variations in drug efficacy, metabolism, and transport.[51]

History

The history of pharmacogenetics goes back to the days of Pythagoras (510 BC) when he recognized only some people had fatal responses to ingestion of fava beans, but not all.[52]

Archibald Garrod's 1902 study of alkaptonuria in humans constituted the first genetic link to disease in humans. He later advanced the hypothesis that genetically determined differences in biochemical processes may be the reason for adverse drug reactions.[53]

Familial clustering of toxic drug responses led to suspicion of a biochemical genetic basis for the toxicities.[48,51] In a seminal article published in 1957, Motulsky[54] outlined many genetic conditions associated with toxic reaction to a specific drug or chemical and proposed that inheritance of certain traits may explain individual variations in drug efficacy and toxic reactions.

Early advances in the field of pharmacogenetics came from research into the biochemical and genetic basis for idiosyncratic drug responses. Several independent observations were made. For example, in the 1950s following reports of prolonged muscle relaxation following administration of succinylcholine during anesthesia, the variation in serum cholinesterase levels was found to be an inherited trait.[55,56] Similarly, hemolytic anemia found in African-American male soldiers after administration of the antimalarial drug primaquine during World War II led to the discovery of a defect in the gene encoding glucose-6-phosphate dehydrogenase (G6PD).[51]

The term *pharmacogenetics* was coined by Vogel in 1959 and defined as "clinically important hereditary variation in response to drugs."[48] In 1962, Kalow wrote a text, *Pharmacogenetics: Heredity and the Response to Drugs*.[48,57]

In the 1960s, twin studies established the role of genetic factors in individual variations in rates of drug metabolism; however, they did not identify the specific genes involved. Gene identification emerged in the 1980s.[48] Now that the human and many animal genomes have been sequenced, huge strides in genomics and drug therapies are occurring. The development of genomics has led to the hope of individualized drug therapy with increased and targeted efficacy and fewer side effects. The characterization of single nucleotide polymorphisms (SNPs) and the effect on drug action has opened new areas of drug research. Recently, the emergence

of pharmacometabonomics assesses the influence of the metabolic factors and the environment on gene expression. The combination of these disciplines permits factors involving the genetic background of individual and exterior interventions to tailor individual therapies.[58,59]

Polymorphisms

Polymorphic genes relevant to pharmacokinetics (absorption, distribution, metabolism, and excretion) and pharmacodynamics (drug targets–receptors and enzymes) can have a significant impact on pharmacotherapy.[60] Pharmacotherapy may be affected by three types of genetic variation. These include variations in target proteins, enzyme metabolism, or idiosyncratic effects.[61]

Polymorphisms are defined as variations in the DNA sequences that occur in at least 1% of the population.[62-65] There are a number of different types of polymorphisms, but most attention has been focused on single nucleotide polymorphisms (SNPs—pronounced "snips") in which one nucleotide is exchanged for another in a given position.[52] Approximately 10 million SNPs exist, and they can occur anywhere on the genome, but only a fraction are likely to prove relevant to drug response. To matter from a pharmacologic standpoint, the differences generally affect either the function or amount of target proteins involved in the biochemical pathways of the disease processes the drugs are used to treat.[61]

The genomes of any two individuals are nearly 99.9% identical regardless of race.[61] Most variations in the human genome (polymorphisms) occur in drug-metabolizing enzyme genes. Others occur in the enzyme receptor genes and drug transporter genes.[45] Much of the observed variability in drug response has a basis in pharmacogenetic polymorphisms arising in genetically determined differences in drug absorption, disposition, metabolism, and excretion. The best-characterized pharmacogenetic polymorphisms are those in the cytochrome P-450 family of drug-metabolizing enzymes.[64]

Most drugs are lipophilic and must be metabolized to polar products for excretion. This involves hepatic enzymes and a sequence of steps dependent on the cytochrome P-450 system. Drugs are first metabolized by phase I enzymes (oxidation) and then phase II enzymes (conjugation that involves sulphation, glucuronidation, or acetylation). Although the effects of polymorphism in phase II enzymes are often less pronounced, the effects of inherited variations in both phase I and II metabolism can be synergistic.

Genetic polymorphisms occur in most if not all of the human cytochrome P-450 (CYP) isoenzymes, but functional polymorphisms reside in only four, which account for 40% of all drug metabolism (CYP2A6, CYP2C9, CYP2C19, and CYP2D6). Thus genetically controlled variations are common.[48] For example, CYP2D6 metabolizes up to 25% of all commonly prescribed drugs and is inactive in 6% of the Caucasian population. Similarly, the CYP2C19 poor metabolizer phenotype occurs in 2% to 5% of Caucasians and 3% to 23% of Asians and results in high sensitivity to diazepam, propranolol, amitriptyline, and hexobarbital.

Individuality in the expression in the P-450 isoenzymes may have a variety of consequences. These include toxic side effects due to impaired metabolism, no therapeutic effect due to ultrarapid metabolism, activation of toxic products, and failure of prodrug activation.

Individual Drug Response/Genetics

Many variations of pharmacogenetic interest have been elucidated, and with the deciphering of the human genome, many innovative opportunities exist. Genetic variations can modify responses to drugs. Variations in target pathways and metabolic enzymes may render a drug ineffective for some, yet effective for others.[62-65]

Recognition of genetic differences among patients has the potential to allow for individualized drug therapy. Further, with the recognition that certain genetic differences are associated with risk of disease, opportunities to identify these individuals and treat them early may improve efficacy and specificity of their treatment.[48]

There are marked ethnic differences that need to be taken into account when drugs subject to polymorphic metabolism are prescribed to patients from different ethnic backgrounds. The variation in CYP2C19 is reflected in a significant dosing reduction for diazepam in Asians, for example.

Genetic variation may also alter pharmacotherapy responses by creating idiosyncratic effects. These are not caused by alterations in target proteins, pathways, or metabolism, but rather result from chance interactions between the medication and the individual's physiology.[61]

The identification of specific polymorphisms and the ability to screen for them opens up the possibility of rational, individualized treatment with ideal dosing, as well as minimization of side effects based on genetic constitution. Recognition of differences may also facilitate identification of good responders versus poor responders to therapy.[51]

SUMMARY

Pharmacokinetics is an integral part of modern anesthesia clinical practice. Anesthesia providers balance the administration of a number of drugs simultaneously to achieve the necessary drug actions that constitute anesthesia. A thorough understanding of the processes that govern drug kinetics allows for safe and effective practice and facilitates operating room efficiency. This knowledge also allows the clinician to anticipate and avoid potential problems and tailor each anesthetic to particular patient characteristics. Recent advances in pharmacokinetics and pharmacogenomics will further impact anesthesia care in years to come. Pharmacogenomics has made a significant impact on the direction of drug research and drug therapy. Diseases and drug therapies are complex processes that may challenge the predictive powers of pharmacogenetics. A systems approach may be needed to integrate overall pharmacotherapeutic effects with polymorphisms in multiple genes.[62,63,65-67]

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CHAPTER 7

Pharmacokinetics of Inhalation Anesthetics

◆ *John J. Nagelhout*

The basic action of an anesthetic in the body is largely a function of the drug's chemical structure and the resulting interaction with a cellular receptor complex (Figure 7-1). A number of heterogeneous compounds exhibit anesthetic properties. The inorganic molecule nitrous oxide and halogenated ethers (e.g., isoflurane, desflurane, and sevoflurane) are all capable of binding to central nervous system and spinal cord neuronal membranes to produce reversible depression. A single specific anesthetic receptor has yet to be found. In fact, multiple sites of action and protein targets probably exist; however, once a critical concentration of drug has entered the brain and spinal cord, loss of consciousness ensues.[1-3]

The administration of inhalation anesthetic gases plays a primary role in modern clinical anesthesia. In anesthesia's early years, administration of a gas such as diethyl ether constituted the entire anesthetic regimen. Now, one or two gas anesthetics are combined with a variety of intravenous drugs to produce an anesthetic state. These intravenous drugs include sedative induction agents, analgesics, neuromuscular blocking drugs, and local anesthetics. This combination allows the use of smaller and more easily manipulated doses of specific receptor agonists and antagonists. Used in the proper combination, the desired amount of anesthesia, analgesia, amnesia, and muscle relaxation can be achieved. Current practice dictates that the anesthetic technique allow for a quick and pleasant induction and recovery with maximum patient safety and efficient caseload management. A sound understanding of inhalation anesthetic pharmacokinetics is essential to safe practice.

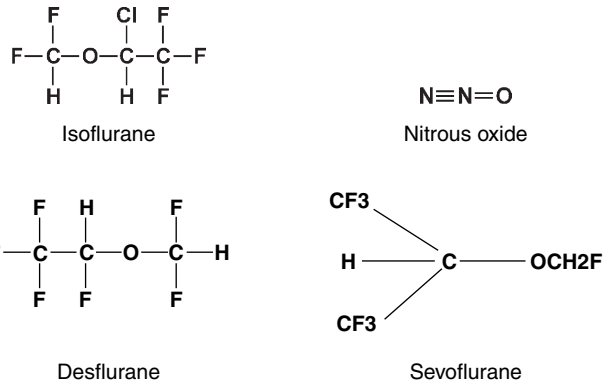

FIGURE **7-1** Chemical structure of anesthetic agents. Nitrous oxide is inorganic, and the rest are halogenated ethers.

PRIMARY FACTORS CONTROLLING UPTAKE, DISTRIBUTION, AND ELIMINATION OF ANESTHETICS

The basic task of anesthetic administration involves taking a drug supplied as a liquid, vaporizing it in an anesthesia machine, and delivering it to the patient's brain and other tissues via the lungs. Therefore the main factors that influence the ability to anesthetize a patient are technical or machine specific, drug related, respiratory, circulatory, and tissue related. The primary factors that influence absorption of the inhalation anesthetics are ventilation, uptake into the blood, cardiac output, the solubility of the anesthetic drug in the blood, and alveolar-to-venous blood partial-pressure difference. Other factors such as the concentration and second gas effects also play a role (Figure 7-2).[4]

A few assumptions are usually made. The level of anesthesia is related to the alveolar concentrations of anesthetic agents, which can be readily and continuously measured or inferred. The concentration or partial pressure of anesthetic in the lungs is assumed to be the same as in the brain, because the drugs are highly lipid soluble and diffusible, and they quickly and easily reach equilibrium among the highly perfused body compartments. For this reason, the dose of an individual drug is expressed in terms of the minimum alveolar concentration (MAC) necessary to produce anesthesia (lack of movement) upon surgical stimulation.[5-8] The faster the lung (and therefore brain) concentration rises, the faster anesthesia is achieved. Conversely, the faster the lung (brain) concentration falls after discontinuation of the drug, the more quickly the patient emerges.[9]

Machine-Related Factors

Concepts regarding the anesthesia machine and its function are described in detail in Chapter 15. Two factors that may affect uptake early in anesthetic administration are drug solubility in the rubber and plastic machine parts and total machine liter flow of the gases chosen.

The rubber and plastic components of the machine, as well as the ventilator and absorbent, can retain small quantities of anesthetic gases. Theoretically, this could slow administration to the patient at the start of anesthetic delivery. The effect on uptake is minimal in actual clinical practice and essentially ceases after approximately 15 minutes of administration.[10] Nonetheless, sequestration of small amounts of gas in the apparatus has other implications, such as when anesthetizing patients with malignant hyperthermia. All gases except nitrous oxide are potent triggering agents for a hyperthermic episode. To avoid exposure resulting from residual trace amounts of gases, a thorough flush of the anesthesia machine with 100% oxygen at 10 L/min for at least 20 minutes, replacement of breathing circuits and the carbon dioxide canister, and draining, inactivation, or removal of vaporizers are advised when preparing for a patient who is susceptible to malignant hyperthermia.[11] Proper preparation may vary with different machines and consultation with the machine manufacturer is advised.[12,13]

Low liter flows of oxygen and nitrous oxide carrier gas, although economical, deliver the anesthetic more slowly at the start of induction. Increasing liter flows for the first few minutes of the anesthetic minimizes this effect without unduly adding to cost.[14]

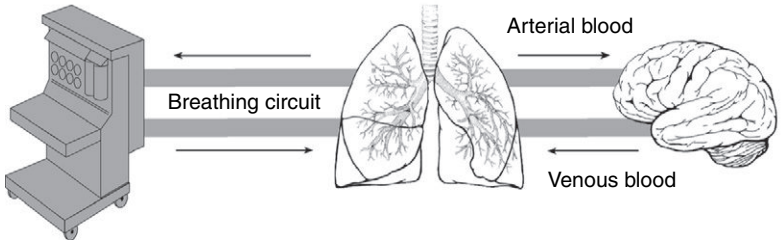

FIGURE **7-2** Transfer of an anesthetic gas from the machine through the lungs into the blood and tissues.

TABLE **7-1** General Anesthetic Properties of Inhalation Agents

Anesthetic	MAC (%)	Blood/Gas Partition Coefficient (at 37° C)	Oil/Gas Partition Coefficient (at 37° C)
Sevoflurane (Ultane)	2	0.6	50
Isoflurane (Forane)	1.15	1.4	99
Nitrous oxide	105	0.47	1.4
Desflurane (Suprane)	5.8	0.42	18.7

MAC, Minimum alveolar concentration.

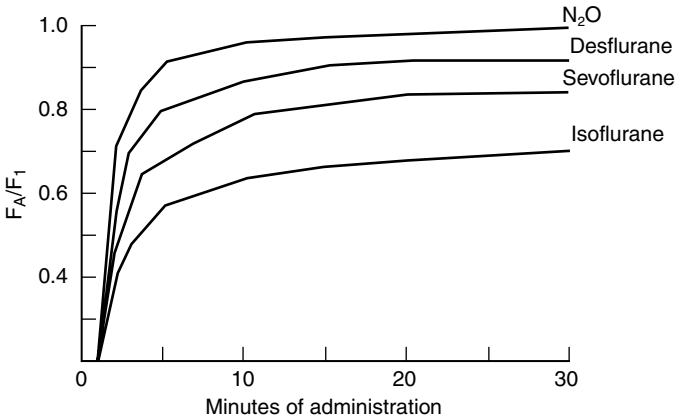

FIGURE **7-3** Rate of rise (F_A/F_1) of alveolar concentration of inhalation anesthetics over time. Low blood/gas anesthetics such as nitrous oxide and desflurane achieve a lung concentration much faster than moderate-solubility gases such as isoflurane. Note that nitrous oxide rises in the lungs more quickly than desflurane, in spite of a slightly higher blood/gas solubility. This is due to the concentration effect.

Drug-Related Factors

Blood/Gas Solubility

The blood/gas solubility coefficient of an anesthetic is an indicator of the speed of uptake and elimination.[15,16] It reflects the proportion of the anesthetic that will be soluble in the blood, "bind" to blood components, and not readily enter the tissues (blood phase) versus the fraction of the drug that will leave the blood and quickly diffuse into tissues (gas phase). The more soluble the drug (high blood/gas coefficient), the slower the brain and spinal cord uptake and therefore the slower the anesthesia achieved by the patient. Soluble drugs stay in the blood in greater proportion than less soluble agents; therefore, less of the drug is released to the tissues during the early, rapid-uptake phase of induction. For example, isoflurane has a blood/gas solubility coefficient of 1.4 or, expressed as a ratio, 1.4:1. Therefore 1.4 times as much stays in the blood as a nonreleasable fraction for every 1 molecule that enters the tissues and produces anesthesia. Conversely, agents with low solubility properties (low blood/gas coefficient) leave the blood quickly and enter the tissues, producing a rapid anesthetic state. Desflurane, for example, has a low blood/gas coefficient of 0.42 or, expressed as a ratio, 0.42:1. Only 0.42 of a molecule stays in the blood for every 1 (greater than twice as much) that enters the brain. Anesthesia is achieved quickly. Blood/gas solubility coefficients for the inhalation anesthetic agents are listed in Table 7-1.[17] The rate of rise of an anesthetic in the alveoli relative to the concentration administered is graphically depicted by plotting the fraction in the alveoli over the fraction inspired (Figure 7-3).

As noted previously, the lower the blood/gas solubility, the faster the rise in lung and brain concentrations. The rate of rise of low-solubility agents such as nitrous oxide and desflurane is greater than moderately soluble drugs such as isoflurane. Note in Figure 7-3 that nitrous oxide exhibits a slightly faster rate of rise compared with desflurane, despite a higher blood/gas coefficient. This variation in the usual trend is a result of the concentration effect—that is, nitrous oxide is given at much higher concentrations (50% to 70%) than desflurane (3% to 9%). Figure 7-4 depicts the effect of anesthetic blood solubility on uptake.

Ventilation Factors

As with all diffusible drugs, anesthetics move down a concentration gradient. Continuous inhalation administration of the agent into the lungs promotes subsequent diffusion into the blood and tissues as the anesthetic progresses. Anesthetic uptake slows throughout the surgical procedure as the tissue compartments become more saturated.[18] The anesthetic is delivered, along with the necessary amount of oxygen or an oxygen mix appropriate for the patient's condition. Supplemental nitrous oxide may also be used. Basically, the faster and more deeply a patient breathes or is ventilated, the faster the patient loses consciousness at the start of anesthesia and emerges at the end.[16,19,20] This is often referred to as the *ventilation effect*.

Ventilation-perfusion deficits or poor lung function hinders inhalation drug administration.[21,22] Rapid-acting (low blood/gas solubility) agents are affected by these deficits to a greater extent than are slower-acting (high blood/gas solubility) drugs.[23] These decreases in speed can be partially compensated for by increasing the concentration of insoluble (fast) agents or increasing ventilation with soluble (slow) drugs.

Concentration or Dose

During the first minutes of gas administration, a higher concentration of the drug than necessary for maintenance, or a loading dose, is delivered to speed initial uptake. This is commonly

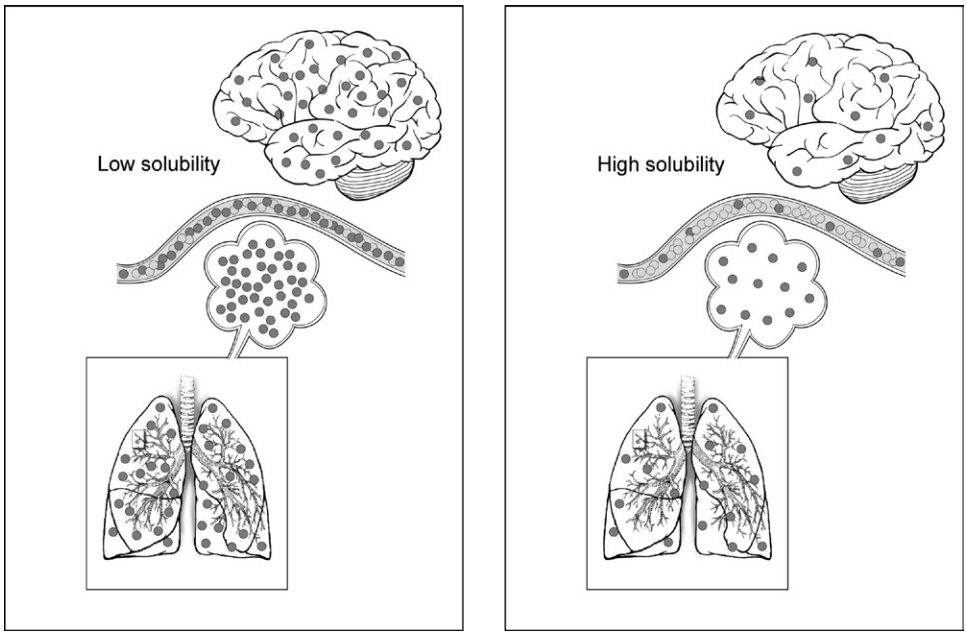

FIGURE **7-4** Effect of anesthetic blood/gas solubility on uptake. *Left*, an anesthetic gas with a low blood/gas solubility is not taken into the blood (*lightly shaded circles*); therefore, the alveolar (thus brain) concentration rises rapidly (*darkly shaded circles*), and the patient achieves anesthesia quickly. *Right*, an anesthetic gas with a high blood/gas solubility is taken up and held in the blood (*lightly shaded circles*), resulting in a slower rise in alveolar (thus brain) concentration (*darkly shaded circles*) and a slower onset of anesthesia.

TABLE **7-2** Inhalation Anesthetic Doses*

Anesthetic	Induction (%)	Maintenance (%)
Nitrous oxide	50-70	Same
Isoflurane (Forane)	1-4	0.5-2
Desflurane (Suprane)	3-9	2-6
Sevoflurane (Ultane)	4-8	1-4

*Doses vary according to patient status, procedure, and types of medications coadministered. Doses are given as vaporizer setting or partial pressures.

referred to as *overpressuring* or the *concentration effect*.[24] Overpressuring during initial administration is a common clinical practice and is more effective the more soluble the anesthetic. Overpressuring can speed the effect of slow agents but has less of an effect on relatively fast agents. This practice follows the kinetic standard of using a loading dose to speed onset. After the first few minutes, the dose is decreased to normal maintenance levels.[25]

As noted previously, the dose of an anesthetic is expressed in terms of MAC—the relative concentration when the anesthetic is combined with all the other gases in the lungs. Induction and maintenance doses are given as vaporizer settings of partial pressure in Table 7-2.

Second-Gas Effect

Simultaneous administration of a relatively slow agent such as isoflurane and a faster drug such as nitrous oxide (in high concentrations) can speed the onset of the slower agent. This is known as the *second-gas effect*.[26] The uptake of the slower agent in the alveoli and to even a greater proportion in the arterial blood, is increased by administering it with a high concentration of the faster anesthetic nitrous oxide.[27] The faster the inherent speed of the second gas on its own, however, the less prominent the augmentation when given with nitrous oxide. For example, sevoflurane, which has low blood solubility (blood/gas solubility coefficient 0.6) is rapidly taken up into tissues. Coadministration of sevoflurane with the slightly faster nitrous oxide produces a small but significant increase in uptake as compared with sevoflurane administration alone.[25,28-30] The mechanism for the second-gas effect is not definitive, but it has traditionally been explained as the large volume uptake of nitrous oxide concentrating the other alveolar gases. Recent data suggests an added effect of ventilation perfusion scatter on the distribution of blood flow and gas uptake in the lung.[27] The second-gas effect also occurs during emergence where the rapid elimination of nitrous oxide produces a clinically significant acceleration in the removal of the accompanying volatile agent.[31]

Tissue-Related Factors

Oil/Gas Solubility

The oil/gas solubility coefficient is an indicator of potency. The higher the solubility, the more potent the drug (see Table 7-1).[32,33] A high solubility coefficient reflects high lipid solubility. Because the anesthetic must traverse the blood-brain barrier and penetrate other lipid membranes to produce its action, highly lipid-soluble drugs tend to be the most potent. Of the current agents, isoflurane (oil/gas partition coefficient 99) is the most potent, and nitrous oxide (oil/gas partition coefficient 1.4) is the least potent. Remember that two factors are at play: how fast the drug is delivered to the tissues (blood/gas solubility) and how efficiently it can access and affect the sites of action (oil/gas solubility). Recent investigations suggest that polarity along with lipophilicity plays an important yet not fully understood role in the mechanism of inhalation anesthetics.[34-36]

Circulatory Factors

The cardiovascular system exerts two major influences on anesthetic uptake and distribution.[37] First, the majority of the blood leaving

TABLE 7-3 Tissue Compartments and Perfusion Comparisons

Characteristic	Vessel Rich	Muscle	Fat	Vessel Poor
Body weight	10%	50%	20%	20%
Cardiac output	75%	19%	6%	0%
Perfusion	75 mL/min/100 g	3 mL/min/100 g	3 mL/min/100 g	0 mL/min/100 g

TABLE 7-4 Anesthetic Metabolism

Agent	Average Metabolism (%)
Sevoflurane	3-6
Nitrous oxide	<1
Isoflurane	<1
Desflurane	<0.1

the lungs with anesthetic is normally distributed to the vital organs or high–blood-flow areas, commonly referred to as the *vessel-rich group* or *central compartment*. Organs such as the heart, liver, kidneys, and brain receive proportionately more anesthetic sooner than the muscle and fat areas (Table 7-3). The longer the anesthetic is given, the greater the saturation of all body compartments.

Second, during induction, increases in cardiac output slow onset. All anesthetics are affected; however, the more soluble the agent (higher blood/gas coefficient, and therefore slower), the greater the effect. An increased cardiac output removes more anesthetic from the lungs, which slows the rise in lung and brain concentration.[38-40] This effect dissipates as the anesthetic proceeds.

Metabolism

The modern anesthetics are minimally metabolized (Table 7-4).[41] Possible toxic metabolite formation is not currently a clinical issue.[42] Drug metabolism has historically been associated with various anesthetic-related toxicities. These include hepatotoxicity from halothane[43] and other agents and nephrotoxicity from methoxyflurane. Nitrous oxide, desflurane, and isoflurane are the least metabolized and do not result in metabolism-related toxicity. Although sevoflurane is metabolized approximately 5%, releasing free fluoride ions, no related clinically significant toxicity has been noted.[44-47]

Emergence

After surgery, when the anesthetic is discontinued, the same principles that influence onset apply. The anesthetic leaves the tissues via the blood and exits the lungs with ventilation. Routine practice is to administer 100% oxygen to assist recovery. If nitrous oxide was given, 100% oxygen prevents diffusion hypoxia. Anesthetics redistribute out of the tissues in a more uniform manner compared with the way they distribute during onset. An equilibrium is approached among tissues during the anesthetic period, so recovery tends to be smoother than induction with respect to the excitatory stage responses. In general, the longer an anesthetic is administered, the slower the patient emerges. This effect is greatest with the most soluble isoflurane and less with sevoflurane and desflurane, respectively. Differences among anesthetics are small but significant and are seen primarily during the final 10% of the elimination process.[48]As expected, the least soluble desflurane exhibits the fastest clinical recovery, with sevoflurane and isoflurane following in that order. Residual anesthetic has been shown to remain in the body for several days following a routine anesthetic.[49]

TABLE 7-5 Nitrous Oxide–Induced Space or Compartment Change*

Air Space	Nitrous Oxide–Induced Change
Pneumoencephalogram	CSF pressure increases to three times baseline in 5 minutes
Intraocular hexafluoride gas	2-18 mmHg increase in pressure in 20 minutes
Middle ear pressure	Increased 1-7 mmHg in 1 hour
Pneumothorax	2-3 times the volume in 5-20 minutes
Intestinal gas	Double in 150 minutes
Air bubble	Immediate increases in size occur

Data adapted from Evers AS, et al, eds. *Anesthetic Pharmacology*. 2nd ed. Cambridge: Cambridge University Press; 2011:393.
*The rate at which the pressure changes depends on the perfusion of surrounding tissue, compliance of the space, and the concentration of nitrous oxide.
CSF, Cerebrospinal fluid.

Diffusion Hypoxia

During emergence, when high concentrations of a rapid (insoluble) anesthetic such as nitrous oxide have been given, the drug exits the body quickly through the lungs and is replaced by less soluble nitrogen in air. This may result in a transient dilution of normal respiratory gases such as oxygen and carbon dioxide. This phenomenon is referred to as *diffusion hypoxia*. Administration of 100% oxygen for several minutes when anesthesia is terminated entirely avoids this potential problem.

Diffusion of Nitrous Oxide into Closed Spaces

Nitrous oxide diffuses into air-containing cavities in the body during an anesthetic procedure. These air-containing spaces are normally rich in nitrogen, which is 34 times less soluble than nitrous oxide. If the space is expandable, it increases in volume. Examples of expandable air cavities include air embolism, pneumothorax, acute intestinal obstruction, intraocular air bubbles produced by sulfur hexafluoride gas injection, and pneumoperitoneum. Rigid air-containing spaces will undergo an increase in pressure. This includes tympanic membrane grafting after tympanomastoid procedures and intracranial air during diagnostic or surgical intracranial procedures. Nitrous oxide should be avoided in these situations. The endotracheal tube cuff, laryngeal mask airway, and balloon-tipped pulmonary artery catheters may expand during nitrous oxide anesthesia, and appropriate precautions and adjustments should be considered.[50-52]

Some characteristics and time courses for air expansion are noted in Table 7-5.[53]

PEDIATRICS

The uptake of anesthetic drugs is faster in children than in adults.[54] In other words, a child goes to sleep faster than an adult patient.[55]

TABLE 7-6 Inhalational Anesthetic Pharmacokinetic Concepts

Concept	Comments
Minimum alveolar concentration (MAC)	The MAC required to achieve surgical anesthesia (immobility) in 50% of patients exposed to a noxious stimulus
Minimum alveolar concentration awake (MAC awake)	The MAC suppressing appropriate response to commands in 50% of patients; memory is usually lost at MAC-awake; approximately 0.3-0.5 MAC
Minimum alveolar concentration—block adrenergic responses (MAC-BAR)	The alveolar concentration of anesthetic that blunts the autonomic response to noxious stimuli; approximately 1.6-2.0 MAC
Ventilation effect	The greater the alveolar ventilation, the faster the patient achieves anesthesia
Concentration effect	The higher the concentration of anesthetic delivered, the faster anesthesia is achieved; this is also referred to as *overpressuring;* as with any drug, the larger the initial dose administered, the faster the onset of action
Blood/gas solubility coefficient	The blood/gas solubility coefficient is the indicator of an anesthetic's speed of onset and emergence: the higher the coefficient, the slower the anesthetic; conversely, the lower the coefficient, the faster the anesthetic
Oil/gas solubility coefficient	The oil/gas solubility coefficient is the indicator of an anesthetic's potency: the higher the coefficient, the more potent the agent
Second-gas effect	The second-gas effect is a phenomenon in which two anesthetics of varying onset speeds are administered together: a high concentration of a fast anesthetic such as nitrous oxide is administered with a slower second anesthetic gas; the slower gas achieves anesthetic levels more quickly than if it had been given alone
Diffusion hypoxia	Diffusion hypoxia occurs when high concentrations of nitrous oxide are administered; at the end of the procedure, when nitrous oxide is discontinued, it leaves the body very rapidly, causing a transient dilution of the oxygen and carbon dioxide in the lungs; hypocarbia and hypoxia may occur; administration of 100% oxygen for approximately 3-5 min when nitrous oxide is discontinued alleviates this problem
Cardiac output effect	Increases in cardiac output decrease the speed of onset of all anesthetics; the more soluble anesthetics are affected to a much greater extent than the insoluble anesthetics
Ventilation-perfusion abnormalities	Ventilation-perfusion abnormalities reduce the speed of onset of all anesthetics and affect the insoluble agents to a much greater degree than the soluble agents
Pediatrics	Children achieve anesthesia more rapidly than adults because of a higher ventilatory rate and vessel-rich-group blood flow; this occurs despite the fact that the required dose and cardiac output are higher in children
Obesity	Obesity has minimal clinical effects on anesthetic induction; however, emergence may be slower because of deposition of anesthetics in fat
Pregnancy	The kinetics of the inhalation anesthetics are similar in pregnant women and nonpregnant women; placental transfer is time dependent as expected

The child's higher alveolar ventilation per weight accounts for this effect.

Infants and children have a higher cardiac output per weight than adults. As noted previously, the higher the cardiac output, the slower the onset. This effect is minimized, however, by the increased cardiac output distributed to the vessel-rich group in children. The infant's lower muscle mass allows more of the agent to concentrate in the vital organs. This overall effect is to promote uptake to the brain.

Finally, anesthetics appear to be less blood soluble (i.e., they work faster) in children than in adults. This effect varies with age and the agent.[56-58] The MAC or required dose of anesthetics is higher in infants and children and decreases with increasing age. Infants aged 6 months have a MAC 1.5 to 1.8 times higher than a 40-year-old adult.[59]

Recent data suggest that during recovery from anesthesia with some inhalation agents, especially sevoflurane, emergence reactions and agitation may occur in infants, children, and young adults.[60-62] Evidence suggests that this phenomenon is not pharmacokinetic or related to rapidity of emergence.[63] Risk factors include preschool age 2 to 5 years, difficult parental separation behavior, and postoperative pain.[62,64] Administration of fentanyl, dexmedetomidine, propofol, or ketamine reduce the incidence of emergence agitation.[65,66] Midazolam or serotonin antagonists have no reducing effect.[62] A glossary of pharmacokinetic concepts is given in Table 7-6.

OTHER FACTORS

Obesity

Obesity has no clinically significant effect on the uptake of the inhalation anesthetics. Some clinicians prefer desflurane due to its low solubility and lipophilicity, which appears to promote a slightly faster recovery. Long procedures and morbid obesity allow for an increase in deposition of anesthetics into fat and may prolong recovery.[67-69]

Pregnancy

Pregnant women have a higher minute ventilation than nonpregnant women, which would predict a faster uptake. Conversely, they also have a higher cardiac output, which tends to slow uptake. Overall, these actions oppose each other so that the uptake of anesthetics in pregnant women will be similar to nonpregnant women.[70] Maternal to fetal transfer of the nitrous oxide has been studied and data suggests that placental transfer

during cesarean section is slower than maternal uptake and time dependent.[71]

SUMMARY

A thorough understanding of the basic pharmacokinetic principles involved in administering anesthetic gases and the development of clinical skills in their use are the cornerstones of modern anesthesia practice. Adults are generally induced with one of the several available intravenous agents and maintained with a combination of inhalation and intravenous drugs. Better anesthesia machines and more sophisticated monitoring have greatly facilitated the quantification of clinical anesthetic levels and depth, contributing to the remarkable safety of modern anesthesia practice.

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Inhalation Anesthetics

◆ *Mark A. Kossick*

CHAPTER 8

In the span of almost two centuries major advances have been made in the development and clinical use of inhalation anesthetics (Table 8-1); this continuum includes the investigation of nitrous oxide (N_2O) in 1800 by Humphry Davy[1] following its preliminary discovery by Dr. Priestly in 1786[2] with what was termed "dephlogisticated air." Then 195 years later the most current inhaled anesthetic (sevoflurane) was approved by the Food and Drug Administration in 1995. Interestingly, each of these agents share a common characteristic that promotes their clinical use today—a low blood:gas solubility coefficient, which portends a favorable pharmacokinetic profile.

The present-day use of N_2O can be credited to Edmund Andrews, a professor of surgery in Chicago. In 1868 he declared that a safer anesthetic could result from combining oxygen (O_2) with N_2O.[3] Before that time N_2O was administered through a mouthpiece with a nose clamp to prevent the rebreathing of air.

One of the earliest "complete" anesthetic agents used was diethyl ether (C_2H_5–O–C_2H_5). The first ether anesthetic was administered in Georgia on March 30, 1842, when Crawford Long anesthetized a patient for a minor operation (excised a tumor).[4] However, the recognition of numerous unfavorable characteristics (excessive secretions with inhalation induction, laryngospasm, excessive depths of anesthesia) prompted its disappearance from clinical practice as newer agents were subsequently developed.

In the 1930s, research into potential anesthetic agents was based on the principle of a structure-activity relationship.[5] One of the earliest inhalation anesthetics developed in this manner was divinyl ether. Halothane was introduced into clinical practice in 1956 by Bryce-Smith and O'Brien in Oxford[6] and Johnstone in Manchester[7] and represented a significant advancement in inhalation anesthesia. Its sweet odor, nonflammability, and high potency offered clinical characteristics that were absent from the previously available inhaled anesthetics. The search for newer and improved inhalation anesthetics persisted as concerns with hepatotoxicity and arrhythmogenicity of this alkane derivative began to be documented.

The two most recently released inhalation agents, sevoflurane (synthesized by Regan in the late 1960s) and desflurane (the 653rd compound of more than 700 synthesized by Terrell and colleagues between 1959 and 1966), are commonly used today for a diverse surgical population, based on their pharmacokinetic and pharmacodynamics profile. Although desflurane and sevoflurane do not possess all of the properties of an ideal inhalation agent, the sufficient number of clinical benefits attributed to these agents has been instrumental in anesthesia providers routinely selecting one or the other for many surgical procedures.

TABLE 8-1 History of the Introduction of Inhalation Anesthetics

Anesthetic	Year(s) Anesthetic Properties Demonstrated/Introduced
Ether (Crawford Long)	1842
N_2O (Horace Wells)	1845
Chloroform (James Simpson)	1847
Cyclopropane (George Lucas, Velyien Henderson)	1934
Fluroxene	1951
Halothane	1956
Methoxyflurane	1960
Enflurane	1973
Isoflurane	1981
Desflurane	1993
Sevoflurane	1995

RELATIONSHIP OF CHEMICAL STRUCTURE AND AGENT CHARACTERISTICS

An understanding of the chemical structure of inhalation agents provides insight into their physical properties (e.g., flammability). However, the relationship between the pharmacologic characteristics (e.g., arrhythmogenic properties) and chemical structure of agents is not as predictable. This section reviews the structure-activity relationship of anesthetic vapors and their clinical relevance. Some selected nomenclature in regard to physical and chemical properties are listed in Table 8-2.

All commonly used inhalation agents are ethers (R–O–R) or aliphatic hydrocarbons (straight-chained or branched nonaromatic hydrocarbons) with no more than four carbon atoms (Figure 8-1). The length of the anesthetic molecule is significant in that immobility (anesthetic effect) is attenuated or lost if carbon atom chain length exceeds a distance of four or five carbon atoms (5 angstroms [Å]).[8] The molecular shape of the agents is spherical or cylindrical with a length less than 1.5 times the diameter.[9]

Of primary importance to the development of volatile agents was the discovery of the impact of halogenation of organic compounds. Halogenation of hydrocarbons and ethers (the addition of fluorine [F], chlorine [Cl], bromine [Br], or iodine [I]) influences anesthetic potency, arrhythmogenic properties, flammability, and chemical stability (e.g., oxidation during storage and reactions with bases).

Anesthetic potency has been shown to increase when a halogen with a lower atomic mass unit (amu) is replaced by a heavier halogen (e.g., bromine at 80 amu substituted for fluorine at 19 amu).[10-12] Nonetheless, a ceiling effect exists with halogenation of anesthetic compounds. For example, adding F atoms to ether results in a continuum in which the ether becomes more potent, then acts as a strong convulsant, and finally changes to an inert compound with full fluorination.[13]

TABLE 8-2 Select Characteristics of Inhalation Anesthetics

Characteristics	Nitrous Oxide	Isoflurane	Desflurane	Sevoflurane
Molecular formula	N_2O	$C_3H_2ClF_5O$	$C_3H_2F_6O$	$C_4H_3F_7O$
Ostwald blood/gas partition coefficient (37° C)	0.47	1.43	0.42	0.68
Oil/gas partition coefficient	1.4	99	18.7	50
Saturated vapor pressure (mmHg, at 20° C)	Gas	238	669	157
Molecular weight (g/mol)	44.01	184.49	168.04	200.05

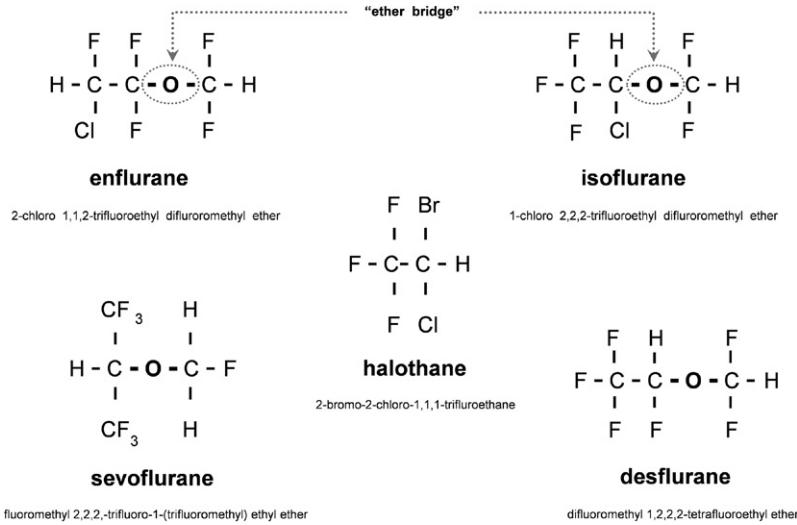

FIGURE **8-1** Chemical structure of volatile agents. The "ether bridges" (R–O–R) are seen with sevoflurane, desflurane, and isoflurane. *R* refers to alkyl group. Halothane (no longer used) is an example of a halogenated hydrocarbon. Enflurane and isoflurane are isomers (have the same molecular formula).

In general, the potency of volatile agents has also been found to correlate with the physical property of lipid solubility. A decline in potency (meaning an *increase* in the minimum alveolar concentration [MAC] of volatile agents) is associated with a proportional decrease in oil/gas partition coefficient values. Exceptions to this principle exist and demonstrate that the correlation between potency and lipid solubility is not perfect.

With regard to arrhythmogenic properties, increasing the number of halogen atoms within a volatile agent favors the genesis of cardiac dysrhythmias.[13] Nevertheless, alkanes that contain five halogens (e.g., halothane) are more prone to induce arrhythmias than ethers with six halogen atoms (e.g., isoflurane).[14]

Flammability is reduced and chemical stability enhanced by substituting hydrogen atoms with halogens. The epitome of this relationship is demonstrated with desflurane, a compound that contains fluorine as its only halogen and thus strongly resists biodegradation; desflurane is metabolized one tenth as much as isoflurane.[15,16]

METABOLISM

As stated previously, the chemical structure of each inhalation agent determines the extent to which it is metabolized. In general, increasing the number of fluorine atoms to a anesthetic molecule retards biodegradation (halothane has 3 and desflurane has 6). The current agents undergo metabolism at the following rates: sevoflurane 5% to 8% and isoflurane, desflurane, and nitrous oxide in trace amounts.[17-20] Desflurane has been shown to resist biodegradation, even after 7.35 MAC-hours, as determined by peak mean urinary excretion rate of trifluoroacetic acid (TFA). This metabolite (TFA) is recognized as being a sensitive marker of desflurane metabolism.[21]

The biodegradation of all currently used volatile anesthetics is predominantly accomplished by way of hepatic metabolism through oxidation (phase I). Sevoflurane has been used in the United States since 1995. Its biotransformation and lack of nephrotoxicity are reviewed later in this chapter.

PHARMACODYNAMICS

Mechanisms of Action

The following properties of anesthetics must be taken into account when developing a theory that attempts to explain their mechanism of action:

- Lipid solubility is directly proportional to potency (Meyer-Overton rule).[22,23]
- Reversal of anesthetic effect can be achieved with the application of pressure, with some exceptions (species variation).[24]
- No common chemical structure for the variety of compounds is capable of producing anesthesia.
- The molecular and structural changes responsible for producing anesthesia must occur within seconds and be reversible.
- A reduction in body temperature lowers anesthetic requirements.

The unitary hypothesis was previously offered as an attempt to meet these prerequisites. This theory proposed that all inhalation

anesthetics work via a similar (undefined) mechanism of action but not necessarily at the same site of action. One factor that supported this hypothesis was the Meyer-Overton correlation, which recognized the more lipid soluble the agent, the greater its potency (the lower its MAC value). This correlation suggested that anesthesia is produced by the volume of anesthetic molecules present (dissolved) at the site, not by the type of inhaled agent present. Nevertheless, continued research on the mechanism of action of inhalation anesthetics has mitigated the utility of this theory.[25]

For the current review on how inhaled anesthetics produce anesthesia, it is important to define "general anesthesia." This would include a drug's capacity to induce and sustain as needed, a state of unconsciousness, amnesia, analgesia, and immobility. Secondary effects of general anesthesia can be therapeutic or problematic (e.g., attenuate stress response to surgical stimuli, appearance of arrhythmias).

It should be understood that the limitations of this chapter do not permit a substantive review of the extensive research done in attempting to explain the mechanism of action of inhalation anesthetics. What investigators have accomplished is to illuminate how diverse and complex is the means by which anesthesia is produced. Grossly, anesthetic sites of action include supraspinal and spinal anatomic structures; and on the molecular level a myriad of protein structures (receptors, channels). For the reader interested in a more comprehensive review of this topic, the *Canadian Journal of Anesthesia* published in 2011 a special issue titled "Mechanisms of Anesthesia" (Vol. 58 [2]).

In vitro, in vivo, animal, and human subject research has permitted the description of the mechanism of action of inhaled anesthetics relative to distinct anatomic regions of the body (including the cellular level) and molecular changes. The spinal cord is known to mediate immobility to a painful stimulus via several mechanisms including (1) enhancing background potassium (K^+) currents in tandem-pore-domain, weak inward-rectifying K^+ channels (TWIK, TASK [TWIK-related acid-sensitive K^+ channel])[26-28] and (2) reducing spontaneous action potential firing of spinal neurons via glycine receptors and γ-aminobutyric acid type A [$GABA_A$]) receptors.[29] Investigators have also demonstrated that nonimmobilizers with lipophilic characteristics (e.g., perfluoropentane) are able to produce amnesia but not immobility to noxious stimuli, which suggests two separate sites and mechanisms of anesthetic action for some drugs.[30] In contrast with other research, spinal *and* cerebral $GABA_A$ receptors (same receptor-clinical effect) were shown to contribute to volatile anesthetic's ability to produce immobility; therefore the anesthetic effect of immobility is modulated at the spinal cord and supraspinal level.[31,32] In summary, research has validated the concept of a distinct anatomic division for the mechanism of action of volatile agents as being oversimplistic (and inaccurate); one example being the isolation of TWIK and TASK (members of the tandem-pore-domain K^+ channel subfamily) in both the spinal cord and brain.[27, 28] Clearly, supraspinal areas of the nervous system are recognized to mediate amnesia and immobility.[28,32-35]

Other specific anatomic sites where volatile anesthetics produce an effect include the reticular formation within the brainstem,[36] cerebral cortex,[37] and hippocampus.[38] Evidence of changes in cortical activity by volatile agents includes alterations in electroencephalogram (EEG) activity. All inhalation agents cause a dose-dependent change in the EEG—an initial increase in voltage (and decrease in frequency), then a peak, followed by a decline.[39,40] Deeper levels of anesthesia produce burst suppression and eventually a flat EEG.[41] Nonspecific generalized EEG changes may also persist for several days postoperatively.[42]

Increased or decreased neuronal excitability and enhanced or depressed inhibitory postsynaptic currents can occur, depending on which anesthetic agent or specific area within the central nervous system (CNS) is manipulated. In addition to supraspinal effects, depression of motor neurons within the spinal cord has also occurred with volatile anesthetics.[43,44]

On a molecular level, researchers have found that the most likely site of action for volatile anesthetics involves interactions with membrane proteins in specific receptors (stereoselective) and not perturbation of lipid bilayers.[45-48] The primary receptor within the CNS believed to modulate anesthetic effects is the GABA receptor, specifically the subtype A.[31,33,34,49] This receptor is located abundantly in the CNS and is a ligand-gated chloride (Cl^-) ion channel.[50] Agonism of this receptor by full anesthetics (volatile agents) results in enhanced Cl^- conductance,[51] which leads to *inhibitory* actions on local neurons.[50] Ultimately, what is expressed is an extension of the amount of time the Cl^- channel remains open. Neuronal nicotinic acetylcholine receptors (nAChRs) have also been shown to be highly sensitive to inhalational anesthetics and are believed to significantly influence several stages of anesthesia.[52]

An investigation by Kaech et al.[53] revealed a new anesthetic site of action within the CNS; chloroform, diethyl ether, methoxyflurane, halothane, enflurane, and isoflurane were each shown (in clinically relevant concentrations) to block the morphologic plasticity of dendritic spines. Prior research has demonstrated that dendritic spines can change shape in seconds.[54] This phenomenon occurs secondary to motile actin, which is abundant in the spines.[55] These volatile agents were found to strongly inhibit actin motility, which blocked changes in dendritic spine shape; the inhibition was fully reversed after removal of the agents. The dendritic spines serve as excitatory postsynaptic contact sites.[56] They are extremely abundant in the cerebral cortex (greater than 10^{13}) and are also located in large numbers in the cerebellum, basal ganglia, and olfactory bulb.[57] The details of how these rapid morphologic changes in dendritic spines contribute to an anesthetic state are unclear and merit further research.

The CNS effects of amnesia and loss of consciousness likely are produced separately from the immobility conceptualized in the theory of MAC. The concept of MAC refers to the concentration required to prevent movement in response to a surgical situation. This is probably the result of an effect at the spinal cord level via glycine, sodium, and *N*-methyl-D-aspartate receptor (NMDAR) action. Potassium, $GABA_A$, opioid, α_2−, $5HT_3$, and acetylcholine receptors are likely not involved in producing immobility.[58] They may be involved in varying degrees in the amnestic and anesthetic effects in the CNS. Lastly, researchers have found halogenated inhaled anesthetics inhibit voltage-gated sodium (Na^+) channels, which may represent a common means for producing an anesthetic effect.[59] A summary of reviewed mechanisms of action of inhalation anesthetics is provided in Box 8-1.

MINIMUM ALVEOLAR CONCENTRATION

A useful means of comparing the potencies of inhalation agents is to use the concept of MAC, defined as the minimum alveolar concentration at equilibrium (expressed as a percentage of 1 atmosphere) in which 50% of subjects will not respond to a painful stimulus (i.e., initial surgical skin incision).[60] The response is defined as gross, *purposeful* movement of the head or extremities. The MAC values for the modern inhalation agents are listed in Table 8-3.[61-64]

The MAC of volatile agents can be affected by numerous factors, surprisingly even hair color.[65,66] With increasing age,

BOX 8-1

Mechanisms of Action of Inhalation Anesthetics

Anatomical/Molecular Sites and Proposed Mechanisms

Brain (Supraspinal)

- Reticular formation, brainstem, cerebral cortex, hippocampus
- Enhanced Cl^- conductance via agonism of cerebral $GABA_A$ receptors (ligand-gated Cl^- channel), which produces an inhibitory effect on neurons
- Neuronal nicotinic acetylcholine receptors
- Abatement of the morphologic plasticity of dendritic spines (cerebral cortex, cerebellum, basal ganglia, olfactory bulb)
- Affecting K^+, opioid, α_2-, $5HT_3$, and acetylcholine receptors
- Modulating two-pore domain K^+ channels (K2P [TWIK, TASK])
- Inhibition voltage-gated Na^+ channels

Spinal Cord

- Immobility in response to painful stimuli via
  - Modulating two-pore domain K^+ channels (K2P [TWIK, TASK])
  - Reducing spontaneous action potential firing of spinal neurons via glycine receptors and $GABA_A$ receptors
  - Interaction with glycine, Na^+, and *N*-methyl-D-aspartate receptors
- Depression of motor neurons (perhaps via hyperpolarization)

$GABA_A$, γ-aminobutyric acid type A; *TWIK*, tandem-pore-domain, weak inward-rectifying K^+ channels and subfamily of K2P, *Cl–*, chloride; *Na+*, sodium; *TASK*, a subfamily of K2P channels.

TABLE 8-3 Potencies of Volatile Anesthetics in Humans with and without N_2O Expressed in MAC Values

Anesthetic	MAC* (expressed as a % of 1 atmosphere)	In 60%-70% N_2O MAC
Nitrous oxide	104	—
Isoflurane	1.17	0.56
Desflurane	6	2.38
Sevoflurane	2	0.66

*Age 30 to 60 years.
MAC, Minimum alveolar concentration; N_2O, nitrous oxide.
MAC-awake is the minimum alveolar concentration of anesthetic that inhibits responses to command in half the patients. It is approximately one-third MAC.
MAC-BAR is the minimum alveolar concentration of anesthetic that blunts the autonomic response to noxious stimuli. It is approximately 1.6 times higher than MAC.

BOX 8-2

Relationship of Physiologic and Pharmacologic Factors to the MAC of Inhaled Anesthetics

Factors That Reduce MAC

- Increase in age
- Hypothermia
- Administration of depressant medications (e.g., opioids, opioid agonist-antagonist analgesics, benzodiazepines, barbiturates, chlorpromazine, hydroxyzine)
- α_2 Agonists
- Acute ethanol consumption
- Hypoxemia
- Anemia (less than 4.3 mL O_2/dL blood)
- Hypotension (MAP less than 50 mmHg)
- Pregnancy
- N_2O, ketamine, lidocaine, clonidine, alpha-methyldopa, reserpine, chronic amphetamine use, lithium

Factors That Increase MAC

- Young age
- Hyperthermia
- Hyperthyroidism
- Chronic alcohol consumption
- Acute administration of amphetamine
- Red-headed females

Factors with No Effect on MAC

- Duration of anesthesia
- Gender
- Hypocapnia and hypercapnia
- Metabolic alkalosis
- Hypertension
- Administration of propranolol, isoproterenol, promethazine, naloxone, aminophylline, and neuromuscular blocking agents.

MAC, Minimum alveolar concentration; N_2O, nitrous oxide.

the MAC of all inhaled anesthetics is reduced; in humans with mean age 18 to 30 years, the MAC of desflurane is 7.25%, in contrast to 6% in humans 30 to 55 years of age.[63] Infants represent an exception to the MAC age concept in that their anesthetic requirements exceed those of neonates. In general, the duration of anesthesia is believed not to effect MAC; however, one group of investigators found the MAC of isoflurane was reduced over time during surgery.[67] Box 8-2 lists variables shown to reduce and increase MAC.

Two other areas related to MAC are MAC-awake and MAC-BAR (block adrenergic response). *MAC-awake* is defined as the minimum alveolar concentration at which 50% of subjects will respond to the command "open your eyes." It has also been described as the anesthetic concentration that is between the end-tidal values that allow and prevent response to a command.[68] This end-tidal concentration is usually associated with a loss of recall and encompasses approximately one third of MAC values. MAC-awake can also be used in combination with MAC values to evaluate the potency of each agent with regard to amnestic properties. This is done by dividing MAC-awake by MAC (MAC-awake/MAC ratio). This parameter indicates that agents with ratios between 0.3 and 0.4 (e.g., desflurane, sevoflurane, isoflurane) are considered potent anesthetics. In contrast, N_2O, which has a ratio of 0.64, is considered a weak amnestic agent.

The MAC-BAR parameter represents the MAC necessary to block the adrenergic response (e.g., changes in plasma norepinephrine concentration, heart rate [HR], rate-pressure product, and mean arterial pressure) to skin incision. It can be expressed as a $MAC\text{-}BAR_{50}$ or $MAC\text{-}BAR_{95}$. The former is similar to AD_{95} values, which represent the anesthetic dose that inhibits somatic evidence of light anesthesia in 95% of subjects in response to skin incision. Established $MAC\text{-}BAR_{50}$ values for volatile agents include (in 60% N_2O) 1.85 MAC for both isoflurane and desflurane. Desflurane's $MAC\text{-}BAR_{50}$ value has been shown to be reduced by 85% with the use of 1.5 mcg/kg of fentanyl given IV 5 minutes before skin incision.[69] When investigating desflurane in 60% N_2O combined with a remifentanil at a target plasma concentration of 1 ng/mL (via a computer-driven infusion device), the

$MAC\text{-}BAR_{50}$ is reduced by 60% and with a target concentration of 3 ng/mL further reduced by 30%.[70]

The $MAC\text{-}BAR_{50}$ for sevoflurane in 66% N_2O is 2.2.[71] In canine studies it has been shown to be reduced (but not in a dose-dependent manner) with intravenous ketamine.[72] It should be emphasized that MAC-BAR values exceed the requirements for ablation of skeletal muscle movement with surgical stimulation; therefore blocking an adrenergic response requires a greater depth of anesthesia than preventing skeletal muscle movement. From a clinical standpoint, patients usually require anesthetic concentrations that exceed MAC by 20% to 30% (1.2 to 1.3 times MAC). At this alveolar concentration, somatic evidence of light anesthesia will commonly be abated, and fewer patients will respond adrenergically to the stresses of surgery.[73]

The concept of MAC has limitations when applied clinically to determine adequacy of anesthesia. It should be viewed as a general guide to the overall depth of anesthesia. One variable that restricts its application is the frequency at which surgical patients receive muscle relaxants, which attenuates the recognition of skeletal muscle movement in response to light planes of anesthesia. This results in the dependence of anesthesia providers on other traditional signs of anesthetic depth, such as changes in heart rate (HR), blood pressure, pupillary size, and sweating. Unfortunately, a light plane of anesthesia can exist even with a decreased blood pressure and a normal heart rate (e.g., patients with limited cardiac reserve). Pupillary changes can also be affected by opioids (miosis) and volatile agents (mydriasis) over time, even in the absence of surgical stimuli.[74] Also, the usefulness of a traditional clinical end-point as a guide to depth of anesthesia can change over time. For example, one investigator found that decreases in blood pressure served as an estimate of anesthetic depth during the first hour of an anesthetic, but after 5 hours they were unreliable—further declines in blood pressure did not occur even with increasing concentrations of halothane.[75] The challenge to the anesthesia provider is to estimate anesthetic depth based on a collation of variables (HR, blood pressure, synergistic and additive effects of anesthetic adjuvants, volume status, physiologic reserve, MAC, MAC-BAR, and MAC intubation values). The last variable (MAC intubation) is similar to MAC-BAR in that its values exceed the anesthetic requirements for surgical skin incision. Clearly, different stimuli require different end-tidal concentrations (brain anesthetic partial pressures) of volatile anesthetics.[76]

INFLUENCE OF INHALATION AGENTS ON ORGANS AND SYSTEMS

Central Nervous System

The volatile agents can adversely affect the care provided to patients with CNS pathology. Such effects include areas related to intracranial compliance, autoregulation of cerebral blood flow (CBF; e.g., cerebrovascular reactivity to carbon dioxide [CO_2]), cerebral metabolic rate, cerebrospinal fluid pressure (CSFP), and neurologic assessment.

Cerebral Metabolic Rate and Cerebral Blood Flow

In general, volatile agents decrease cerebral metabolic rate of O_2 consumption ($CMRO_2$) in a dose-dependent manner, whereas their effect on cerebral blood flow is variable; the latter has been reported by various researchers to be unchanged,[77,78] increased (dose-dependent and time-dependent manner),[79-81] or decreased.[82] When vascular resistance is decreased, CBF, cerebral blood volume (CBV), and CSFP increase. The order of potency for increasing CBF varies; it is affected by the dose of volatile anesthetic,[81,83] the administration of other drugs (e.g., propofol, N_2O),[84] the rate of change in end-tidal concentration of agent,[79] and the animal model used.[85] In other cases, differences in research findings lack a plausible explanation. A distinct picture of a homogeneous versus heterogeneous change in CBF, $CMRO_2$, and other anesthetic effects of volatile agents has been noted.[86,87] For example, in rats halothane has been shown to globally increase CBF, whereas isoflurane's sphere of influence predominates in the subcortical regions and hindbrain structures.[88]

Uncoupling of Cerebral Blood Flow and Metabolism

When decreases in $CMRO_2$ are accompanied by increases in CBF, *uncoupling* is said to occur. As noted earlier, volatile anesthetics are capable of producing this effect. This paradoxic response (decreased $CMRO_2$ occurring in conjunction with increased CBF) seems not to occur with 1.0 MAC or less of halothane and isoflurane[89]; the magnitude of change is variable and dose dependent,[81] meaning some flow-metabolism coupling mechanism is preserved.[90, 91]

Nitrous oxide reduces cerebrovascular tone significantly. This effect is unmasked and enhanced when N_2O is combined with a volatile anesthetic (decreased autoregulation).[92] The mechanism for increased CBF may be related to a sympathoadrenal-stimulating effect of N_2O. The changes produced by N_2O in the $CMRO_2$ are the reverse of what takes place with volatile agents (i.e., increased $CMRO_2$).[93] Thus N_2O increases $CMRO_2$ and CBF. Nevertheless, the combination of elevated CBF and $CMRO_2$ still results in an uncoupling between flow and metabolism, because the increase in $CMRO_2$ exceeds, albeit slightly, the elevation in CBF.[94] In summary, N_2O use in neurosurgical procedures is acceptable, as long as the anesthesia provider recognizes that its vasodilatory effects might adversely affect surgical outcome in patients with reduced intracranial compliance. Mild hyperventilation to low normal ranges of carbon dioxide helps attenuate the increase in CBF that accompanies the use of N_2O.[95]

Cerebral Vasculature Responsiveness to CO_2

The normal physiologic response of the cerebral vasculature to CO_2 is to vasoconstrict in the presence of hypocapnia and vasodilate with hypercarbia. This reflex is effective in the acute setting when used during neurosurgical procedures to counteract drug-induced vasodilation and to reduce brain bulk within a closed compartment (cranial vault).[96] The usual goal for patients in which a reduction in intracranial volume is desired is a $P_{a}CO_2$ of 30 to 35 mmHg with a duration of effectiveness being perhaps no more than 4 to 6 hours.[97]

Differences exist among the volatile agents in their ability to interfere with the cerebral vasculature's responsiveness to CO_2. Variables that affect the reported differences include the type of surgical procedure the patient is undergoing, associated pathophysiology, and the presence of any coexisting disease(s). For example, patients with hypertension given 1 MAC isoflurane with 67% N_2O have better control of CBF via manipulation of arterial CO_2 than those receiving 1 MAC sevoflurane with 67% N_2O.[98] Similar results have been reported by other investigators.[99] In contrast, CO_2 reactivity in insulin-dependent patients is equally impaired by 1 MAC isoflurane and 1 MAC sevoflurane, each given with 67% nitrous oxide.[100]

On a side note, sevoflurane has been shown (in rodents) to impair glucose metabolism and produce hyperglycemia.[101] Other investigators have suggested that sevoflurane is less vasoactive than halothane, isoflurane, and desflurane and recommend it as a good alternative to propofol in patients with normal intracranial

pressure.[102] It has also been reported to better preserve dynamic cerebral autoregulation than isoflurane when both are given at 1.5 MAC in combination with 100% O_2.[103] Desflurane administered to patients undergoing craniotomy for tumor resection with an air-O_2 mixture at 1.0 to 1.5 MAC has been shown to act similarly to isoflurane and maintain cerebrovascular reactivity to CO_2 and cerebrospinal fluid pressure.[104-106] These research findings suggest that increases in CBF produced by isoflurane, desflurane,[106] and sevoflurane[107] can be effectively prevented by very mild hyperventilation and using concentrations less than 1.5 MAC. In addition, anesthesia consisting of sevoflurane and remifentanil appears to be similar to total intravenous anesthesia (TIVA [i.e., propofol combined with remifentanil]) during supratentorial craniotomy procedures in regard to emergence times, adverse effects, intraoperative hemodynamic events, and brain relaxation scores.[108]

Electroencephalogram and Evoked Potentials

The volatile agents produce a dose-related suppression of EEG activity (initial increase [later a decline] in amplitude and decreased frequency) and at high concentrations produce electrical quiescence.[109] At deeper levels of anesthesia, the EEG may temporarily stop recording; at such time, burst suppression is said to have occurred.

For those procedures requiring monitoring of the integrity of the spinal cord or mapping of cortical regions of the brain, the anesthetist should be aware that inhalation agents can skew cortical somatosensory, motor, brainstem, auditory, and visual evoked potentials. Isoflurane, desflurane, sevoflurane, and N_2O produce a dose-dependent reduction in these evoked potentials, with visual evoked potentials being most sensitive and brainstem-evoked potentials most resistant.[109,110] Two evoked-potential variables commonly assessed are latency and amplitude. An increase in latency or decrease in amplitude of evoked potentials can reflect ischemia or be secondary to the volatile agent. Latency is the time between the initiation of a peripheral stimulus (e.g., electrical stimulation of the median nerve at the wrist) and onset of the evoked potential (e.g., cortical) recorded by scalp electrodes.

Isoflurane has been shown to interfere with the recording of cortical somatosensory evoked potentials (cSSEP) at light planes of anesthesia (0.5 MAC with 60% N_2O)[111] and desflurane and sevoflurane have been found to produce fewer changes than isoflurane in amplitude reduction of cSSEP at 0.7, 1.0, and 1.3 MAC (without N_2O). In contrast, no difference exists among the volatile anesthetics' effect on latency.[112] The addition of N_2O to isoflurane, desflurane, and sevoflurane can also produce a significant reduction in the amplitude of cSSEPs.[113,114] It may be prudent to avoid the use of this agent in patients who have baseline low-amplitude evoked potentials.

Sevoflurane,[115,116] unlike desflurane[117] and isoflurane,[39] can predispose pediatric and adult[118] patients to epileptic activity, even though sevoflurane[119-121] can suppress drug-induced convulsive activity in a manner similar to desflurane[122] and isoflurane.[122] Sevoflurane combined with N_2O has produced epileptiform EEG activity during inhalation induction with adults in a single-breath technique. A hyperdynamic response can accompany the EEG changes if concurrent hyperventilation occurs. The incidence of epileptiform EEG changes has been shown to nearly double in the presence of hypocapnia (100% versus 47%).[123] Similar results have been observed in children aged 2 to 12 years.[116] In contrast, intravenous induction with thiopental followed by anesthetic maintenance with 2% end-tidal sevoflurane in air does not produce seizure-like changes in the EEG in children.[115] Epileptiform activity has also been reported to occur during emergence from sevoflurane.[124]

Emergence and Neurologic Assessment in Adults

Although the objective of a smooth and rapid emergence from a general anesthetic is desirable for all surgical patients, it is especially meaningful for neurosurgical candidates. Delayed emergence in this specialty of anesthesia can have devastating consequences. A slow return of consciousness makes it difficult to perform the initial postoperative neurologic examination. It can also add to unnecessary therapeutic or diagnostic intervention and predispose the patient to respiratory complications.[125]

Because of this, the bias of some anesthesia providers is to administer TIVA techniques such as propofol with remifentanil and/or dexmedetomidine for neurosurgical procedures involving supratentorial tumors. Some investigators report a more rapid awakening (after approximately 2 hours of anesthesia) from TIVA in non-neurosurgical patients compared with sevoflurane and desflurane combined with N_2O.[126] Recovery profiles for sevoflurane and desflurane indicate they are superior to isoflurane.[127,128] In side-by-side comparisons of desflurane and sevoflurane, desflurane permits for a more rapid awakening than sevoflurane in volunteers after 8 hours of exposure.[129] In contrast, sevoflurane allows for acute changes in vaporizer settings without evoking neurocirculatory excitation (i.e., significant increases in sympathetic nerve activity, norepinephrine concentrations, heart rate, and mean arterial blood pressure); of particular interest was the finding that desflurane's sympathomimetic response occurred in response to a controlled adjustment in vaporizer settings (i.e., changing from 6% to 9%)—that is, in the absence of overpressurization.[130] Sevoflurane may be preferred over desflurane if concentrations equal to or in excess of 1 MAC are used during neurologic surgery.[79] One study also found no difference in early postoperative recovery and cognitive function between a balanced sevoflurane-fentanyl technique versus propofol-remifentanil (TIVA) management in patients undergoing supratentorial intracranial surgery.[131] Similarly, a multicenter randomized controlled trial of patients scheduled for elective supratentorial craniotomy surgery found no significant difference between sevoflurane-remifentanil and propofol-remifentanil techniques.[108] Further research will help to illuminate whether any substantive differences exist in neurosurgery outcome secondary to the choice of inhaled anesthetic or primary TIVA techniques employed.

An area of ongoing research has been the application of volatile anesthetics via preconditioning and postconditioning techniques for neuroprotection following global and/or focal ischemia/hypoxia.[132] One of the etiologies of neurodeficits occurring in this setting is ischemia/reperfusion injury. In vitro and in vivo (animal) cerebral, spinal, and cardiac studies have demonstrated that isoflurane, and especially sevoflurane, can reduce cerebral infarct volume, improve learning and memory deficits, attenuate ischemia/reperfusion injury to the spinal cord, and lessen hypoxia-induced neuronal cell damage.[133-137] Problematic with transitioning from bench research to clinical practice is recognizing that the application of inhaled anesthetic preconditioning treatments would require a need to predict when a reperfusion insult would occur; in contrast, volatile anesthetic postconditioning interventions would ideally occur when the patient develops clinical symptoms.

Several foundational questions remain unanswered regarding anesthetic conditioning with humans: What is the ideal time and duration of anesthetic prior to postconditioning? Also, what is the optimal anesthetic dose for producing a neuroprotective effect? Current research suggests that a dose-response relationship and

ceiling effect do exist. For example, in one study it was demonstrated that 1.0 MAC sevoflurane reduced infarct size in the setting of reperfusion injury, whereas 0.75 MAC sevoflurane had no effect[138]; in a second study it was shown that 1.0 MAC and 1.5 MAC sevoflurane given at the start of reperfusion was neuroprotective (focal cerebral ischemia) and yet at 0.5 MAC, no protection was seen.[135] Current research suggests that anesthetics can provide long-term durable protection against ischemic injury that is mild to moderate in severity. Experimental data do not provide support for the premise that anesthetics reduce injury when the ischemic injury is severe.[139] Anesthetics consistently and meaningfully improve outcome from experimental cerebral ischemia, but only if present during the ischemic insult.[140] To summarize, although research continues to help define the future role of inhaled anesthetics in the context of reperfusion injury, currently there is insufficient evidence to definitively recommend the use of one agent over another in the operating room setting.[141]

Emergence Phenomenon in Children

Sevoflurane and desflurane are associated with emergence agitation or delirium in children.[142] The emergence phenomenon is short-lived but troublesome, and the etiology is uncertain. A variety of factors have been suggested to play a potential role in emergence delirium (ED). Restless behavior upon emergence causes discomfort to the child, postanesthesia recovery nurses, and parents. Some suggested factors related to transient emergence agitation are noted in Box 8-3. These children may require analgesics or sedatives, which can delay discharge. Emergence delirium is self-limiting and devoid of apparent sequelae, as long as the child is protected from self-injury. Preventive measures include reducing preoperative anxiety and postoperative pain and providing a quiet, stress-free environment for postanesthesia recovery. Treatment may include small doses of fentanyl, clonidine, or dexmedetomidine. Reuniting the child with the parents is also helpful.

BOX 8-3

Possible Etiologic Factors of Pediatric Emergence Agitation/Delirium

- Intrinsic characteristics of an anesthetic
- Postoperative pain
- Surgery type
- Age
- Preoperative anxiety
- Child temperament
- Adjunct medication
- Behaviors including nonpurposefulness; eyes averted, staring, or closed; and unresponsiveness during early emergence.

From Vlajkovic GP, Sindjelic RP: Emergence delirium in children: many questions, few answers. *Anesth Analg.* 2007; 104(1):84-91; Malarbi S et al: Characterizing the behavior of children emerging with delirium from general anesthesia. *Paediatr Anaesth.* 2011 Sep;21(9):942-50.

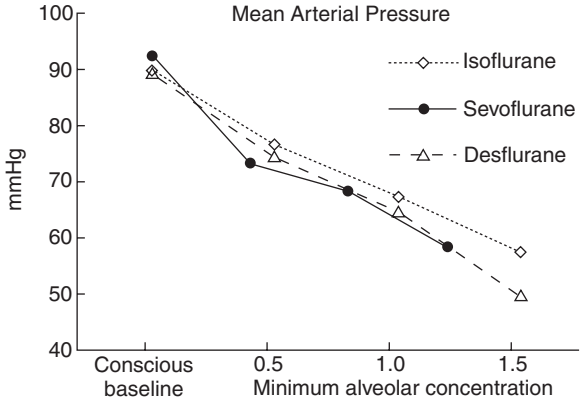

FIGURE **8-2** Mean arterial pressure response to the administration of isoflurane, sevoflurane, and desflurane in healthy volunteers. With increasing minimum alveolar anesthetic concentration, progressive decreases in blood pressure occurred with each of the volatile anesthetics. (Adapted from Ebert TJ, Muzi M: Sympathetic hyperactivity during desflurane anesthesia in healthy volunteers: a comparison with isoflurane. *Anesthesiology. 1993; 79*(3):444-453; Ebert TJ, Muzi M, Lopatka CW: Neurocirculatory responses to sevoflurane anesthesia in humans: a comparison to desflurane. *Anesthesiology.* 1995; 83(1):88-95.)

Cardiovascular System

All inhalation agents are capable of altering hemodynamics, the extent being related to various preoperative and intraoperative factors (e.g., American Society of Anesthesiologists physical status classification, coadministration of vasoactive drugs, opioids, benzodiazepines). This section reviews the influence of volatile agents on the cardiovascular system.

Systemic Hemodynamics

Isoflurane, desflurane, and sevoflurane all reduce mean arterial pressure (MAP) (Figure 8-2) and cardiac output (CO) and cardiac index (CI) in a dose-dependent fashion.[130,143-145] The mechanism by which each accomplishes this varies. For example, desflurane, sevoflurane, and isoflurane predominantly reduce MAP via a reduction in systemic vascular resistance (SVR), with the dose-response relationship being least with sevoflurane (Figure 8-3).[130,146] Halothane, by comparison, causes less disruption in inherent vascular tone and therefore predominantly reduces MAP by direct myocardial depression versus a reduction in preload.[147] Nitrous oxide activates the sympathetic nervous system and increases SVR,[148] which can also lead to an increase in central venous pressure (CVP) and arterial pressure. This sympathetic nervous system response appears to be intact during coadministration of volatile agents.[144]

In general, N_2O used in combination with inhalation agents increases SVR and helps support arterial blood pressure. In contrast, with opioids, the addition of N_2O augments cardiac depression instead of supporting it[149] because N_2O also produces a direct negative inotropic effect. This property can be unmasked in patients with decreased left ventricular function secondary to coronary artery disease or valvular heart defects.[150] Desflurane supports CI better than halothane at both low and high MAC levels (i.e., 1.66 MAC)[151] (Figure 8-4). With light levels of anesthesia, desflurane maintains the CI without an accompanying elevation in HR. For deeper levels of anesthesia, the CI is probably supported by the associated rise in HR. Some investigators believe the favorable circulatory profile of desflurane, isoflurane, and sevoflurane results from their ability to attenuate the body's circulatory compensatory mechanisms in a dose-related manner.[130,152] In summary, there is no appreciable difference in the ether anesthetics' ability to produce dose-dependent depression in arterial pressure and cardiac output.[143-145,151]

Regarding the impact of the duration of anesthesia on hemodynamics, isoflurane, sevoflurane, and desflurane produce a similar response—that being as MAC-hours of anesthesia increase, CI

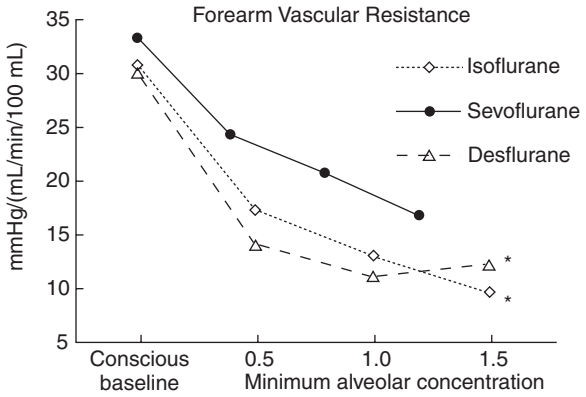

FIGURE **8-3** Forearm vascular resistance response to the administration of isoflurane, sevoflurane, and desflurane in healthy volunteers. In general, forearm vascular resistance was progressively decreased with increasing minimum alveolar anesthetic concentrations of each of the volatile anesthetics; however, this decline was less in the group receiving sevoflurane. (Adapted from Ebert TJ, Muzi M: Sympathetic hyperactivity during desflurane anesthesia in healthy volunteers: a comparison with isoflurane. *Anesthesiology*. 1993; 79(3):444-453; Ebert TJ, Muzi M, Lopatka CW: Neurocirculatory responses to sevoflurane anesthesia in humans: a comparison to desflurane. *Anesthesiology*. 1995; 83(1):88-95.)

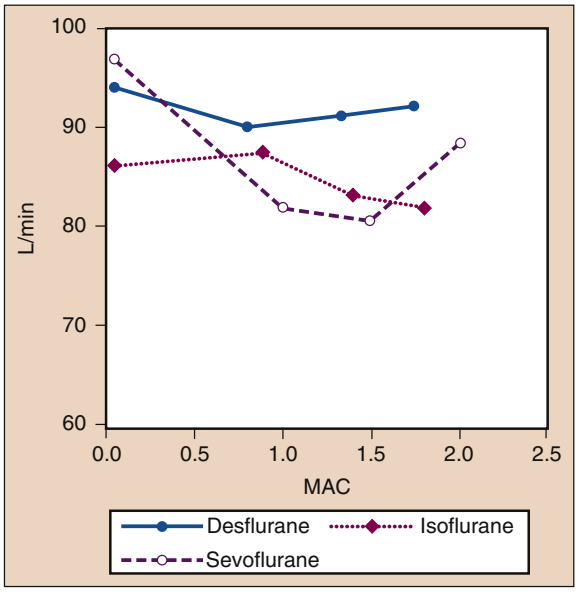

FIGURE **8-4** The effects of increasing concentrations (MAC) of isoflurane, desflurane, and sevoflurane on cardiac index (L/min) when administered to healthy volunteers. MAC, Minimum alveolar concentration. (From Cahalan MK: *Hemodynamic Effects of Inhaled Anesthetics. Review Courses*. Cleveland: International Anesthesia Research Society, 1996, pp 14-18.)

and HR increase slightly.[144,151] The CI effect may be secondary to a continued reduction in SVR and increase in HR following prolonged exposure to each of the agents. Protracted anesthesia (8 hours) in healthy volunteers anesthetized with desflurane and sevoflurane leads to an increase in pupil size and HR independent of surgery.[74] These changes are not associated with increases in plasma catecholamines, blood pressure, or CO_2 production; therefore mydriasis and tachycardia as signs of anesthetic depth could be misleading at times.

Although anesthetic changes produced at the cellular level have already been discussed, it is sensible to briefly review the cellular effects of inhaled anesthetics on the aforementioned areas of the cardiovascular system. In vitro and in vivo studies have revealed that isoflurane, sevoflurane, and desflurane reduce intracellular free calcium (Ca^{2+}) concentrations in cardiac and vascular smooth muscle.[143,145] The mechanism for this is believed to be a reduction in Ca^{2+} influx through the sarcolemma and a depression of depolarization-activated Ca^{2+} release from the sarcoplasmic reticulum.[143,145,153] The end result is a depression in the contractile state of the myocardium, along with dilation of the peripheral vasculature. Other reported cellular effects of volatile agents include augmentation and attenuation of endothelium-derived relaxation factor, inhibition of acetylcholine-induced vascular relaxation,[154] and attenuation of sodium (Na^+)/Ca^{2+} exchange that leads to a reduction in the quantity of intracellular Ca^{2+}.[155] Future research is needed to clarify the effect of volatile agents in patients with cardiovascular dysfunction (hypertension, diabetes, geriatric patients) in which vascular responses can be altered. In these populations (compared to patients with normal physiology) the mechanisms for regulating vascular tone at the cellular level are altered.

Heart Rate

Volatile agents and N_2O induce changes in HR relative to the concentration of the anesthetic being used. Alterations in HR are a result of several variables: antagonism of SA node automaticity,[156] modulation of baroreceptor reflex activity,[157] and sympathetic nervous system activation via activation of tracheopulmonary and systemic receptors.[158]

Sevoflurane produces only minor alterations in HR, even when used in excess of 1 MAC,[159] although a rapid and large increase in the inspired concentration (i.e., from 0.5 MAC to 2.9 MAC) of sevoflurane (and isoflurane) may produce an increase in plasma epinephrine concentrations.[160] Isoflurane and desflurane can cause an increase in HR,[161] and when more than 1 MAC of desflurane is used (even without overpressurization), the dose-response relationship becomes more prominent, particularly when compared with sevoflurane (Figure 8-5).[130] Desflurane's steep dose-response to HR can potentially be problematic by diminishing the reliability of HR as a guide to anesthetic depth and by predisposing patients at risk for coronary artery disease to myocardial ischemia secondary to an increased myocardial oxygen demand.

Research has shown pretreatment with fentanyl (1.5 or 4.5 mcg/kg) 5 minutes before an increase in end-tidal desflurane concentration from 4% to 8% modulates (not abolishes) an increase in HR by 61% and 70%, respectively.[162] In this same study, increase in MAP was attenuated by 31% and 46%. Another group of investigators found 5 mcg/kg of fentanyl followed by a continuous infusion of 2 mcg/kg/hr initiated 12 minutes before induction significantly blunted the HR and MAP response to a rapid increase in end-tidal desflurane concentration (5.4% to 11%).[163] The acute change in desflurane concentration occurred 20 minutes after intubation. Fentanyl's efficacy was also assessed 2 minutes after induction when desflurane was given in three incremental 1-minute steps (3.6%, 7.2%, 11%). Of interest was the finding that fentanyl was ineffective in diminishing the desflurane stimulatory effect during this induction period. Therefore the optimal use of fentanyl may be during steady-state periods of anesthesia when acute adjustments of desflurane are desired.

Esmolol (0.75 mg/kg) has been shown to attenuate HR response but not MAP and therefore may be less desirable than

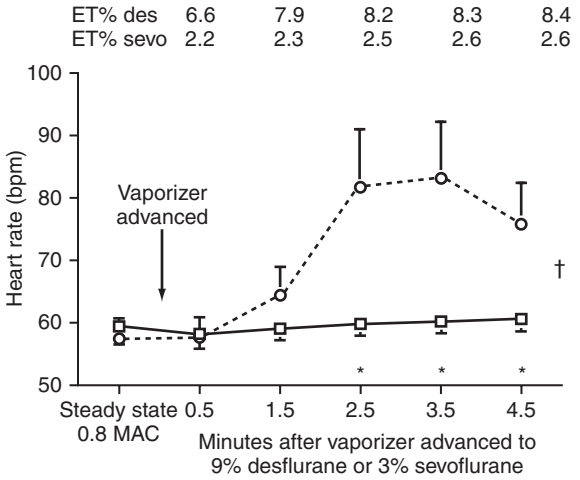

FIGURE **8-5** The effects of sevoflurane *(solid line with squares)* and desflurane *(dashed line with circles)* on heart rate in healthy young volunteers when the inspiratory concentration is rapidly increased from a steady-state value of 0.83 MAC to 1.25 MAC. MAC, Minimum alveolar concentration. *(Reprinted with permission from Ebert TJ, Muzi M, Lopatka DW: Neurocirculatory responses to sevoflurane in humans: a comparison to desflurane.* Anesthesiology *1995; 83(1):88-95.)*

fentanyl.[162] Prior administration of intravenous lidocaine (1.5 mg/kg) has not been shown to be effective in modulating the sympathetic response associated with an acute change in desflurane end-tidal MAC value of 0.7 to 1.5.[164]

Coronary Blood Flow

The term *coronary steal* is defined as a reduction in perfusion of ischemic myocardium with simultaneous improvement of blood flow to nonischemic tissue. Simply stated, blood has been taken from the "poor" and given to the "rich" (a "reverse–Robin Hood" syndrome). In addition, this phenomenon has been demonstrated to occur more easily with "coronary steal–prone anatomy" (i.e., multivessel disease models).[165] Several articles have suggested that isoflurane and perhaps desflurane are capable of producing a coronary steal with clinically relevant concentrations,[166,167] but other researchers have not found this to occur.[168,169] One investigator's results suggest that the use of 0.5% isoflurane in combination with 50% N_2O might be protective to the myocardium (i.e., improve the tolerance to pacing-induced myocardial ischemia).[170]

An important qualifier to isoflurane's ability to maldistribute coronary blood flow is the presence of hypotension; when normotension is maintained, a steal phenomenon is abated.[171] Reduced blood flow to ischemic myocardium can also be reversed if normotension is reestablished with phenylephrine administration.[172] To summarize the effects of isoflurane, desflurane, and sevoflurane on the coronary circulation, it can be stated that each produces vasodilation, with sevoflurane doing so the least.[167,173] In the presence of hypotension, a steal phenomenon can occur (as it can with inappropriate use of intravenous nitroglycerin or sodium nitroprusside), and this effect is reversible if normotension is reestablished. The magnitude of coronary vasodilation also is markedly less for isoflurane than that which occurs with dipyridamole[174] and the endogenous nucleoside, adenosine,[175] both of which produce coronary vasodilation even in the presence of normotension. Any of these three volatile anesthetics can be used in patients with a history of ischemic heart disease. If ECG monitoring demonstrates ST-segment or T-wave changes suggestive of myocardial ischemia (in the absence of abnormal hemodynamics), a change in primary anesthetic techniques may be warranted (e.g., substituting isoflurane for sevoflurane).[169]

As mentioned previously, volatile agents may produce a neuroprotective effect; similarly, the heart appears to benefit from isoflurane, sevoflurane, and desflurane inhaled anesthetics via initiating the phenomenon of preconditioning.[176-180] Anesthetic preconditioning (APC) results in a cascade of intracellular events that help protect the myocardium from ischemic and reperfusion insult, potentially limiting infarct size. The mechanism for this effect is multifactorial and includes such things as improving contractile function, preventing the down-regulation of major sarcoplasmic reticulum Ca^{2+} cycling proteins, thereby reducing calcium overload in the myocardial cells. The latter effect has been shown to be independent of potassium-sensitive adenosine triphosphate (K_{ATP}) channels[181] and confers 30% to 40% of the cardioprotective effect produced by inhalational anesthetics.[182]

On the molecular level, sevoflurane has been found to produce in healthy male volunteers late preconditioning (24 to 48 hours after sevoflurane administration), as evidenced by altering gene expression in white blood cells (e.g., reduced proinflammatory L-selectin [CD62L] expression on granulocytes).[183] A theoretic application of APC, along with other cardioprotective substances such as insulin and adenosine, is administering preconditioning drugs during early coronary artery reperfusion, as is currently done with antiplatelet and antithrombotic therapies. Research has shown the administration of volatile agents during myocardial reperfusion activates a group of prosurvival kinases called the *Reperfusion Injury Salvage Kinase* (RISK) pathway. These prosurvival kinases produce potent cardioprotective effects. The RISK pathway has also been found to be activated during ischemic preconditioning (a brief stimulus of myocardial ischemia/occlusion leading to cardioprotection).[184]

Other factors that have been identified with preconditioning include protein kinase C activation of K_{ATP} channel opening, adenosine receptors (α_1 and α_2 subtypes), and inhibitory G proteins.[185-187] The recent American College of Cardiology/American Heart Association Guidelines on perioperative cardiac evaluation and care note that it can be beneficial to use volatile anesthetic agents during noncardiac surgery for the maintenance of general anesthesia in hemodynamically stable patients at risk for myocardial ischemia.[188] This is due to a protective effect on the myocardium associated with preconditioning.

It has been advocated that sulfonylurea oral hyperglycemic drugs be discontinued 24 to 48 hours prior to elective surgery, owing to their ability to close K_{ATP} channels. Insulin is recommended as replacement therapy during this time period to abate the negative impact of hyperglycemia on preconditioning.[189] Finally, it should be recognized that not all research supports a positive correlation between inhaled anesthetics and cardioprotection.[190-192]

Arrhythmias

The arrhythmic potential of inhalation agents has long been recognized. All of the agents, with the exception of isoflurane and probably desflurane, are conducive to the development of bradycardia and disturbances in atrioventricular (AV) nodal conduction (excluding second- or third-degree AV block). The mechanism for this is their ability to depress slow-response (sinoatrial and atrioventricular nodal tissue) and fast-response (atrial or ventricular musculature, Purkinje fibers) action potentials. When fibers become ischemic or injured, the volatile agents are prone to produce reentrant excitation.[193] In addition, desflurane and sevoflurane[194] have been shown to prolong action potential duration (APD). This effect is consistent with the clinical finding of

a prolonged QTc interval in healthy adults[194,195] and in children receiving desflurane.[196] The mechanism by which desflurane prolongs the action potential is that of reducing the peak transient outward K^+ current in ventricular myocytes.[197]

The ability of the volatile agents to reduce the quantity of catecholamines necessary to evoke arrhythmias is commonly but inaccurately called "sensitization." It is more accurate to describe this phenomenon as an adverse drug interaction. Researchers have determined the nasal and oral submucosal ED_{50} dosage (median effective dose) of epinephrine for volatile agents to be 2.11 ± 0.15 mcg/kg for halothane and 6.72 ± 0.66 mcg/kg for isoflurane.[198] With these dosages, 50% of subjects developed three or more premature ventricular contractions or ventricular tachycardia during or immediately after a single injection of epinephrine (which required 3.5 to 11 minutes to complete). Variables that may influence epinephrine ED_{50} values are differences in systemic absorption, route of administration, animal model,[199] existing plasma catecholamine levels, and preexisting atrial or ventricular arrhythmias. The infusion of ketamine in a feline model has been shown to produce no appreciable change in the arrhythmogenic dose of adrenaline when administered during isoflurane or sevoflurane anesthesia.[200] When these variables are taken into consideration it is not surprising that data regarding volatile agent "sensitization" are conflicting. Regarding the two newest volatile agents, desflurane and sevoflurane, both appear to be similar to isoflurane in their epinephrine-arrhythmogenic potential.[201,202]

In general, it is reasonable to anticipate the fewest difficulties with arrhythmias in physical status I and II patients if the submucosal epinephrine dose remains 7.0 mcg/kg or less with 1.0 to 1.3 MAC desflurane,[201] or 5.0 mcg/kg or less with 1.0 to 1.3 MAC sevoflurane or isoflurane.[202] Additional protection may be achieved by combining 0.5% lidocaine with epinephrine, the net effect being an increase in the minimum threshold dose of epinephrine.[198]

One other point is worth mentioning in relation to rhythm disturbances and inhalation agents: patients who are given a general anesthetic (primary opioid supplemented with a volatile anesthetic) and who are on amiodarone can have significant arrhythmias intraoperatively or postoperatively (e.g., atropine-resistant bradycardia requiring isoproterenol infusions, atrioventricular sequential pacing). These significant rhythm disturbances can also result in death.[203] For clarification and emphasis, it should be understood that amiodarone and its major metabolite are detectable in plasma for up to 9 months after discontinuation of therapy.[204] Lastly, isoflurane and sevoflurane have been shown to be associated with an attenuation of arrhythmias associated with digitalis toxicity,[205] occlusion/reperfusion ischemia,[206] and postmyocardial infarction.[207] Isoflurane has also been demonstrated to increase the effective refractory period of the accessory pathway with preexcitement syndrome. It is possible these inhaled anesthetics may be preferred agents if a significant concern exists for the appearance of intraoperative arrhythmias related to the pathologic states described previously.

Pulmonary Circulation

Pulmonary vascular resistance (PVR) is also affected by the volatile agents and N_2O. The effects of N_2O on PVR vary with age and preexisting levels of PVR. In adults with normal PVR, the addition of N_2O results in a small increase in PVR,[208] presumably due to an increase in sympathetic nervous system tone.[148] If a subject has preexisting pulmonary hypertension, the addition of N_2O results in larger increases in PVR,[208] which may become clinically significant. Volatile agents (including 0.8 or 1.2 MAC desflurane) decrease pulmonary artery pressure[144,151]; the opposite effect occurs when desflurane is administered at 1.6 MAC.[151]

The pulmonary vasculature also minimizes changes in alveolar-arterial oxygen tension gradient via hypoxic pulmonary vasoconstriction (HPV). This normal physiologic response to atelectasis or hypoxia is attenuated in vivo by isoflurane and markedly by N_2O.[209] All of the currently used volatile agents only marginally affect HPV.[210-212] Consistent with this finding, one group of researchers noted only minimal impairment in oxygenation (approximately 20% reduction in HPV at 1 MAC) in patients having one-lung ventilation performed during thoracotomy procedures. Desflurane and sevoflurane delivered at 1 MAC without N_2O have also been shown to only slightly affect arterial oxygenation in patients placed in a lateral position while undergoing esophagogastrectomy.[211,212]

Respiratory System

As seen with other systems of the body, the volatile agents exert a dose-response effect on the respiratory system, primarily tidal volume (TV). Responsiveness to CO_2 is depressed and the TV reduces as concentrations of the agents are increased. The compensatory mechanism for the diminished TV with isoflurane, sevoflurane, desflurane, and N_2O is an increase in respiratory rate (RR).[213-215] However, the increase in RR is not sufficient to prevent elevations in arterial CO_2 tension. Nevertheless, surgical stimulation is a variable that helps to overcome the respiratory-depressant effects of volatile agents.[216]

Emergence from an anesthetic can be associated with hypercarbia if minute volume (MV) is not adequately supported, owing to a volatile agent's capacity to depress the ventilatory response to $PaCO_2$ and PaO_2.[215, 217-219] Hypercarbia also represents an increase in the apneic threshold (higher $PaCO_2$ values are required for spontaneous ventilation to occur). Patients should be closely monitored during emergence from an anesthetic and following adequate reversal of muscle relaxants to avoid acidemia or hypercarbia. During this phase of the anesthetic, significant end-tidal values of residual volatile anesthetic may persist, particularly if there was recent administration of an opioid (synergistic effect). It is important to recognize that impairment of the hypoxic ventilatory response by volatile agents is not abated with central nervous system arousal or acute pain[220]; even as little as 0.1 MAC of a volatile agent (excluding desflurane) can suppress ventilatory drive to hypoxia.[221] These research findings have implications for patients whose MVs are maintained via a hypoxic drive (e.g., emphysematous patients with depressed central chemoreceptors).

The smoothness of an inhalation induction is directly related to the ability of an inhalation agent to avoid provoking an irritant response. Nitrous oxide and sevoflurane are considered the standards by which other agents are measured because of the low incidence of breath holding, coughing, secretions, and laryngospasm encountered during inhalational induction.[222] In contrast, desflurane is considered a respiratory irritant when used for mask induction in concentrations greater than 6%[222, 223]; therefore it is generally not used to induce anesthesia in pediatric[224] and adult patients. One alternative method to incorporate desflurane in the pediatric population is to induce the child with sevoflurane, then change to desflurane for maintenance. Researchers have shown that reactive airway problems encountered during inhalational induction with desflurane are lost when this agent is used for anesthetic maintenance.[225] Lastly, the volatile agents have been

shown to relax airway smooth muscle and produce bronchodilation. They have also been used in the treatment of refractory status asthmaticus.[226]

Kidneys

In general, autoregulation of the renal circulation remains intact during the administration of inhalation agents. Reductions in systolic blood pressure are accompanied by decreases in renal vascular resistance.[227] Nevertheless, compensatory reductions in renal vascular resistance can still lead to a decline in the glomerular filtration rate. This may contribute to the commonly observed intraoperative reduction in urinary output.

The potential for a volatile agent to produce renal damage is commonly assessed by the extent to which it elevates creatinine, blood urea nitrogen (BUN), and serum inorganic fluoride (F^-) concentrations.[228] With the older volatile agent methoxyflurane, a "toxic threshold" for peak serum concentration of F^- was established (50 μmol/L)[229]; at this value, vasopressin-resistant polyuric renal insufficiency occurs.[230]

Of the currently used inhalation agents, desflurane has been shown in both healthy and chronic renal disease patients[231] to alter indices of renal integrity the least, including no change in the renal function tests of urinary retinol-binding protein and *N*-acetyl-β-glucosaminidase (NAG).[232] The significance of this is that NAG is considered a sensitive indicator of drug-induced proximal tubular necrosis,[233,234] and retinol-binding protein has been shown to be a specific marker for indicating the presence of tubular damage of any cause.[235] Recent advancements in clinical markers for renal integrity have shown two new, perhaps better, biomarkers of tubular injury. Isoforms of glutathione-*S*-transferase (GST) include alpha GST, which is located exclusively in the proximal tubules, and pi GST, found only in the distal tubules.[236] In humans the urinary levels of each of these enzymes have been shown to increase after acute tubular necrosis and renal infarction.[237]

In contrast to studies involving desflurane[238] (and isoflurane[239]), early research with sevoflurane generated concerns about compromised renal function. However, the current debate has settled on the degradation of sevoflurane by carbon dioxide absorbents. Most researchers now accept that serum inorganic fluoride (F^-) levels associated with sevoflurane administration do not represent a significant risk to patients, including those with compromised renal function.[240-244] Millions of sevoflurane anesthetics worldwide have failed to demonstrate any significant untoward renal outcomes in the general surgical population, including patients having coronary artery surgery.[245] Nevertheless, FDA (Food and Drug Administration) guidelines recommend sevoflurane be used with caution in patients with renal insufficiency (creatinine greater than 1.5 mg/dL). In morbidly obese patients, researchers have found no appreciable difference in sevoflurane's biotransformation and subsequent fluoride levels, compared to nonobese patients.[246]

A concern still exists regarding sevoflurane's degradation within anesthesia circuits by soda lime,[247, 248] with each having a chemical makeup of monovalent hydroxide bases (potassium hydroxide [KOH] and sodium hydroxide [NaOH]). These carbon dioxide absorbers break down all modern-day volatile agents.[249] The two by-products of sevoflurane's degradation that have been measured in a closed circuit are fluoromethyl-2,2-difluoro-1(trifluoromethyl)-vinyl ether (also known as *compound A*, an olefin) and fluoromethyl-2-methoxy-2,2-difluoro-1-(trifluoromethyl) ethyl ether (compound B).[250] The former is known to produce proximal corticomedullary tubular necrosis in rats.[251] Clinical studies involving low-flow (1 to 2 L/min) sevoflurane given over approximately 3 to 8 MAC-hours[240] in healthy patients[252] and in patients with stable renal insufficiency[240] were found to have no statistically significant changes in serum creatinine, blood urea nitrogen, urine protein, and glucose. It has also been reported that sevoflurane with desiccated soda lime can yield excessive temperatures that produce anesthesia machine fires and patient injuries,[253,254] the potential explanation being the by-product of hydrogen (3 moles) following the chemical reaction of sevoflurane with heated desiccated absorbent.[255]

In summary, it is widely recognized that the following variables do increase compound A content: low fresh gas flows, high concentrations of sevoflurane, and drying of soda lime CO_2 absorbant.[256,257] One way to eliminate compound A is to replace soda lime with a newly formulated absorbent such as Amsorb or DragerSorb Free.[258-260] These new CO_2 absorbents do not contain strong bases (NaOH or KOH), which are responsible for the degradation of sevoflurane to compound A, as well as the production of carbon monoxide from the breakdown of desflurane and isoflurane.[261,262] In the absence of Amsorb or DragerSorb Free carbon dioxide absorbents, current FDA dosing guidelines recommend sevoflurane exposure not exceed 2 MAC-hours at flow rates of 1 to less than 2 L/min.[263] Fresh gas flow rates less than 1 L/min are not recommended.

Liver

All of the volatile anesthetics have been shown to decrease total hepatic blood flow and increase or maintain hepatic artery blood flow, thereby limiting any accompanying attenuation in portal vein blood flow.[264-267] Hepatocyte hypoxia is of clinical concern, and its etiology can be multifactorial (e.g., volatile agents, surgical manipulation, enzyme induction). One significant outcome of liver hypoxia is increased reductive metabolism, which fortunately does not occur with ether-based anesthetics. The previously used halogenated hydrocarbon, halothane, has been investigated since 1963 regarding its potential to produce "halothane hepatitis."[268] A better understanding of the pathophysiology of this phenomenon has improved diagnostic capabilities for volatile-agent hepatitis.[269,270]

Isoflurane and desflurane are similar to halothane in that each possesses a common metabolic pathway via cytochrome P-450 that eventually yields TFA-protein molecules.[269,271] However, because of differences in the rate of biodegradation, these volatile agents are probably less likely to produce hepatic injury than halothane. For example, isoflurane is metabolized 100-fold less than halothane, and as such it is estimated that fulminant hepatic failure caused by isoflurane may occur in 1:3,500,000 anesthetics.[269]

Several case reports and clinical studies suggest that a potential immunologic mechanism (including cross-sensitization) may exist for the development of "isoflurane hepatitis,"[272] "sevoflurane hepatitis,"[273] and "desflurane hepatitis."[274] In one report, following isoflurane anesthesia the patient developed fulminant hepatic failure that led to death.[275]

Although desflurane is metabolized the least of all volatile anesthetics, it has also been associated with hepatotoxicity.[274] In one case report, a 65-year-old woman without a history of liver disease developed desflurane hepatitis 12 days postoperatively. The patient had a rash, nausea, polyarthralgias, marked elevations in liver transaminases, and jaundice. Serologic markers for hepatitis A, B, and C were negative. It was significant that the patient had undergone two prior halothane anesthetics lasting approximately 45 minutes each (death from a halothane anesthetic given 28 years after primary exposure has been documented[276]). The patient was discharged from the hospital 27 days after surgery, with continued improvement in liver function. This patient's exposure

to halothane decades earlier combined with the ether-based anesthetic produced hepatic damage, probably secondary to "immunologic memory" and possible cross-sensitization.[274]

Sevoflurane is unique among the volatile anesthetics in that it is the only one that appears not to be biodegraded to TFA-protein molecules.[277] This step is a prerequisite to the formation of TFA-protein antibodies, so it is unlikely that sevoflurane will produce fulminant hepatic failure via an immunoallergic mechanism.[278] Nonetheless, there have been several case reports of hepatic injury associated with sevoflurane use,[273,279,280] including one that involved a child.[281]

In spite of the case reports listed, it is extremely rare for isoflurane, sevoflurane,[245] and desflurane to produce clinically significant liver damage. Their molecular structure (increased fluorination) resists hepatic degradation, and their pharmacodynamic profile is associated with no changes or slight reductions in hepatic blood flow.[282-285]

In vitro research suggests that N_2O is metabolized minimally (0.004%) by intestinal microflora, yielding molecular nitrogen (N_2).[286] The limited metabolism does not necessarily mean that N_2O is an inert substance within the body. On the contrary, studies have demonstrated that chronic exposure to N_2O can lead to inactivation of the vitamin B_{12} component of methionine synthetase,[287] which can disrupt deoxyribonucleic acid (DNA) synthesis. For routine surgical cases this is generally not an issue, but caution should be exercised with patients who are pregnant, patients who receive a general anesthetic more than once a week, or patients who are debilitated and have problems with wound healing.[288]

In summary, the ether-based volatile agents have an extremely low risk for evoking hepatic injury. Future research will help to further clarify the incidence and cellular mechanism by which isoflurane, sevoflurane, and desflurane evoke hepatic pathophysiologic processes. Nonetheless, with the knowledge that cross-sensitization and immunologic memory are factors to be considered in any patient who has received a prior halothane anesthetic, even decades before, vigilance by anesthesia providers is still required.

Neuromuscular System

All volatile agents produce a dose-dependent relaxation of skeletal muscle, as well as potentiation of the effects of depolarizing and nondepolarizing muscle relaxants.[289] The mechanism by which this occurs is multifactorial, involving reduced neural activity within the CNS and a presynaptic or postsynaptic effect at the neuromuscular junction.[43, 290] Of the synaptic changes produced, the volatile agents predominantly affect the postjunctional membrane.[291]

With the exception of halothane, it is variable as to which volatile agent potentiates neuromuscular blocking agents the most.[292] Studies incorporating a broader methodology indicate that the greatest degree of potentiation of neuromuscular blockade occurs with sevoflurane, then isoflurane, and finally halothane.[293,294] Desflurane has been found by some investigators to potentiate the effects of neuromuscular blockers to the same extent as isoflurane[295] and sevoflurane. Similarly, other studies have shown that sevoflurane and isoflurane equally augment[296] and prolong[292] neuromuscular blockade produced by nondepolarizing muscle relaxants. In contrast, one investigation found that desflurane and sevoflurane enhanced the intensity of neuromuscular blockade with rocuronium, whereas isoflurane's effect was no different than that observed with a total intravenous anesthetic (TIVA).[289]

The discrepancies reported with interactions between volatile agents and muscle relaxants may be the result of differences in research methodology (e.g., type of muscle relaxant used in the study). For example, recovery of neuromuscular blockade after the use of cisatracurium and rocuronium is prolonged with sevoflurane but not isoflurane.[293,296] In contrast, the recovery profile for both volatile agents is the same after the use of vecuronium.[292]

Isoflurane[297] and N_2O[298] have been shown to potentiate the effects of succinylcholine. The former can accelerate the transition from a phase I to phase II block during an infusion of succinylcholine.[297] In general, nondepolarizing muscle relaxant dosages are decreased by approximately 25%[289,299] (sometimes as much as 50%)[293] of that required with TIVA when they are used in combination with a volatile agent. Of interest are two studies that found no difference in potentiation of nondepolarizing muscle relaxants and neuromuscular recovery profiles between an isoflurane/N_2O and TIVA technique.[293,296]

The volatile agents have also been shown to produce a time-dependent potentiation of nondepolarizing muscle relaxants (beginning in 5 to 10 minutes),[300] as well as a delayed recovery. For example, after 30 minutes of exposure to sevoflurane, recovery from vecuronium to 25% of baseline neuromuscular function is prolonged by 89%, and after 60 minutes, recovery exceeds 100%.[301] The inhalation agents have also been implicated in impairing reversal of nondepolarizing neuromuscular block.[302,303] For the reasons listed, anesthetists should carefully titrate muscle relaxants used in combination with inhalation anesthetics. Also, in select cases, a volatile anesthetic alone may produce adequate skeletal muscle relaxation without concurrent use of muscle relaxants.[304,305]

Malignant Hyperthermia

All of the volatile agents are capable of triggering malignant hyperthermia. These agents should not be used in malignant hyperthermia–susceptible patients. If a reaction occurs, it is treated instituting a hyperthermia protocol that includes intravenous dantrolene; the recommended dose is 1.0 to 2.5 mg/kg repeated every 5 minutes up to 10 mg/kg (although with some patients a larger dose may be necessary).[306] Of interest is the observation that a delayed response (e.g., 6 hours) to malignant hyperthermia provoked by inhalation agents has been reported to occur with the use of nondepolarizing muscle relaxants and with desflurane if it is administered in the absence of succinylcholine.[307]

Nitrous oxide is considered at most a weak trigger of malignant hyperthermia in susceptible patients.[308-310] Overall, the clinical use of N_2O, in combination with many other agents (e.g., barbiturates, propofol, ketamine, etomidate, opiates, and amide and ester anesthetics), is considered acceptable in patients susceptible to malignant hyperthermia.[311]

SUMMARY

Inhalation agents remain the most common class of drugs used to maintain a general anesthetic. The pharmacokinetic and pharmacodynamic profile of desflurane and sevoflurane facilitate meeting the anesthetic goals of an ever-increasing, same day–surgery population. The ease of administration of all ether-based volatile anesthetics, with or without N_2O, lends itself to common use among a diverse surgical population. Continued research will help guide anesthetists in the selection and application of a variety of inhalation anesthetic techniques. A summary of the systemic effects of the major inhalation anesthetics is given in Table 8-4. Some advantages and disadvantages of selected inhalation anesthetics are given in Table 8-5.

TABLE 8-4 Effects of the Inhalation Anesthetics

Variable	Isoflurane	Desflurane	Sevoflurane
Kinetics			
Alveolar equilibration	Moderate	Fast	Fast
Recovery	Moderate	Very fast	Fast
Liver			
Hepatotoxicity	No	No	No
Metabolism (%)	0.2	0.02	5-8
Musculoskeletal relaxation	Moderate	Moderate	Moderate
Cardiovascular System			
Heart rate	Mild increase	Moderate increase	Stable
Cardiac output	Slightly reduced	Slightly reduced	Slightly reduced
SVR	Reduced	Reduced	Reduced
MAP	Reduced	Reduced	Reduced
Respiratory System			
Respiratory irritation	Significant	Significant	No
Central Nervous System			
Seizure activity on EEG	No	No	Yes
Renal System			
Renal toxic metabolites	No	No	No

Modified from Aitkenhead AR, et al: *Textbook of Anaesthesia*, 5th ed. Edinburgh: Churchill Livingstone, 2007, pp 26-27.
EEG, Electroencephalogram; *SVR*, systemic vascular resistance; *MAP*, mean arterial pressure.

TABLE 8-5 Clinical Advantages and Disadvantages of Selected Inhalation Anesthetics

Anesthetic	Advantages	Disadvantages
Nitrous oxide	Analgesia Rapid uptake and elimination Little cardiac or respiratory depression Nonpungent Reduces MAC or the more potent agents	Expansion of closed air spaces Requires high concentrations Amount of oxygen delivered is reduced Diffusion hypoxia
Isoflurane	Moderate muscle relaxation Decreases cerebral metabolic rate Minimal biotransformation No significant systemic toxicity Inexpensive	Pungent odor Airway irritant Trigger for malignant hyperthermia
Desflurane	Rapid uptake and elimination Stable molecules Minimal biotransformation No significant systemic toxicity Decreases cerebral metabolic rate	Airway irritant Expensive compared to the other agents Needs special electrically heated vaporizer Rapid increases in inspired concentration can lead to reflex tachycardia and hypertension Trigger for malignant hyperthermia
Sevoflurane	Rapid uptake and elimination Nonpungent Excellent for inhalation induction Cardiovascular effects broadly comparable to those of isoflurane	Reacts with soda lime Trigger for malignant hyperthermia

MAC, minimum alveolar concentration.

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CHAPTER 9

Intravenous Induction Agents

◆ *John J. Nagelhout*

An historic milestone in anesthesia was reached in 2011 with the decision to cease marketing sodium pentothal, a thiobarbiturate, in the United States and many other countries. Thiobarbiturates, when they were introduced in the 1930s, changed the way anesthesia was delivered. Although their use has declined dramatically in recent decades with the introduction of propofol, the practice of using intravenous push boluses of sedatives to initiate anesthesia remains the standard. Induction refers to the start of anesthesia when the patient is rendered unconscious. The intravenous induction agents allow the patient to experience a pleasant loss of consciousness while also rapidly achieving surgical levels of anesthesia.

A single ideal intravenous anesthesia induction drug has yet to be developed; however, the agents currently available can be exploited to select an appropriate drug for all surgical and anesthetic requirements. Desirable properties for an induction agent include rapid and smooth onset and recovery, analgesia, minimal cardiac and respiratory depression, antiemetic actions, bronchodilation, lack of toxicity or histamine release, and advantageous pharmacokinetics and pharmaceutics. Propofol is the current standard agent and is widely used for induction of general anesthesia and intravenous sedation. Etomidate and ketamine are valuable agents for select anesthetics when propofol use is undesirable. Dexmedetomidine is gaining popularity for niche uses as well. This chapter discusses the advantages and limitations of the currently used intravenous anesthesia induction agents.

NONBARBITURATE INTRAVENOUS ANESTHETICS

Propofol

Chemical Structure and Pharmaceutics

Propofol is a 2, 6-diisopropyl phenol (Figure 9-1). It is prepared as a 1% solution in a lipid emulsion of 10% soybean oil, 2.25% glycerol, and 1.2% purified egg lecithin. The pH of propofol (Diprivan) is 7 to 8.5, and the pK_a (negative logarithm of the acid ionization constant) is 11. The pH of the generic form of propofol is 4.5 to 6.4, and the pK_a is 11.[1] This unique vehicle is especially favorable to bacterial contamination. The original trade product, Diprivan, contains 0.005% disodium edetate (EDTA [ethylenediamine tetraacetic acid]) as a preservative to inhibit bacterial and fungal growth. Generic forms of propofol contain 0.025% sodium metabisulfite or benzyl alcohol depending on the manufacturer. Clusters of infections reported after mishandling of earlier preservative-free preparations prompted the addition of these preservatives.[2] Careful handling is still important. It is recommended that aseptic conditions be maintained and the drug be used immediately upon withdrawal from a vial for a single patient. Any remaining drug should be discarded. Syringes or vials should never be used for more than one patient. Opened vials or syringes should be discarded within 12 hours or 6 hours if propofol was transferred from the original container.

The pharmaceutical preparations are shown in Table 9-1.

Reformulations of Propofol

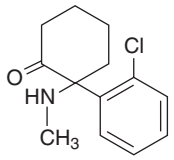
Newer formulations of propofol are being investigated that will have a more favorable vehicle than the lipid emulsion. These include other soybean and albumin emulsions, micelles and nanoemulsion cyclodextrins among others.[1,3]

A clear aqueous preparation of propofol as a phosphate prodrug is available for conscious sedation. A prodrug is a drug administered in an inactive or significantly less active form. Once administered, the prodrug is metabolized in the body into the active compound. Although propofol has many advantages such as rapid onset and offset when given for minor procedures such as colonoscopy or bronchoscopy, it can also present some challenges. It has a narrow therapeutic index, and hemodynamic and respiratory depression as well as general anesthesia can easily result from minor dose adjustments. Unlike the benzodiazepines, there is no pharmacologic antagonist. Fospropofol (Lusedra®) is being marketed as a safer formulation for mild to moderate sedation.[4] As a prodrug it requires metabolic conversion to active propofol. The resulting slow onset makes it unsuitable for general anesthetic induction. The aqueous preparation avoids the injection pain associated with lipid emulsions. Figure 9-2 depicts the conversion of the prodrug of propofol by plasma alkaline phosphatases to the active propofol molecule, releasing formaldehyde and phosphate. Formaldehyde is further metabolized to formate by formaldehyde dehydrogenase. Select pharmacokinetic and clinical properties of fospropofol are listed in Box 9-1.[4-6]

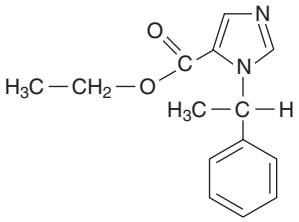
Pharmacokinetics

Propofol exhibits a generally favorable kinetic profile, which is one of its main clinical benefits in comparison with other induction drugs (Table 9-2).[7,8] Rapid distribution following an IV (intravenous) bolus dose into the brain and other highly perfused areas results in a fast onset of generally one circulation time. Rapid redistribution from the central to the peripheral compartments as the drug more evenly distributes to the entire body produces a quick initial decline in blood levels. As distribution continues, the drug is circulated to less well perfused tissues such as muscle, and the brain concentration falls. This effect leads to a rapid reawakening after sedative and anesthetic doses. The time to awakening is dose and patient dependent but is usually in the range of 5 to 15 minutes. The movement of propofol through various body compartments over time is depicted in Figure 9-3. A visual conceptualization of the redistribution of drugs given by rapid push bolus is shown in Figure 9-4.

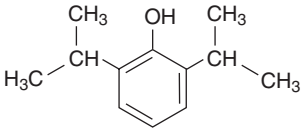
A complete discussion of the pharmacology of the barbiturates is available in the 4th edition of this textbook.



Ketamine

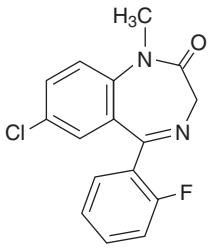


Etomidate

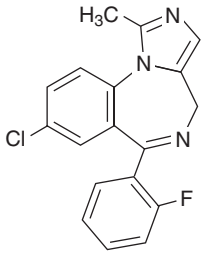


Propofol

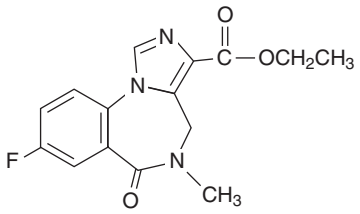
BENZODIAZEPINES



Diazepam



Midazolam



Flumazenil

FIGURE **9-1** Agents used for the induction of general anesthesia, sedation, and benzodiazepine reversal.

TABLE 9-1 Pharmaceutic Preparation of Intravenous Anesthetic Agents

Class	Drug Name	Available Solution	Pain on Injection*
Benzodiazepines	Diazepam (Valium)	0.5% in 40% propylene glycol and 10% alcohol	+++
	Lorazepam (Ativan)	0.4% in propylene glycol	+
	Midazolam (Versed)	0.5% buffered aqueous solution (pH 3.5)	0
Imidazoles	Etomidate (Amidate)	Water soluble at acidic pH, lipophilic at physiologic pH (pK_a 4.24); 0.2% solution in 30% propylene glycol (pH 5)	+++
	Dexmedetomidine (Precedex)	Dexmedetomidine HCl is freely soluble in water and has a pK_a of 7.1 with a pH of 4.5-7.0. The solution is preservative free. Prepare by adding 2 mL of dexmedetomidine (100 mcg/mL) to 48 mL of 0.9% sodium chloride injection for a total of 50 mL. The final concentration is 4 mcg/mL.	0
Alkylphenol	Propofol (Diprivan)	1% solution in an aqueous emulsion containing 10% soybean oil, 2.25% glycerol, and 1.2% egg phosphatide, EDTA (pK_a 11)	++
	Generic propofol	Generic formulations vary; may contain metabisulfite (use with caution in patients with allergies and asthma); formulations that contain benzyl alcohol pH 7-8.5 (benzyl alcohol should be avoided in infants)	++
	Lusedra (fospropofol)	Water-soluble prodrug of propofol that undergoes hydrolysis by alkaline phosphatases to propofol	0
Arylcyclohexylamines	Ketamine (Ketalar)	White crystalline salt 1% or 10% aqueous solution (pH 3.3-5.5; pK_a 7.5)	0

*0, None; +, mild; ++, moderate; +++, marked.

EDTA, Disodium ethylenediamine tetraacetic acid.

Metabolism plays little role in the initial awakening of the patient but is important in the eventual clearance of the drug. An interesting characteristic of propofol is its rapid metabolic clearance, which actually exceeds hepatic blood flow.[8] These extra hepatic sites of metabolism probably account for the lack of changes in elimination seen in patients with severe cirrhosis. [9] Less than 1% of propofol is excreted unchanged. It is rapidly metabolized in the liver by CYP2B6, UGTHP4, and CYP2C6.[10] The drug's kinetics are also influenced by age, with the elderly requiring lower doses.[11] Children require higher doses because they have an increased volume of distribution based on body weight. Their rate of clearance is also higher.[12] Some accumulation can occur with prolonged infusion secondary to tissue saturation.[13] The elimination half-life is 1 to 2 hours.

Concerns that the traditional concept of half-life is misleading when drugs are given for prolonged periods by infusion led to the introduction of context-sensitive half time. The context is the duration of the infusion.[14] It is the time required for a 50% decrease in plasma concentration after an infusion. Further refinements have described decrement times that include the 20% and 80% declines.[15] The decrement time is from the end of the infusion to 50% recovery and includes pharmacokinetic data related to concentration decrease and pharmacodynamic data correlating with recovery. These concepts are discussed in Chapter 6.

Propofol reversibly binds to erythrocytes (50%) and plasma proteins, most commonly to plasma albumin (48%). The free concentration is less than 2%.[16] Decreased plasma protein levels resulting from severe renal or hepatic disease and those patients in the third trimester of pregnancy may lower drug binding and increase the free active fraction. This may increase the effects of propofol. Clinically this may be a factor when prolonged infusions are used.[17] Factors that can alter protein binding are noted in Table 9-3. Drugs that are highly lipid soluble cross cell membranes rapidly, including the blood-brain and placental barriers. Propofol being highly soluble easily enters all body compartments.[18]

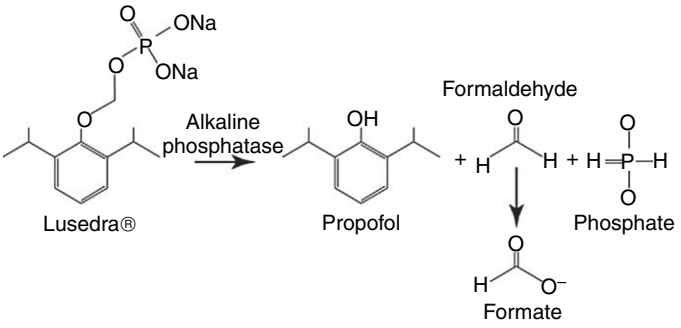


FIGURE **9-2** Conversion of the prodrug of propofol to the active propofol molecule by alkaline phosphatases.

Mechanism of Action

Like many other sedatives and anesthetics, propofol appears to exert its effect via an interaction with the inhibitory neurotransmitter γ-aminobutyric acid (GABA) and the $GABA_A$ glycoprotein receptor complex.[19] γ-Aminobutyric acid (GABA) is a major inhibitory transmitter in the central nervous system (CNS). The $GABA_A$ receptor, which is a ligand-gated ion channel receptor, is activated by the binding of the neurotransmitter GABA. This binding of

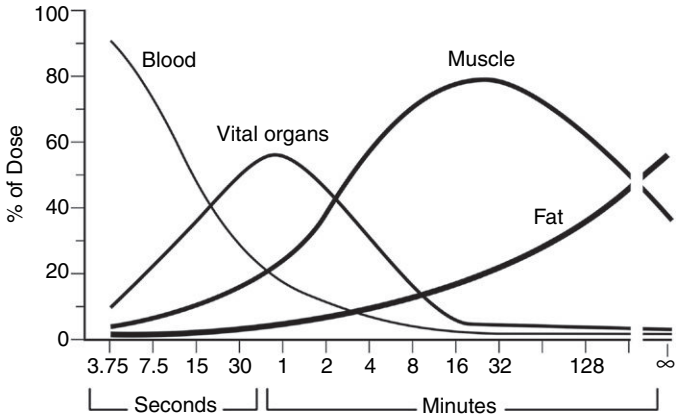


FIGURE **9-3** Propofol kinetics. Note that propofol rapidly enters the brain and other vital organs, with peak effects at 1 minute after bolus injection. The brain concentration then falls rapidly over the next 10 to 15 minutes as the drug redistributes more evenly throughout the body to muscle and fat.

BOX 9-1

Clinical Pharmacology for Fospropofol (Lusedra)

Indication

Intravenous sedation in adults undergoing diagnostic or therapeutic procedures

Dose and Administration

- Standard dose: Initial dose 6.5 mg/kg
- Supplemental dose: 1.6 mg/kg no more frequently than every 4 minutes
- For patients 65 years old or younger and without severe systemic disease: Standard doses apply
- For patients 65 or more years old or with severe systemic disease: Modified dose 75% of standard dose

Pharmacokinetic Profile Compared to Propofol

- Onset: 5-13 minutes
- Duration: 15-45 minutes (depending on dose)
- Volume of distribution (L/kg): Fospropofol: 0.3; propofol: 5.8
- Total body clearance (L/hr/kg): Fospropofol: 0.36; propofol: 3.2
- Terminal elimination half-life (hours): Fospropofol: 0.88; propofol: 1.13

Most Frequent Adverse Events (Incidence 5% or greater)

Perineal paresthesia, pruritus, hypoxemia, hypotension

TABLE 9-2 Select Pharmacokinetic Values for Intravenous Anesthetic Agents

Drug Name	Distribution Half-Life (min)	Elimination Half-Life (hr)	Clearance (mL/kg/min)	Volume of Distribution (L/kg)	Protein Binding (%)
Diazepam	10-15	20-50	0.3	0.8-1.3	98
Lorazepam	4-5	10-16	0.8-1.8	0.8-1.3	90
Midazolam	7-15	2-4	7-11	1-1.7	94
Etomidate	2-4	2-5	22.5	2.5-4.5	75
Propofol	2-4	1-5	25	2-8	98
Ketamine	11-17	2-3	14.5	2.5-3.5	12
Dexmedetomidine	6-8	2-2.6	8.9	1.54	94

GABA to the $GABA_A$ receptor initiates the movement of chloride (Cl^-) through ion channels into the cell. This results in hyperpolarization of postsynaptic cell membrane and the inhibition of neuronal cell excitation. A model has been developed that includes sites of action for GABA on the postsynaptic membrane, as well as sites for numerous other drugs. Propofol directly stimulates $GABA_A$ receptors and potentiates the actions of endogenous GABA. The GABA receptor and its function are described in Figure 9-5.

Pharmacodynamics

Central Nervous System Effects. Propofol produces a rapid and pleasant loss of consciousness and emergence from anesthesia. Low-dose infusions for conscious sedation result in dose-dependent anxiolysis, sedation, and amnesia.[20] There are dose-dependent reductions in cerebral blood flow (CBF), cerebral metabolic rate of oxygen consumption ($CMRO_2$), intracranial pressure (ICP), and cerebral perfusion pressure(CPP).[21] These effects result in part from the decreased mean arterial pressure, depressed metabolic rate, and cerebral vasoconstriction produced by standard doses in a manner comparable to the effects of barbiturates and etomidate.[22,23] Cerebral autoregulation and reactivity to changes in carbon dioxide (CO_2) are preserved with propofol. Hyperventilation should be applied cautiously in patients with an increase in ICP to avoid hypocarbia-induced cerebral circulatory compromise.[24]

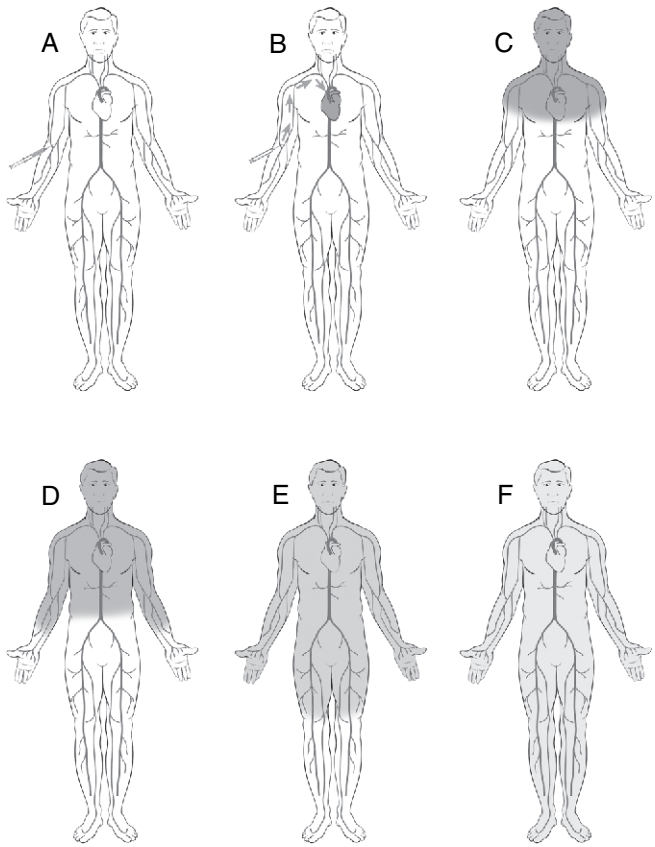


FIGURE **9-4** Redistribution of intravenous drugs is shown. **A** and **B,** A drug is administered in the arm and follows the venous circulation to the heart. **C,** The high cardiac output and circulatory flow initially distribute the drug to the brain and upper body, and rapid central nervous system effects begin. **D, E,** and **F,** As time passes, usually minutes, the drug more evenly distributes throughout the body, lowering the initial high brain concentration, and the patient awakens.

Electroencephalogram (EEG) data produced a delta rhythm without evidence of epileptiform activity and burst suppression with higher doses.[25] Even with these findings, controversy exists over the use of propofol in the patient with epilepsy.[26] Three epileptic patients were reported to experience increased epileptiform activity on EEG after the administration of propofol 2 mg/kg.[27] Studies in patients with epilepsy showed a different response in that the EEG showed no increase in epileptogenic activity at any of the sites monitored.[28] It was also found that activation or extension of EEG activity was greater with thiopental than with propofol (although not statistically significant).[29] Propofol has been used successfully to manage status epilepticus.[30] Myoclonia induced by propofol results in spontaneous excitatory movements secondary to selective disinhibition of subcortical centers. Adequate dosage may prevent the occurrence of these movements. Myoclonia may occur on induction, but the incidence appears to be lower than that with etomidate. Opisthotonos has also been associated with propofol. Intraocular pressure is decreased by propofol.[31] Evidence for a neuroprotective effect is controversial because studies in both animals and humans have not been consistent. Propofol cannot be indicated as a clinical neuroprotectant alone, but it might play an important role in multimodal neuroprotection. Beneficial effects include preservation of cerebral perfusion, temperature control, prevention of infections, and tight glycemic control.[32]

The use of propofol for electroconvulsive therapy (ECT) has been somewhat controversial as a result of the drug's effects on seizure duration. Several studies have shown that propofol reduces the duration of the ECT-induced seizure when compared with barbiturates. Evaluating the efficacy of ECT as an antidepressant was typically based on the duration of the seizure; a shortened seizure implied a less effective therapy. However, researchers have found that a reduction in seizure duration does not decrease the efficacy of the ECT, and that propofol is an appropriate agent for use in this procedure.[33-35]

CNS effects of the intravenous induction drugs are shown in Table 9-4.

Cardiovascular Effects. Propofol usually results in a mild to moderate transient decrease in blood pressure in healthy adults and children during anesthesia induction. The decrease in blood pressure is not usually clinically significant. The effects are more pronounced than those seen with equivalent doses of etomidate or midazolam. It can, however, result in significant hypotension in usual induction doses in select patients. Predictors of hypotension during induction are age greater than 50 years, ASA (American Society of Anesthesiologists) class 3 to 4, baseline mean arterial pressure less than 70 mmHg, and coadministration of high doses of fentanyl. Hypotension usually occurs within 10 minutes after induction and is more prevalent in the second half of the 0- to10-minute interval.[36] As with most cardiovascular-depressing sedatives, these effects result from varying degrees of a combination of CNS, cardiac

TABLE **9-3** Factors That Alter Protein Binding

Factors	Percent Bound
Decreased lipid solubility	Decreases binding
Increased pH (≤8.0)	Increases binding
Increased drug concentration	Decreases binding
Increased protein concentration	Increases binding
Increased competition for binding sites with other drugs	Decreases binding

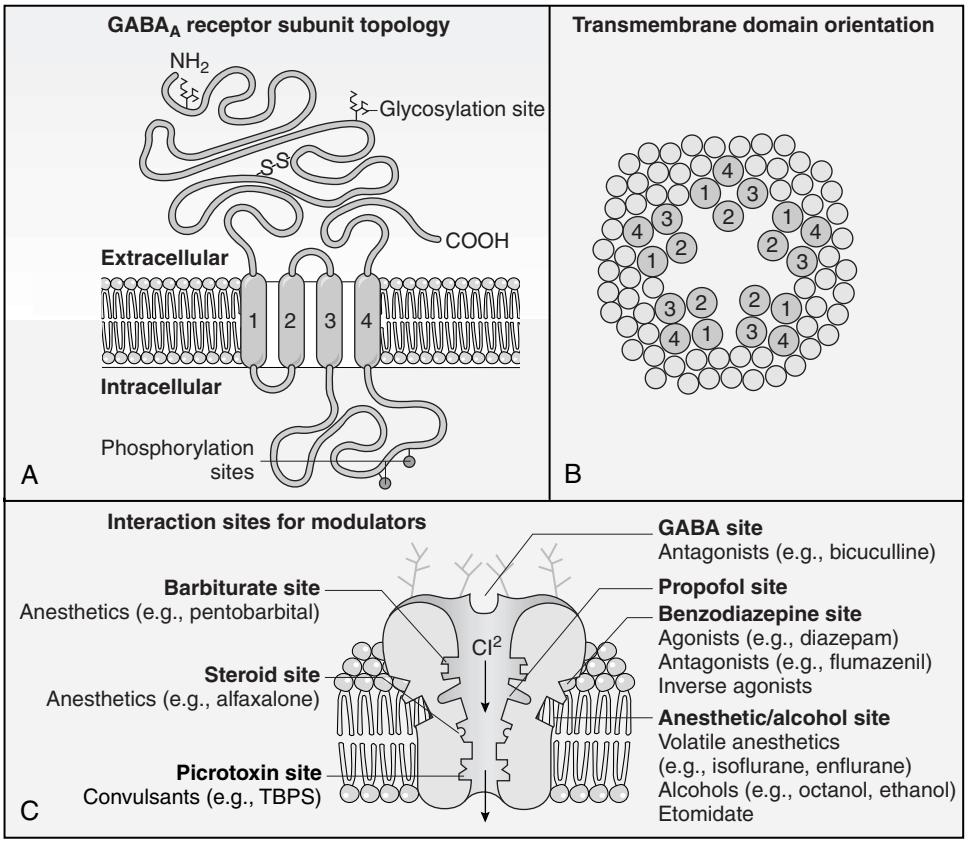


FIGURE **9-5** The GABA$_A$ receptor. **A,** The generic GABA$_A$ receptor subunit has four hydrophobic transmembrane segments that are thought to form amphipathic α-helices. The *N*-terminal domain contains *N*-glycosylation sites and a conserved cysteine bridge; it forms the agonist-binding site. The large intracellular loop undergoes phosphorylation in several isoforms. **B,** Plane view of the transmembrane hydrophobic segments showing interactions to form a central ion-conducting pore lined by the second transmembrane domains. The hetero-oligomeric structure consists of five subunits, with each subunit contributing to the ion channel pore. **C,** The GABA$_A$ receptor gates an anion channel permeable to Cl^- and HCO_3^-. The general anesthetics are distinguished from the benzodiazepines (which allosterically modulate GABA binding to potentiate GABA responses) by their ability to activate/gate the GABA$_A$ receptor channel directly. A separate site at the interface between the third and fourth transmembrane segments appears to interact with volatile anesthetics, alcohols, and etomidate, as demonstrated by site-directed mutagenesis studies. *(From Hemmings HC, Hopkins PM, (eds):* Foundations of Anesthesia Basic and Clinical Sciences, *2nd ed. St Louis: Mosby; 2006.)*

TABLE **9-4** Central Nervous System Effects of Intravenous Anesthetics

Agent	CBF	CPP	$CMRO_2$	ICP	IOP
Etomidate	↓↓	↓↓	↓↓	↓↓	↓
Propofol	↓↓	↓↓	↓↓	↓↓	↓↓
Ketamine	↓↓	↑	↑	↑	↑
Midazolam	↑↓	↓	↓	↓	↓
Dexmedetomidine	↓	↑↓	0	↓	↓

CBF, Cerebral blood flow; *CPP,* cerebral perfusion pressure; *$CMRO_2$,* cerebral metabolic rate of oxygen consumption; *ICP,* intracranial pressure; *IOP,* intraocular pressure.
↓, Decreases; ↑, increases; 0, no effect.

and baroreceptor depression, and decreases in sympathetic tone and systemic vasodilation. The primary reasons for propofol-induced hypotension are decreased sympathetic tone and vasodilation.[37] Central nervous system and direct cardiac depression play less of a role. A decrease in dose or alternative agents should be considered in the elderly or cardiac-compromised patients. Propofol has been used successfully for cardiac anesthesia when combined with fentanyl in low-dose or infusion regimens (Table 9-5).[38]

Respiratory Effects. Transient respiratory depression, more prominent than that seen with etomidate, is common with induction doses of propofol. Decreases in tidal volume are greater than decreases in respiratory rate, although apnea is common on initial administration of induction doses.[39] The frequency and duration of apnea are dependent on the dose, speed of injection, patient characteristics, and the presence of other respiratory depressant medications.[40] Dose-dependent respiratory depression is also common with maintenance infusions. This appears to result from a decreased sensitivity of the respiratory center to carbon dioxide.[41]

Propofol has a minimal bronchodilating effect in patients with or without asthma and in patients who smoke. It does not cause histamine release and has been used successfully for anesthesia induction in asthmatic patients. After tracheal intubation, respiratory resistance is lower, and the incidence of wheezing is decreased, compared with the effects of etomidate.[42,43] Propofol or ketamine are the preferred induction agents in patients with asthma.[44]

TABLE 9-5 Cardiac and Respiratory Effects of Intravenous Anesthetic Agents

Drug Name	Mean Arterial Pressure	Heart Rate	Cardiac Output	Venous Dilation	Systemic Vascular Resistance	Respiratory Depression	Bronchodilation
Etomidate	0	0	0	0	0	0/–	0
Propofol	– –	–	–	++	– –	– –	0/+
Ketamine	++	++	+	0	+/–	0	+
Diazepam	0/–	–/+	0		–/0	0	0
Midazolam	0/–	–/+	0	+	–/0	0	0
Dexmedetomidine	–	– –	0/–	0	0	0	0

–, Mild decrease; – –, moderate decrease; +, mild increase; ++, moderate increase; 0, no effect.

Other Pharmacologic Actions. Propofol possesses mild antiemetic effects that are most prominent when given by continuous infusion.[45,46] The mechanism for the antiemetic effects is unclear. It also exhibits antipruritic effects against opioid-induced pruritus.[47,48]

Patients experience mild to moderate pain on injection with propofol. The incidence is approximately 60% and is most frequently related to the use of smaller veins for injection The two most effective interventions to reduce pain on injection are the use of the antecubital vein or pretreatment with lidocaine 20 to 40 mg in conjunction with venous occlusion when the hand vein was chosen. Other effective pretreatments are using a lidocaine-propofol admixture, opioids, ketamine, and nonsteroidal antiinflammatory drugs.[49] Intraarterial injection of propofol does not cause vascular injury.

Obstetric Use. As you would expect from a highly lipid soluble drug, propofol easily passes the placental barrier when administered to a pregnant woman. Sedative effects occur in the neonate when propofol is used for cesarean delivery. Lower 1- and 5-minute Apgar scores have been noted.[50]

The anti-emetic effects of propofol may be an advantage in these patients. It is also used for sedation and hypnosis in postpartum tubal ligations and assistive reproductive techniques.

Contraindications and Precautions

Few absolute contraindications exist for propofol other than cases in which a known hypersensitivity exists to propofol or its components or the patient has a disorder of lipid metabolism.[51,52] New generic formulations of propofol, which contain sodium metabisulfite, should not be used in sensitive patients. The sulfite may cause allergic-type reactions such as anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. Sulfite sensitivity is more common in patients with asthma than in patients without asthma.[53] As noted, caution is advised in elderly, debilitated, and cardiac-compromised patients.

Allergy

Propofol lipid emulsion formulations have been scrutinized because of their lecithin content. Lecithin (from the Greek *lekithos*, meaning "egg yolk") is a phospholipid compound composed of a range of phosphatidyl esters such as phosphatidylcholine, phosphatidylethanolamine, and phosphatidylserine. These are combined with varying amounts of triglycerides and fatty acids. Lecithin was originally obtained from eggs, although now soybeans and other vegetables with high lecithin content have also become useful sources. Apart from its use as an antioxidant synergist, lecithin has important surfactant properties and is used as an emulsifying agent.[54]

Controversy exists regarding whether propofol should be avoided in patients who are allergic to eggs, soy, or peanuts. Egg allergy is most common in children and usually outgrown by adulthood.[55] The 2009 guidelines published by the Association of Anesthetists of Great Britain and Ireland claim there is no evidence that propofol should be avoided in egg- or soy-allergic patients.[56,57] The warning labels differ among countries for the same formulation of propofol supplied by the same company. The product information for Diprivan 1% warns of its use in egg- or soy-allergic individuals in Australia, soy/peanut (but not egg) in the United Kingdom, and lists no food allergy warnings in the United States. This is despite all three formulations being supplied by the same company.[56]

A retrospective case review of 28 egg-allergic patients was recently reported. Two of the 28 patients had documented egg anaphylaxis. All but the two children with a history of egg anaphylaxis safely received propofol.[58] Data on the two children with documented egg anaphylaxis were not conclusive. The authors suggest propofol is likely to be safe in most egg-allergic children; however, propofol should not be administered to any child with a history of egg anaphylaxis until further evidence is available. Other authors note that there are no confirmed reports of propofol-induced anaphylaxis in egg-allergic patients. They generally demonstrate immediate hypersensitivity to proteins from egg whites. Lecithin is from egg yolks, so there is no reason to contraindicate propofol in egg-allergic patients.[59]

Soy allergy is a common early onset food allergy in children. Many children outgrow the allergy by age 7.[60] Refined soy oil of the types used in propofol have the allergenic proteins removed during refining; therefore it is safe in patients with soy allergy. The suggestion that peanut-allergic patients may exhibit propofol allergy is due to cross reactivity between these leguminous plants; therefore just as with soy allergy, there are also no data to support the avoidance of propofol in patients with peanut allergy.[59]

Propofol Infusion Syndrome

Propofol is frequently used in adult and pediatric intensive care units for prolonged sedation. Numerous case reports, however, describe findings of various metabolic derangements and organ system failures known collectively as propofol infusion syndrome (PRIS) with long-term high-dose infusions of propofol.[61] This has not occurred in anesthesia, even with prolonged administration of relatively high doses, because it seems to require long-duration infusions of increasing doses, as only encountered in critical care units.[62] This syndrome is associated with significant morbidity and mortality. A precise mechanism of action of PRIS has yet to be demonstrated.[63] Risk factors include young age, doses greater than 4 to 5 mg/kg/hr, duration greater than 48 hours, critical illness,

BOX 9-2

Clinical Features of Propofol Infusion Syndrome

Cardiovascular
- Hypotension
- Widening of the QRS complex
- Bradycardia
- Ventricular tachycardia or fibrillation
- Asystole

Respiratory
- Hypoxia (preexisting)

Renal
- Acute kidney injury
- Hyperkalemia

Musculoskeletal
- Rhabdomyolysis

Metabolic
- Hyperthermia
- Metabolic acidosis

Hepatic
- Hepatomegaly
- Transaminitis
- Steatosis
- Hypertriglyceridemia
- Lipidemia

high-fat low-carbohydrate intake, inborn errors of mitochondrial fatty acid oxidation, concomitant catecholamine infusion, and steroid administration. Many of the patients who developed this syndrome have been children, but several cases in adults have been identified as well.

The syndrome has occurred in patients with acute inflammatory disease with infection or sepsis or acute neurologic disease. One common denominator was the presence of impaired systemic microcirculation with tissue hypoperfusion and hypoxia. Propofol seemed to be a triggering agent when catecholamines and corticosteroids are also administered. Fatty acid metabolism and mitochondrial activity are impaired, creating an oxygen supply-and-demand mismatch that results in cardiac and peripheral muscle necrosis. The current theory proposes that propofol inhibits oxidative phosphorylation by (1) inhibition of the transportation of long-chain fatty acids into the cell as well as (2) inhibitory effects on the mitochondrial respiratory chain. Symptoms include severe metabolic acidosis, refractory cardiac failure, persistent bradycardia refractory to treatment, fever, and severe hepatic and renal disturbances.[64] The clinical features are noted in Box 9-2. Treatment is supportive and includes discontinuing the propofol, improving gas exchange, cardiac pacing for bradycardia, phosphodiesterase inhibitors, glucagon, extracorporeal membrane oxygenation, and renal replacement therapy.[63]

Key points regarding propofol are listed in Box 9-3. Induction doses of the intravenous anesthetics are shown in Table 9-6.

BOX 9-3

Key Points for Propofol Anesthesia

- Propofol is the most commonly used intravenous anesthetic as an induction drug and for sedation.
- Respiratory effects include transient respiratory depression or apnea, depending on dose. Although not a bronchodilator, safe use in asthmatics has been well established.
- Propofol is unique among induction agents in that it exhibits mild antiemetic properties.
- Propofol has a rapid onset and emergence after bolus or continuous infusions of the drug.
- Patients emerge with a mild euphoria followed by rapid dissipation of the sedative effects.
- Propofol reduces cerebral blood flow, $CMRO_2$, and ICP.
- Propofol decreases blood pressure, cardiac output, and systemic vascular resistance to a greater extent than etomidate at equipotent doses.
- The induction dose is 1-2 mg/kg followed by a maintenance infusion of 100-200 mcg/kg/min. Conscious sedation doses are 25-75 mcg/kg/min.

$CMRO_2$, *Cerebral metabolic rate of oxygen consumption*; ICP, *intracranial pressure*.

TABLE 9-6 Induction Doses of the Intravenous Anesthetics

Agent	Dose (mg/kg)
Etomidate	0.2-0.3
Propofol	1-2
Fospropofol (Lusedra)	6.5
Ketamine	(see Box 9-5)
Dexmedetomidine	1 mcg/kg infused over 10 minutes followed by 0.2-0.7 mcg/kg/hr
Midazolam	0.1-0.2

Etomidate

Etomidate (1-[1-phenylethyl]-1*H*-imidazole-5-carboxylic acid ethyl ester) is an intravenous induction agent whose current clinical niche is as an alternative to propofol with little if any cardiorespiratory effects. No intrinsic analgesic properties are associated with the use of this drug.[65] Side effects such as pain on injection, myoclonia, nausea and vomiting, and adrenocortical suppression, however, have limited wider acceptance of the drug. Etomidate is a carboxylated imidazole derivative that was synthesized in 1965 and introduced to European anesthesia practice in 1972.[66] Etomidate has two isomers, but the (+) isomer is the only one with hypnotic properties (see Figure 9-1 for the chemical structure of etomidate).[67]

Etomidate is currently supplied as a 2-mg/mL preparation; each milliliter contains 35% propylene glycol as a solvent and has a pH of 8.1 and a pK_a of 4.2. This formulation has been changed over the years in an effort to decrease the incidence of pain on injection and spontaneous muscle movements or myoclonia. It is also supplied as a lipid emulsion, Etomidate-Lipuro.[68] The lipid emulsion is associated with significantly less injection pain than propofol with added lidocaine in children.[69] Previously used preparations included polyethylene glycol, aqueous ethanol, Cremophor EL, and an aqueous solution.[70]

New formulations are in clinical trials that are designed to maintain the favorable clinical features of etomidate while reducing the primary undesirable effect of prolonged inhibition of adrenal steroidogenesis. Methoxycarbonyl (MOC) etomidate is a "soft" analog that contains a second ester bond distal to the existing etomidate ester linkage.[71] MOC etomidate is rapidly metabolized by nonspecific esterase enzymes in blood and tissue to inactive metabolites. The elimination half-life is a few minutes. No adrenal suppression is found 30 minutes after bolus administration because of the rapid elimination.[72]

Pharmacokinetics

Etomidate is rapidly metabolized in the liver by hepatic microsomal enzymes and plasma esterases. Ester hydrolysis is the primary mode of metabolism in the liver and plasma. Etomidate is hydrolyzed to form inactive carboxylic acid metabolites. Approximately 10% of the administered dose can be recovered in bile, 13% can

be recovered in feces, and the remainder of the metabolites are eliminated by the kidney.[73]

The rapid redistribution of etomidate accounts for its extremely short duration of action (see Table 9-2). The drug is lipid soluble and has a volume of distribution that is several times greater than its body weight. Shortly after intravenous injection (within 1 minute), the brain concentration rises rapidly because of the drug's lipid solubility, and over the next several minutes extensive redistribution to other organs and tissues occurs and the patient regains consciousness.

The total body clearance of etomidate is rapid. The hepatic extraction ratio is 67%. Studies examining dose-response relationships have found a lack of accumulation with this compound.[65] The terminal half-life is 2 to 5 hours.[72]

Awakening occurs 5 to 15 minutes after bolus administration. Like other intravenous induction drugs, this occurs secondary to rapid redistribution to non-nervous sites. Etomidate is 76% protein bound, mostly to albumin. Variations in the amount of available plasma protein alter the amount of free drug available to exert pharmacologic actions. Disease states that produce alterations in plasma protein content could theoretically effect the action although this rarely happens clinically. Compensatory increases in metabolism and elimination can readily compensate for changes in protein binding.

The mechanism of action of etomidate, like many other CNS depressants, involves GABA modulation (see Figure 9-5).[74] In a clinical investigation of 2500 cases, Doenicke et al.[75] confirmed that no histamine is released by etomidate.

Pharmacodynamics

Central Nervous System Effects. Etomidate produces a dose-dependent CNS depression within one arm-brain circulation. Its duration of action is also dose dependent,[65] with awakening occurring 5 to 15 minutes after a 0.2- to 0.4-mg/kg dose. The drug is devoid of analgesic properties.

Cerebral blood flow and cerebral metabolic rate of oxygen consumption are both decreased by etomidate.[76,77] In a study of fully alert patients without neurologic deficit or impaired consciousness, an etomidate induction was followed by an infusion of 2 to 3 mg/min. Cerebral blood flow decreased 34%, and cerebral metabolism was also reduced (mean decrease of 45%). Decreased oxygen consumption and the associated decrease in carbon dioxide production can cause cerebrovascular vasoconstriction, decreased cerebral blood flow, and decreased intracranial pressure. Also noted during this trial was the maintenance of cerebral blood vessel responsiveness to changes in carbon dioxide levels.[76]

In a study of patients with intracranial pathology, etomidate (0.2 mg/kg given intravenously) was shown to decrease intracranial pressure while maintaining cerebral perfusion pressure. Because of the cardiovascular stability of this drug, mean arterial pressure did not decrease below cerebral autoregulation values at which cerebral blood flow would become pressure dependent. Cerebral perfusion pressure was maintained adequately in all study subjects.[77]

The electroencephalographic changes that follow administration of etomidate are similar to those that follow administration of other intravenous induction anesthetics. When compared with thiopental, a lack of beta-wave activity was present during induction, along with a longer duration of stages III and IV.[78]

One negative characteristic of etomidate is its excitatory phenomenon of muscle movements and tremors.[78,79] Referred to as *myoclonia*, this phenomenon is defined as sudden, generalized, asynchronous muscle contractions.[80] Myoclonia can affect many muscle groups or a single muscle. The movements can be so severe that they resemble, and are often mistaken for, seizures. In EEG patterns monitored during etomidate anesthesia, no specific EEG disturbances occurred during or after myoclonic episodes.[78] The origin of these muscle movements is thought to be related to uneven drug distribution into the brainstem or deep cerebral structures and not to CNS stimulation.[78,81] The incidence of myoclonia ranges between 10% and 60% and varies with the type and the amount of premedication given. Investigators associated the 35% incidence of myoclonic movement with painful stimuli (e.g., drug injection, mandibular lifting). Horrigan et al.[79] reported that premedication with fentanyl (100 mg) given intravenously 2 minutes before induction did not significantly decrease motor activity. However, pretreatment with small doses of etomidate, dexmedetomidine, midazolam, rocuronium, and lidocaine are all effective in reducing myoclonia.[82-86] Etomidate is shown to decrease intraocular pressure.

Electroencephalographic changes with etomidate are similar to those of other intravenous induction drugs. Bispectral index (BIS) monitor values decrease after a bolus of etomidate and correlate well with sedation scores. Etomidate decreases the amplitude and increases latency of auditory evoked potentials. The duration of epileptiform activity after ECT is longer after induction with etomidate versus propofol. Somatosensory-evoked potential amplitudes are enhanced by etomidate and motor-evoked potential amplitudes are suppressed less by etomidate than propofol.[87-89]

Cardiovascular Effects. The primary clinical advantage of etomidate over propofol is the hemodynamic stability upon induction in healthy or modestly debilitated patients. In patients with compensated heart disease, changes in heart rate, pulmonary artery pressure, cardiac index, systemic vascular resistance, and systemic blood pressure were not significant.[90] In one study of high-risk patients with significant cardiac disease, hemodynamic stability was maintained with induction doses of 0.3 mg/kg. Also, minimal changes in heart rate, blood pressure, central venous pressure, and intrapulmonary shunting have been demonstrated after etomidate administration.[91] Patients with aortic and mitral valve disease, however, are noted to have significant decreases in systemic blood pressure (17% to 19%), pulmonary artery pressure (11%), and pulmonary capillary wedge pressure (17%).[92] Slight decreases in blood pressure are thought to be caused by decreases in systemic vascular resistance. The hemodynamic stability seen with etomidate has been attributed to a unique lack of depression of sympathetic nervous system and baroreceptor function.[93] Myocardial oxygen supply and demand are kept constant by a balance of decreased myocardial blood flow and decreased oxygen consumption.[94] No significant cardiac dysrhythmias are associated with etomidate administration. Both renal and hepatic blood flows are maintained by the stability of cardiac output (see Table 9-5). In summary, at equivalent anesthetic doses, propofol depresses cardiorespiratory function to the greatest degree and etomidate depresses it the least.

Respiratory Effects. Etomidate affects the respiratory system in a dose-dependent manner. Minute volume decreases, but respiratory rate increases. The respiratory depression seen with propofol use is significantly greater than that seen with etomidate.[94] The ventilatory response to carbon dioxide is decreased, and etomidate administration may cause brief periods of apnea following induction. Etomidate has little effect on bronchial tone and does not cause histamine release (see Table 9-5).[95,96]

Adrenocortical Effects. Adrenal cortical suppression by etomidate has been widely studied, and this effect significantly limits it clinical use. It is useful as a single-dose anesthesia induction

agent, but infusions are no longer used. The issue elicited widespread concern after 10 years of use in Europe. Researchers found an increased mortality rate in critically ill patients who received etomidate infusions. This phenomenon was attributed to adrenocortical hypofunction, demonstrated by decreased levels of plasma cortisol.[97] Multiple studies have shown adrenal hormone levels to be decreased for up to 8 to 24 hours after a single induction dose or more than 24 hours with infusion.[98-104] These effects are caused by a reversible dose-dependent inhibition of adrenal steroidogenesis. The enzymes inhibited are the cytochrome P-450–dependent mitochondrial enzymes and 11β-hydroxylase. To a lesser degree, 17α- and 18-hydroxylases are also affected. This results in an increase in cortisol precursors but a decrease in cortisol, aldosterone, and corticosterone levels. This enzyme inhibition results in decreased ascorbic acid synthesis, which is necessary for steroid production.[105] In summary, these effects are primarily caused by a reversible dose-dependent inhibition of the adrenocortical enzyme 11β-hydroxylase. The mechanism for the adrenocortical hypofunction following administration of etomidate is shown in Figure 9-6.

The clinical significance of this pharmacologic effect continues to be discussed. There have been several reports of single doses of etomidate resulting in patient morbidity. Critically ill patients given corticosteroid therapy for septic shock had poorer results when etomidate was also administered.[106] A large-scale follow-up study (CORTICUS) evaluating low-dose corticosteroid therapy in septic shock suggested that patients receiving etomidate before enrollment had a 28-day mortality, significantly higher than other patients in the trial, and that steroids provided no benefit to those who received etomidate.[107,108] A further analysis of the data led the authors to report that the use of a bolus dose of etomidate in the 72 hours before inclusion in the study was associated with an increased incidence of inadequate response to corticotropin and an increase in mortality. They recommend that clinicians exercise caution in the use of etomidate in critically ill patients with septic shock.[108] The duration of adrenal insufficiency after single-dose etomidate and its effect on outcomes in this population is longer than 24 hours and may last up to 72 hours.[109] The administration of supplemental steroids to counter this effect is controversial. It did not appear effective in septic patients[108]; however, others suggest that the empirical use of steroid supplementation for 48 hours after a single dose of etomidate in critical patients without septic shock should be considered.[109] Further research is needed to define the safe use of single boluses of etomidate in critical patients. The use of new formulations such as methoxycarbonyl (MOC)-etomidate with short durations of adrenal suppression of less than 1 hour may help alleviate this issue.

Adverse Effects

Other than the adrenal suppression and myoclonia that were discussed previously, the primary adverse effects of etomidate are pain on injection, thrombophlebitis, and nausea and vomiting. Etomidate has been formulated in various solvents in an effort to decrease pain on injection and also thrombophlebitis. The current formulation containing propylene glycol results in burning and pain on injection in up to 90% of patients.[110,111] The incidence of subsequent venous sequelae up to 7 days postoperatively is 50%.[110] Some of the variables identified as contributing to pain on injection include site and speed of injection, size of vessel used, and type of premedication. The incidence of injection pain is significantly less with the lipid formulation.[112] As with other venous irritating drugs, injection pain can be decreased with lidocaine 20 to 40 mg pretreatment and use of larger veins. No vascular injury occurs after intraarterial injection of etomidate.

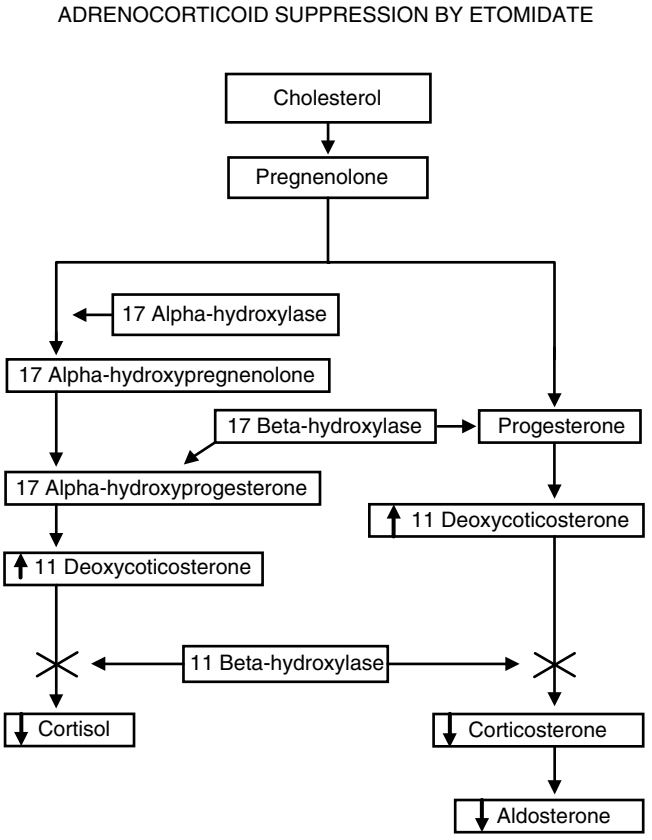


FIGURE **9-6** Adrenocorticoid suppression by etomidate. Etomidate produces prolonged inhibition of 11β-hydroxylase, which leads to reductions in cortisol and aldosterone.

Nausea and vomiting is common with etomidate (30% to 40%).[113,114] Nausea and vomiting are less common with the lipid emulsion of etomidate.[115] Opioids also increase the susceptibility to nausea and vomiting.

Contraindications

Etomidate is contraindicated in patients with a known sensitivity, adrenal suppression, and acute porphyrias.

The porphyrias are a group of rare metabolic conditions caused by deficiencies in the enzymes involved in the biosynthetic pathway of heme, a building block of hemoglobin. They are usually inherited but may be acquired diseases. Depending on deficient enzymatic steps, various porphyrins and their precursors accumulate in tissues and may lead to toxicity. They are classified as acute or nonacute and according to the specific biosynthetic step deficiency. The acute types of porphyria are inducible by various enzyme-inducing drugs that may precipitate an attack. The acute forms are acute intermittent porphyria; variegate porphyria; hereditary coproporphyria, and plumboporphyria. The nonacute forms are porphyria cutanea tarda; erythropoietic porphyrias; congenital erythropoietic porphyria, and erythropoietic protoporphyria.

The rate limiting enzyme in the biosynthetic pathway of porphyrins is ALA-synthetase. Drugs that induce this enzyme must be avoided. Symptoms of an attack may include skin lesions and neurovisceral symptoms such as abdominal and nonabdominal pain, vomiting, psychological symptoms, convulsions, muscle weakness, sensory loss, hypertension, tachycardia, and hyponatremia.

Etomidate and barbiturates are contraindicated. General anesthesia can be readily accomplished, however, with the current agents. Propofol is the induction agent of choice. Ketamine is safe

BOX **9-4**

Key Points for Etomidate

- Etomidate is used in compromised patients when the use of the other intravenous anesthetics may be problematic.
- The major advantage of etomidate is minimal cardiorespiratory depression.
- Etomidate reduces intracranial pressure, cerebral blood flow, and $CMRO_2$.
- The mechanism of action of etomidate appears to be GABA-mimetic.
- Involuntary movements or myoclonia during onset is common.
- Etomidate frequently causes burning on injection.
- Etomidate inhibits the enzyme 11β-hydroxylase, which is essential in the production of both corticosteroids and mineralocorticoids. Clinically significant reductions in steroid production may occur with single doses or prolonged infusions.
- Etomidate increases postoperative nausea and vomiting.
- The induction dose is 0.2-0.3 mg/kg.

$CMRO_2$, *Cerebral metabolic rate of oxygen consumption*.

as well. Most muscle relaxants appear to be reasonably safe, and all of the current inhalational agents may be used. Analgesia can be provided with any of the currently used opiates. Local anesthetics may also be safely used.[116,117]

Key points of etomidate pharmacology are shown in Box 9-4.

Ketamine

Ketamine has a long history of anesthetic use although its popularity has varied over the years. In modern practice several specific situations exist in which it has unique advantages as an alternative to the more commonly used drugs. Recent research has led to new uses as well as a renewed interest in possible untoward effects. It can be very useful for anesthesia and sedation in high-risk, pediatric, and asthmatic patients. Ketamine also has excellent analgesic properties that can be exploited for treatment of perioperative pain.

Ketamine was introduced into clinical practice in 1970 and has a mechanism of action and pharmacologic effects that differ greatly from the classic anesthetic drugs. The anesthetic state is unique because it does not encompass the usual signs and stages of anesthesia with a typical CNS depressant. It produces a cataleptic state in which the patient feels separated from the environment and has profound analgesia and amnesia yet retains most protective reflexes. This ketamine-induced anesthetic state was coined *dissociative anesthesia*, a concept described by Corssen and Domino.[118]

Chemical Structure

The structural formula for ketamine is shown in Figure 9-1. The chemical structure of ketamine is 2-(O-chlorophenyl)-2-(methylamino)cyclohexanone. It has a pK_a of 7.5, is partially water soluble, and is slightly acidic (pH 3.5 to 5.5). Ketamine is an optically active drug with a chiral center that exists as two optical isomers.[119] A racemic mixture is available in the United States and the S(+) isomer is available elsewhere. The S(+) isomer was believed to have a better safety profile, but the advantages of this pure enantiomer are minor.[120]

Mechanisms of Action

Ketamine causes antagonism at *N*-methyl-D-aspartate amino acid (NMDA) receptors in the brain, resulting in a selective depressant effect on the medial thalamic nuclei that is responsible for blocking afferent signals of pain perception to the thalamus and cortex. The primary site of the analgesic action of ketamine is the thalamoneocortical system. Ketamine has been shown to enhance opioid-induced analgesia and prevent hyperalgesia.[121] The NMDA receptor is a ligand-gated ion channel where anions Ca^{2+} and Na^+ are voltage dependent. L-glutamate, an amino acid, is probably the most important excitatory neurotransmitter in the CNS. At the NMDA receptor, it causes the opening of the ion channel. A rapid influx of Na^+, Ca^{2+}, and K^+ results in the depolarization of the normally negative postsynaptic membrane that initiates the action potential. Ketamine is a noncompetitive antagonist at this receptor.[122,123] Afferent impulses are transmitted to cortical regions of the brain but are not interpreted, so responses to visual, auditory, and pain stimuli are inappropriate.[124] Although cortical association areas are depressed, the limbic system, which is thought to cause excitatory behavior, is simultaneously activated. Ketamine also has effects on opiate, monoamine, cholinergic, purinergic, and adenosine receptors.[125,126] It inhibits tumor necrosis factor-alpha (TNF-alpha) and interlukin-6 (IL-6) gene expression, which may account for the antiinflammatory and antihyperanalgesic effects.[127,128] The NMDA receptor is shown and described in Figure 9-7.

The analgesia produced by ketamine has a spinal cord component. By injecting bradykinin intraarterially as a noxious stimuli, Nagasaka et al.[129] were able to demonstrate that ketamine blocked the stimulated excitatory activity of wide-dynamic-range neurons in the dorsal horn, thereby preventing transmission of noxious stimuli to the brain.

Metabolism

Hepatic microsomal enzyme systems are responsible for the biotransformation of ketamine. The primary pathway for ketamine metabolism by the cytochrome P-450 system is demethylation to form the metabolite I, norketamine. Hydroxylation of norketamine occurs at one of two positions in the cyclohexone ring to form hydronorketamine metabolites I, II, and III. These metabolites form a glucuronide derivation via conjugation to produce a more water-soluble compound that is eliminated primarily via renal excretion. Thermal dehydration forms dehydroxynorketamine, a cyclohexene derivative (metabolite II).[67,130]

The pharmacologic activity of the metabolite norketamine is approximately 20% to 30% of the activity of ketamine. The activity of the other metabolites is unknown.[131]

Pharmacokinetics

The distribution kinetics of ketamine follows a two-compartment model. Ketamine is able to cross the blood-brain barrier quickly to achieve rapid pharmacologic effect.[132] The onset of a standard 2 to 2.5 mg/kg dose is slower than propofol or etomidate, and it can take 3 to 5 minutes to achieve clinical anesthesia. Reawakening usually occurs within 15 minutes; however, there is wide patient variability. A much longer duration can be seen with high or repeat doses. Ketamine is protein bound approximately 12%. Like other induction drugs, brain concentrations decrease rapidly as ketamine is redistributed from the central compartment to peripheral tissue compartments. Redistribution to low-blood-flow tissue compartments accounts for the termination of drug effect and return to consciousness. The slow elimination half-life of the drug is the result of hepatic metabolism and excretion. A large amount of ketamine remains in peripheral tissues as active drug and may be responsible for prolonged or cumulative effects.[133] The elimination half-life is 2 to 3 hours. Hepatic extraction of ketamine is high

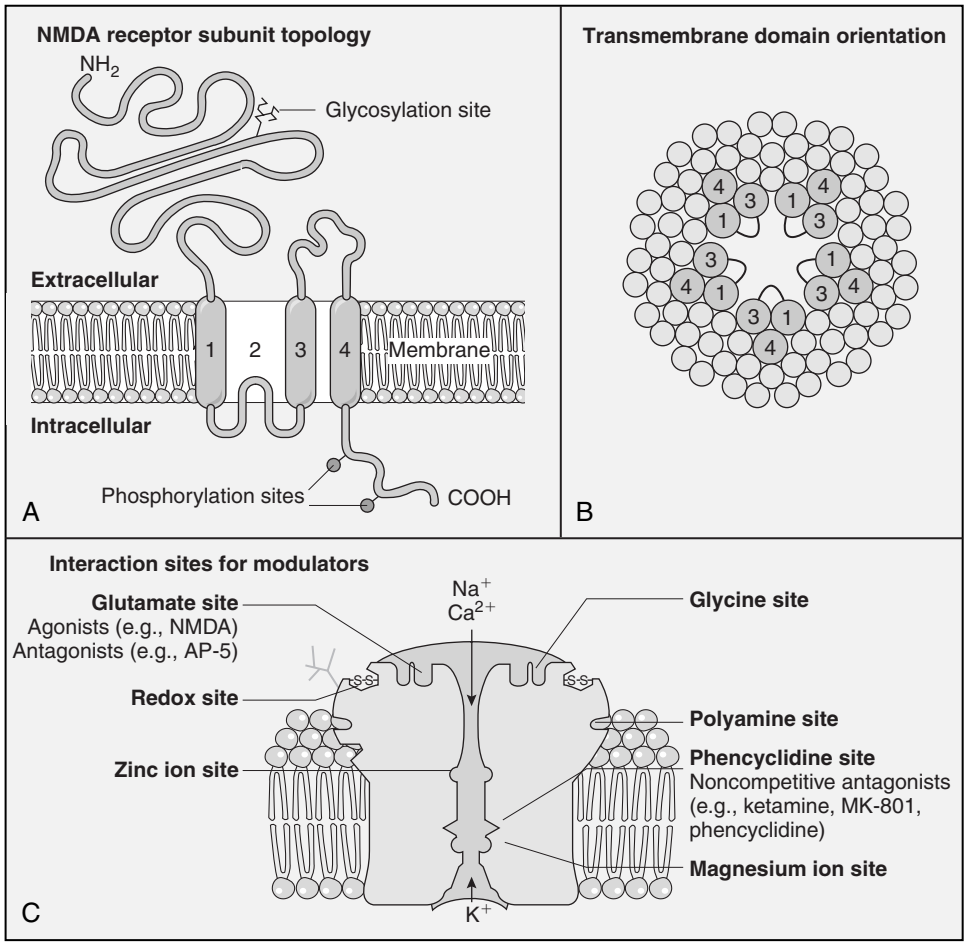


FIGURE **9-7** The *N*-methyl-D-aspartate amino acid (NMDA) receptor. **A,** The NMDA NRI receptor has three transmembrane segments and a fourth hydrophobic segment *(designated 2)* that loops into the membrane without traversing it. Mutation studies suggest that this loop is the putative channel-lining segment and that blockade by dizocilpine (MK-801), phencyclidine, and ketamine occurs through binding to a site that overlaps the Mg^{2+} site in the pore. The C-terminal domain undergoes phosphorylation, which regulates channel activity and mediates interactions with intracellular anchoring proteins. **B,** Transmembrane hydrophobic segments interact to form a central ion-conducting pore lined by the second hydrophobic segments. The stoichiometry of the heterooligomer is not known but may be four or five (as shown), by analogy with the homologous nicotinic cholinergic receptor. **C,** The NMDA receptor gates a cation channel that is permeable to Na^+, Ca^{2+}, and K^+ and is gated by Mg^{2+} in a voltage-dependent fashion. Agonists (glutamate, NMDA) and the coagonist glycine, required for full activation, bind to the extracellular domain. *(From Hemmings HC, Hopkins PM, (eds):* Foundations of Anesthesia Basic and Clinical Sciences*, 2nd ed. St Louis: Mosby; 2006.)*

because the mean total body clearance is approximately the same as the hepatic blood flow.[134] Ketamine elimination is therefore dependent on hepatic blood flow. Pharmacokinetic values remain consistent with analgesic and anesthetic doses of ketamine, which implies that distribution of ketamine is not dose dependent. Anesthetic levels are present with plasma levels of 640 to 1000 mcg/mL, and analgesic levels are present with plasma ketamine concentrations of 100 to 150 mcg/mL (see Table 9-2).[130]

Intramuscular and Oral Route. Given intramuscularly, ketamine reaches peak plasma concentrations within 22 minutes.[135] Dosages range from 4 to 6 mg/kg.[122] The onset of anesthetic effects is seen within 5 to 15 minutes depending on dose. Analgesic doses of ketamine (0.44 mg/kg) can be used for painful procedures without causing loss of consciousness and psychic disturbances.[67] After intramuscular administration, approximately 93% of the drug is bioavailable.[136] A consideration with the intramuscular route is the delayed onset of anesthesia. Ketamine can also be used orally in doses of 10 mg/kg. It is usually mixed in cherry syrup or soda to facilitate ingestion. Onset is 10 to 20 minutes. Box 9-5 gives complete dosing information.

Pharmacodynamics

Central Nervous System Effects. Ketamine produces a dissociative state of anesthesia, so called because the patient appears to be dissociated from the environment. The onset of anesthesia is slower than with propofol or etomidate and may make judgments regarding the onset of sleep and analgesia difficult. In the dissociative state, as originally described by Corssen,[67] the patient is cataleptic: the eyes remain open, the pupils are reactive to light, the corneal reflexes are intact, and horizontal nystagmus is present. Lacrimation and eye blinking continue, and salivary gland secretions are increased. Airway reflexes also remain intact (e.g.,

BOX **9-5**

Recommendation Doses of Ketamine

Premedication
- A benzodiazepine such as midazolam is administered if patient status allows. An antisialagogue may also be given to decrease secretions.

Induction of Anesthesia
- Ketamine 2-4 mg/kg IV, or 4-6 mg/kg IM (Oral dose is 10 mg/kg).

Maintenance of Anesthesia
- Ketamine 15-45 mcg/kg/min (1-3 mg/min) by continuous IV infusion or 0.5-1.0 mg/kg supplemental IV doses as needed.

Sedation and Analgesia
- Ketamine 0.2-0.8 mg/kg IV (over 2-3 min) followed by a continuous ketamine infusion (5-120 mcg/kg/min) 10-20 mg may produce preemptive analgesia.

IM, *Intramuscular;* IV, *intravenous*.

laryngeal reflex, pharyngeal reflex, coughing, sneezing, and swallowing). Skeletal muscle tone is increased, and occasional purposeless movements occur that are unrelated to painful stimuli.

Because the usual signs of anesthesia are not evident with ketamine, movement in response to painful stimuli is often required for judgments of adequate anesthesia. After administration of a single dose, full reorientation to person, place, and time takes place in 15 to 30 minutes, though as noted earlier, wide variability in durations have been noted.[137] Ketamine is a profound analgesic that has a preference for skin, bone, and joint pain. Analgesia occurs with subanesthetic doses, and it is widely used for sedation in combination with low doses of benzodiazepines, propofol, and other analgesics.[138,139]

Cerebral blood flow (CBF) and regional and possibly global $CMRO_2$ and ICP are increased by ketamine. The effect on glucose utilization varies by brain region.[140-142] The response of cerebral vessels to carbon dioxide is left intact. For these reasons ketamine has traditionally been thought to be contraindicated in patients with a head injury or an increased ICP. Recently, however, it has been noted that ketamine can be used safely in neurologically impaired patients under conditions of controlled ventilation, coadministration of a GABA receptor agonist such as midazolam or propofol, and avoidance of nitrous oxide.[141] Trauma patients with multiple injuries may still benefit from the favorable cardiovascular effects while avoiding untoward neurologic adverse actions.[139] Ketamine produces atypical anesthesia; thus EEG patterns also differ from standard anesthetics. On loss of consciousness and onset of analgesia, ketamine induces a transition from alpha to theta waves (slow waves with moderate to high amplitude) on the EEG. Alpha waves do not reappear until after consciousness returns and analgesia is lost.[124,143] Ketamine alone does not decrease the bispectral index (BIS) even when patients are unconscious. Several researchers have in fact noted an increase in BIS levels when ketamine is added to a propofol, fentanyl, or sevoflurane anesthetic.[144-146] Ketamine does not alter auditory evoked potentials (AEPs), mid-latency auditory evoked potential (MLAEP), or A-line autoregressive index monitors based on MLAEPs.[143] Ketamine appears advantageous for use in ECT.[147]

Ketamine anesthesia emergence is associated with psychic disturbances immediately on return of consciousness.[148] These emergence reactions are the result of visual, auditory, proprioceptive, and confusional illusions. Descriptions of this phenomenon include vivid illusions, sensations of drunkenness, delirium, restlessness, altered states of consciousness, extracorporeal sensations, and combativeness.[149] The onset occurs with the first verbal contact and usually resolves in a few hours with full return of orientation to person, place, and time. The incidence of emergence reactions is approximately 12%.[150] The incidence appears to be influenced by age, dose, gender, and psychological predisposition and concurrent medications. Recurrent dreams have been reported to occur weeks after a ketamine anesthetic.[151] The benzodiazepines diazepam, lorazepam, and midazolam were found to significantly decrease the incidence of these reactions. Subanesthetic doses of ketamine are being used for short-term treatment of acute and chronic pain. Low doses of ketamine are being used for sedation, postoperative pain relief, analgesia during regional or local anesthesia, and opioid-sparing effect.[150] Emergence reactions with low-dose ketamine are less frequent, but vivid dreaming may still occur. The use of positive mood elevating suggestion helps reduce the recall of unpleasant dreaming.[151,152] Ketamine has little effect on postoperative nausea and vomiting (PONV). Subanesthetic doses used for analgesia may reduce opioid requirements.[153]

Cardiovascular Effects. Ketamine, unlike other intravenous anesthetics, acts as a circulatory stimulant, producing increases in systemic blood pressure, heart rate, cardiac contractility and output, and central venous pressure.[148] Systemic vascular resistance responded differently among patients undergoing cardiac catheterization and angiography (±25%), possibly because of patient variability in autonomic tone and disease states. Other studies have failed to show significant effects in systemic vascular resistance but have found evidence of an increase in pulmonary vascular resistance (42%), pulmonary artery pressure (47%), and right ventricular stroke work. These values persisted throughout the 12-minute measurement period, although they were somewhat decreased (pulmonary vascular resistance 42% at 3 to 5 minutes and 25% at 12 minutes; mean pulmonary arterial pressure 47% at 3 to 5 minutes and 23% at 12 minutes). In patients with congenital heart disease and increased pulmonary pressure and resistance, ketamine administration did not adversely affect myocardial function (ejection fractions remained constant).[154]

Ketamine administration causes an increase in myocardial contractility, thereby affecting the myocardial oxygen balance. This increase in myocardial oxygen consumption has not been shown to cause inadequate myocardial perfusion, because a concomitant rise in coronary artery perfusion occurs.[154]

Ketamine-induced activation of the sympathetic nervous system that results in endogenous catecholamine release is believed to be one of the mechanisms for the cardiostimulatory properties experienced after administration of the drug. Injection of ketamine directly into the CNS via the carotid artery causes an immediate increase in blood pressure, heart rate, and cardiac output.[155] The positive inotropic effect of ketamine also results from an inhibition of neuronal and extraneuronal uptake of norepinephrine.[156] The in vitro negative inotropic effects of ketamine are the result of a decrease in the available calcium ions (Ca^{2+}) intracellularly, caused by an interference with Ca^{2+} delivery mechanisms (net transsarcolemmal Ca^{2+} influx).[157] When the positive inotropic effects of ketamine are blocked, the negative inotropic effects predominate and may result in decreased blood pressure and cardiac output. This phenomenon may be seen clinically in the critically ill patient who, as a result of protracted illness, has decreased available catecholamine stores and limited ability to compensate. With an intact sympathetic nervous system, the positive inotropic effects dominate and counteract the negative inotropic effects. By

decreasing sympathetic responses, some inhalation anesthetics are able to block the cardiovascular effects of ketamine to produce a decrease in systemic blood pressure and cardiac output.[158] The cardiovascular stimulation produced by ketamine may be deliberately decreased by the prior administration of benzodiazepines in patients in whom that response should be avoided.[148]

Ketamine has been used successfully in patients who are hemodynamically compromised because of shock, trauma, debilitation, or hypovolemia.

Changes in systemic blood pressure are dose related; systolic and diastolic blood pressures increase when larger doses of ketamine are administered (0.5 to 2.0 mg/kg). However, the heart rate response to different dosages reaches a plateau, with no significant change in rate occurring between doses of 0.5 and 2 mg/kg.

Ketamine has been used successfully for both pediatric and adult cardiac surgery patients with congenital and acquired disease processes.[154,159] The cardiac and respiratory actions of ketamine are summarized in Table 9-5.

Respiratory Effects. The effects of ketamine on the respiratory system are minor and of short duration. Ventilation is generally preserved, as is normal respirations. Transient apnea upon initial administration may occur with rapid administration of larger doses although it is rare. Arterial blood gases remain within normal limits, and the central response to carbon dioxide is maintained.[148]

Ketamine increases pulmonary compliance and decreases pulmonary resistance in patients with bronchospastic disease. It is the only active bronchodilating induction agent and the agent of choice in any patient with active asthma who requires surgery. Increased catecholamine levels stimulated by ketamine, along with bronchial smooth muscle relaxation and vagolytic actions, are thought to be the reason for the bronchodilating effects of the drug. Tracheal, bronchial, and salivary muscle gland secretions are increased with ketamine, which may require the use of an antisialagogue. Atropine is superior to glycopyrrolate for this application.[160] The muscle tone of the tongue and jaw is retained, and protective pharyngeal and laryngeal reflexes are left intact. Coughing, gagging, swallowing, and vomiting reflexes remain intact in response to airway stimulation, although some diminution may be present and silent pulmonary aspiration has occurred in some patients (see Table 9-5).

Intraocular Effects. Research into the effects of ketamine administration on intraocular pressure (IOP) has yielded varied results.[161-164] Measurement techniques and adjunctive anesthetics may play a role in the conflicting reports. Ketamine usually increases IOP, but the effect appears dose dependent.[165] A 6 mg/kg dose raises IOP but a 3 mg/kg dose does not. Ketamine causes nystagmus, increased muscle tone, and muscle spasms, which may not be appropriate for some ophthalmic procedures.[166] It blocks oculocardiac reflex-induced arrhythmias better than propofol during sevoflurane anesthesia for strabismus surgery.[167] The common clinical effects of ketamine are shown in Box 9-6.

Obstetric and Pediatric Use. Ketamine can be used in obstetrics for analgesia or anesthesia. It is a highly lipid soluble and readily crosses the placenta into fetal tissue. As an induction agent, ketamine in doses of 0.5 to 1 mg/kg produces rapid anesthesia without compromising uterine tone, uterine blood flow, or neonatal status at delivery. For analgesia, 0.25 mg/kg of ketamine provides pain-related relief, airway stability, and a sustained maternal blood pressure and uninhibited uterine contractions. Use of doses reserved for surgical procedures (2 to 2.5 mg/kg) results, however, in a depressed neonate on delivery.[168,169] Decreasing this dose to 0.2 to 1 mg/kg spared the newborn this CNS depression because of the rapid redistribution of the drug in the mother and less fetal transfer.

Ketamine is a very popular drug for neonates and children. Sedation, analgesia, amnesia, cardiac and respiratory stability, and a short duration offer advantages in many procedures in these patients.[170] Clinicians have noted it may be the agent of choice for children with a difficult airway or reactive airway diseases

BOX 9-6

Primary Clinical Characteristics and Effects of Ketamine

- Phencyclidine derivative
- Causes unconsciousness; amnesia referred to as *dissociative anesthesia*
- Increases cerebral metabolic rate, cerebral blood flow, and intracranial pressure
- Causes nystagmus; increased intraocular pressure
- Moderate analgesic
- Increases blood pressure and pulse
- Potent bronchodilator
- Maintains respirations and airway reflexes (NOTE: A period of initial apnea may occur, especially with high doses and rapid administration.)
- Increases salivation and respiratory secretions
- Increases muscle tone
- Associated with emergence delirium, nightmares, and hallucinations
- Requires caution in patients with hypertension, angina, congestive heart failure, increased intracranial pressure, increased intraocular pressure, psychiatric disease, and airway problems

BOX 9-7

Clinical Uses of Ketamine

Induction of Anesthesia in High-Risk Patients
- Shock or cardiovascular instability
- Hypovolemia
- Cardiomyopathy
- Trauma
- Bronchospasm

Obstetric Patients

Induction of General Anesthesia
- Severe hypovolemia/trauma
- Acute hemorrhage
- Acute bronchospasm

Low Dose for Analgesia
- To supplement regional anesthetic techniques
- As an additive to opioids in patient-controlled analgesia

Adjunct to Local and Regional Anesthetic Techniques
- For sedation and analgesia during intravenous sedation or when a regional block is used
- To supplement an inadequate block

Outpatient Surgery
- For brief diagnostic and therapeutic procedures
- To supplement local and regional block techniques

Use Outside the Operating Room
- In burn units (e.g., débridement, dressing changes)
- In emergency rooms for minor procedures
- In intensive care units (e.g., sedation, painful procedures)
- During radiology procedures

such as asthma. It can be used intramuscularly or orally for an uncooperative child requiring intravenous access.[171]

A controversy exists with regard to anesthetic neurotoxicity caused by ketamine. Neuroapoptosis has been noted in several animal models when ketamine is used in the developing brain.[172] How this relates to the use of ketamine and other anesthetics in newborns and children is unclear. This is an area of intense research interest.[173,174]

Clinical uses of ketamine are given in Box 9-7. Recommendations for using ketamine as a sedative, analgesic, or anesthetic during the postoperative period are listed in Box 9-5. Key points of ketamine pharmacology are given in Box 9-8.

BENZODIAZEPINES

Benzodiazepines are used in many clinical situations due to their desirable pharmacologic properties, including sedation, hypnosis, muscle relaxation, anxiolysis, anticonvulsant effects, and amnesia. They also have a low incidence of side effects. Benzodiazepines used clinically in the United States are listed in Table 9-7.

BOX 9-8

Key Points for Ketamine Anesthesia

- Site of action of ketamine appears to be the NMDA receptor, where it inhibits glutamate as a noncompetitive antagonist. Other actions are likely.
- Ketamine produces an anesthetic state referred to as *dissociative anesthesia.*
- Onset of effect is relatively slow compared to other induction drugs (2-5 min).
- Ketamine produces a rise in cerebral perfusion pressure.
- Ketamine is a bronchodilator, preserves airway reflexes, and increases secretions.
- Emergence phenomena—including vivid dreams, floating sensations, and delirium—can occur after ketamine administration. They are more common in adults than children and are reduced by benzodiazepine or other sedative administration.
- Ketamine is an indirect sympathomimetic, releasing catecholamines. This action accounts for the cardiac stimulation and bronchodilation

NMDA, N-*methyl*-D-*aspartate*.

Although similar compounds were first synthesized in 1933, the first benzodiazepine synthesized was chlordiazepoxide (Librium) in 1955. It was not introduced into clinical practice until 1960, when it was found to have antianxiety and hypnotic effects. Diazepam was synthesized in 1959, and its metabolite, oxazepam (Serax), was synthesized in 1961. Lorazepam (Ativan) was derived from oxazepam in 1971.[175] The last benzodiazepine to be developed was midazolam (in 1976, by Fryer and Walser), which was the first of the benzodiazepine group to be formulated with anesthesia as its target clinical use. The benzodiazepines available for clinical use have many similarities but there are differences in potencies, pharmacokinetics, and intensities of clinical properties. Midazolam is widely used in anesthesia and other areas as an anxiolytic, sedative, hypnotic, and amnestic drug. It is rarely used to induce anesthesia due to a prolonged effect at the high doses required. Diazepam and lorazepam, which are also available as intravenous preparations, are occasionally used as well. They are usually reserved for inpatients requiring prolonged sedation.

Chemical Structure and Pharmaceutics

The chemical structures of the benzodiazepines share some common features: (1) the benzodiazepine ring system; (2) the presence at positions 1 and 4 of two nitrogen atoms; (3) a phenyl group at position 5; and (4) an electronegative group at position 7 (see Figure 9-1).[175]

Midazolam has a unique chemical structure in comparison with the other benzodiazepines. The imidazole ring is responsible for its basic formulation, which permits the preparation of salts that are water soluble at a pH of 4.0. In a chemical reaction that depends on the environmental pH, the diazepine ring opens reversibly between positions 4 and 5. Midazolam is water soluble and does not require a lipoidal vehicle (such as propylene glycol) for parenteral use. Minimal if any side effects of venous irritation or phlebitis occur. Once in physiologic solution with a pH greater than 4.0, the diazepine ring closes, and midazolam becomes lipophilic, an effect that accounts for its rapid onset of action.[175,176]

Injectable midazolam is compounded with 0.8% sodium chloride and 0.01% disodium edetate and 1% benzyl alcohol as a preservative. A pH of 3 is adjusted with hydrochloric acid and, if necessary, sodium hydroxide. Each milliliter of preparation contains 1 or 5 mg of midazolam. An oral solution is also available for pediatric sedation.

In each milliliter of solution of diazepam, 0.4 mL of propylene glycol and 0.1 mL of ethyl alcohol are present as solvents, 0.015 mL

TABLE 9-7 Benzodiazepines Used Clinically in the United States

Generic Name	Trade Name	Half-Life (hr)	Clinical Application
alprazolam	Xanax	12-15	Anxiolysis
chlordiazepoxide	Librium	8-18	Treatment of alcohol withdrawal, etc.
clonazepam	Klonopin	18.7-39	Treatment of epilepsy
clorazepate	Tranxene	2.4	Treatment of epilepsy and alcohol withdrawal
diazepam	Valium	36-50	Sedation; induction and maintenance of anesthesia
estazolam	ProSom	14	Treatment of insomnia
flurazepam	Dalmane	2-3	Treatment of insomnia
lorazepam	Ativan	10-22	Anxiolysis and sedation
midazolam	Versed	1.7-2.6	Sedation; induction and maintenance of anesthesia
oxazepam	Serax	3-21	Anxiolysis
quazepam	Doral	25-41	Treatment of insomnia
temazepam	Restoril	10-21	Treatment of insomnia
triazolam	Halcion	2-3	Treatment of insomnia
flumazenil	Romazicon	0.7-1.3	Reversal of benzodiazepine agonists

of benzyl alcohol is present as a preservative, and sodium benzoate or benzoic acid in water is present as a buffer. Each milliliter contains 5 mg of diazepam and the pH is 6.2 to 6.9.[175]

Each milliliter of lorazepam solution contains 0.18 mL of polyethylene glycol and 2% benzyl alcohol, a preservative. Lorazepam is available in solutions of 2 or 4 mg/mL (see Table 9-1 for the preparations of the benzodiazepines).[176]

Mechanisms of Action

The clinical effects of benzodiazepines are a result of an agonist action at what are termed *benzodiazepine receptor binding sites* on the $GABA_A$ receptor throughout the CNS. Gamma amino butyric acid is the major inhibitory neurotransmitter in the CNS. The receptor complex is composed of a pentameric array of protein subunits that contain binding sites for GABA itself, benzodiazepines, barbiturates, ethanol, propofol, and many other sedatives. The $GABA_A$ receptor exerts its actions by modulating chloride channels. Many different families of the $GABA_A$ receptors exist and these subtypes vary in location, function, and pharmacologic effects. When these binding sites are occupied by an agonist, GABA receptor modulation increases the frequency of chloride channel opening, which results in postsynaptic membrane hyperpolarization, and neuronal transmission is inhibited.[177-179]

Three classes of ligands that bind to the benzodiazepine receptors have been identified: agonists, antagonists, and inverse agonists. Midazolam, diazepam, and lorazepam are receptor agonists that allosterically increase binding affinity for GABA, resulting in the opening of the chloride channels. Antagonists (e.g., flumazenil) form reversible bonds with the agonist receptor but produce no agonist activity. Inverse agonists cause CNS stimulation by interfering with GABA transmission, which is inhibitory.[176,180] Because the benzodiazepines work allosterically to enhance endogenous GABA binding and not directly, there is a physiologic ceiling to their effect. Their safety and low toxicity is attributed to this built-in limit on their effect.[181] Peripheral benzodiazepine binding sites, not associated with the $GABA_A$ receptor, exist in the mitochondrial membranes of many cells and may modulate cardiovascular and immune function (see Figure 9-5).[182]

Pharmacokinetics

The introduction of new generations of benzodiazepines since their initial release in the 1960s has largely focused on chemical alterations that improve the clinical pharmacokinetics. These changes have resulted in simplified metabolism with fewer active metabolites and thus more predictable time courses. The elimination pharmacokinetics of benzodiazepines can be examined in both two- and three-compartment models. Benzodiazepines have been classified according to their elimination half-lives. These classifications take into account the elimination half-lives of both the parent drug and the active metabolites. Diazepam is long acting ($T_{½}$ greater than 24 hours) lorazepam is intermediate ($T_{½}$ 6-24 hours) and midazolam is short acting ($T_{½}$ less than 6 hours).[183] The pharmacologic effects of the benzodiazepines, as with the other anesthesia induction drugs, are terminated primarily by redistribution of the drug out of the CNS.

Their pharmacokinetics are influenced by age, gender, obesity, race, and hepatic and renal status to varying degrees. The pharmacokinetics of the three intravenous benzodiazepines are similar with a few important differences. Midazolam exhibits a higher clearance rate and therefore is shorter acting. Lorazepam is less dependent on hepatic cytochrome enzymes for metabolism because it is undergoes phase 2 conjugation to a significant extent. Liver disease as well as hepatic enzyme induction or inhibition therefore does not influence lorazepam as much as other drugs. Diazepam has a very slow distribution half-life, which limits its usefulness as an acceptable induction agent. Diazepam is extremely lipid soluble, a characteristic that promotes extensive distribution to the tissues. The volume of distribution is large, a characteristic of all benzodiazepines. Also characteristic is extensive protein binding, which theoretically may be affected by disease states that decrease plasma protein levels. All three drugs are primarily bound to albumin. Diazepam is 99% protein bound, lorazepam 85% to 90%, and midazolam 95%. The total body clearance of diazepam is 0.24 to 0.53 mL/min/kg and is totally dependent on hepatic metabolism.

Diazepam exhibits a near-linear relationship between elimination half-life and patient age.[184] Pharmacokinetics in the elderly are altered as a result of slowed drug absorption; increased percentage of adipose tissue in body mass; decreased plasma proteins, hepatic blood flow, and metabolism; and decreased cardiac output and circulation time. A prolonged circulation time allows for a slower onset and a higher plasma drug level that remains in the CNS longer before it redistributes; this phenomenon exaggerates the effects of the drug.[185]

Hepatic microsomal enzymes are responsible for the metabolism of diazepam. Diazepam is demethylated to dimethyl diazepam (nordiazepam), which is an active metabolite that, although less potent, is responsible for prolonged drug effect as a result of its slower metabolism. Diazepam can also be hydroxylated to 3-hydroxydiazepam, which is then demethylated to oxazepam, which is also pharmacologically active and commercially marketed. The termination of action of diazepam is caused by redistribution and eventual metabolism. The terminal half-life is 20 to 50 hours, much longer than that of other benzodiazepines and induction agents.

Pharmacodynamics

Central Nervous System Effects. All three intravenous drugs produce the characteristic dose-dependent CNS depressant effects of the benzodiazepines, from anxiolysis to sedation, sleep and with high enough doses of anesthesia. They all produce anticonvulsant effects, amnesia, and muscle-relaxing properties and are useful for inhibiting alcohol withdrawal symptoms. They are not antiemetic; however, lorazepam is used for its sedative, amnestic, and anxiolytic effects in reducing anticipatory chemotherapy-induced nausea and vomiting.

At higher doses they reduce $CMRO_2$ and CBF. They increase the threshold to local anesthetic-induced seizure activity, and midazolam is frequently used as a premedicant in patients having regional anesthesia requiring large volumes of local anesthetics.

All benzodiazepines produce dose-related anterograde amnesia. They generally do not produce reliable retrograde amnesia. Intravenous administration of midazolam produces anterograde amnesia in low doses. Amnesia occurs within 2 to 5 minutes of administration and remains for 20 to 30 minutes.[186-189] Deficits are seen in both short- and long-term memory. These include interfering with episodic, semantic, and iconic memory function.

Benzodiazepines also possess anticonvulsant activity and are effective in the treatment of status epilepticus and sedative-hypnotic withdrawal syndromes. EEG changes include disappearance of the alpha rhythm and the onset of higher-frequency beta-rhythm activity.[190] Tolerance, dependence, and withdrawal

BOX **9-9**

Alpha$_2$ Receptors Subtype and Functions

Alpha-2A receptors (α_{2A})
- Presynaptic feedback
- Inhibition of norepinephrine release
- Sedation
- Hypnosis
- Analgesia
- Neuroprotection
- Hyperglycemia
- Diuresis
- Sympatholysis
- Hypotension
- Anticonvulsant
- Hypothermia
- Modulation of insulin secretion

Alpha-2B receptors (α_{2B})
- Presynaptic feedback
- Inhibition of norepinephrine release
- Vasoconstriction, antishivering
- Analgesia
- Analgesic effect of nitrous oxide
- Hypertension
- Placenta angiogenesis

Alpha-2C receptors (α_{2C})
- Presynaptic feedback
- Inhibition of norepinephrine release
- Learning and stress responses
- Feedback inhibition of adrenal epinephrine release
- Modulation of insulin secretion

symptoms occur and vary among the benzodiazepines. Midazolam produces synergistic CNS, cardiovascular, and respiratory effects with fentanyl (see Table 9-4).

Cardiovascular Effects. In commonly used clinical doses the benzodiazepines have minimal cardiovascular effects. A decrease in blood pressure is occasionally seen when midazolam is given with opioids in patients with heart disease or the elderly.

Respiratory Effects. Benzodiazepines produce dose-dependent respiratory depression. Midazolam is the most respiratory depressing. Some respiratory depression occurs with diazepam, as evidenced by a decrease in minute ventilation and slope of the carbon dioxide response curve.[191] Increased respiratory depression and apnea are possible when benzodiazepines are combined with other CNS depressants such as opioids.

Contraindications and Precautions

The most common adverse effects of the benzodiazepines are unexpected respiratory depression and oversedation. In the doses used currently, other adverse actions are rare. They should be avoided in patients with acute porphyrias.

Uses

Midazolam is the standard drug given for preoperative medication. Its rapid onset and short duration and half-life and lack of adverse effects make it ideal for use as a preoperative anxiolytic, sedative, and amnestic.[192]

Flumazenil

Flumazenil is the sole benzodiazepine antagonist available in the United States (see Figure 9-1). It is a competitive antagonist with a high affinity for the receptor site. It produces prompt and effective specific reversal of benzodiazepine agonist effects after anesthesia and overdose.[193,194] As with any drug antagonist, its antidotal efficacy depends on the amount of free benzodiazepines at the receptor sites. Its relatively short duration and half-life make the possibility of resedation clinically relevant, especially in overdose situations. A slow titration of 0.2-mg doses (2 mL) is given intravenously (up to 1 mg) until the desired level of consciousness is achieved. Doses rarely exceed 1 mg for the reversal of midazolam-induced sedation and 3 mg for suspected benzodiazepine overdose. Onset is 1 to 2 minutes and duration of action is 45 to 90 minutes depending on total flumazenil dose and the amount of agonist requiring reversal. Withdrawal reactions are possible in patients who are benzodiazepine dependent, and its use in these patients is contraindicated. Flumazenil does not reverse the actions of ethanol or barbiturates.[195] Side effects are rare, although mild anxiogenic effects have been reported.[196] Seizures have been reported in patients with suspected tricyclic and antidepressant overdose, and the use of flumazenil in these situations and in patients with a known history of seizures should be avoided.[197,198]

Dexmedetomidine

The sedative and analgesic effects of alpha-2 (α_2) receptor agonists were long recognized from the use of clonidine and the veterinary anesthetic xylazine. Dexmedetomidine was developed as a more selective α_2 agonist, which allows for greater sedation. There are three main chemical classes of α_2 receptor agonists: the phenylethylates such as methyldopa and guanabenz; the imidazolines such as clonidine, dexmedetomidine, mivazerol, and azepexole; and the oxaloazepines. The imidazolines are used in anesthesia. Stimulation of imidazoline receptors account for the hypotensive side effects. The primary effects of dexmedetomidine are sedation, analgesia, anxiolysis, reduced postoperative shivering and agitation, and cardiovascular sympatholytic actions.[199,200]

Mechanism of Action

Alpha-2 adrenoreceptors are involved in various physiologic functions, particularly in the cardiovascular and central nervous systems. There are three subtypes of α_2 receptors. The subtypes and their putative functions are noted in Box 9-9.[201,202] Dexmedetomidine is highly specific for α_2 versus α_1 receptors at a ratio of 1600:1. Alpha-2 presynaptic receptors function as autoreceptors in the negative feedback loop controlling neurotransmitter release. When α_2 receptors are stimulated by an agonist such as dexmedetomidine, it results in a decreased catecholamine release. The main site of action for the sedative actions of dexmedetomidine is the pontine noradrenergic nucleus the locus coeruleus. The α_2 receptors are G-protein–coupled receptors, which when activated, result in the inhibition of calcium channels, the activation of potassium channels, and the direct modulation of the exocytic release of proteins. This produces hyperpolarization of the cells and thus inhibition.[201,203]

Chemistry and Pharmaceutics

Precedex (dexmedetomidine hydrochloride injection) is a sterile, nonpyrogenic solution for intravenous infusion following

dilution. Dexmedetomidine hydrochloride is the S-enantiomer of medetomidine and is chemically described as (+)-4-(S)-[1-(2,3-dimethylphenyl)ethyl]-1H-imidazole monohydrochloride. Dexmedetomidine HCl is freely soluble in water and has a pK_a of 7.1. Its partition coefficient (n-octanol/water) at pH 7.4 is 2.89. Precedex is supplied as a clear, colorless, isotonic solution with a pH of 4.5 to 7.0. Each 1 mL of Precedex contains 118 mcg of dexmedetomidine HCl (equivalent to 100 mcg dexmedetomidine base) and 9 mg of sodium chloride in water. The solution is preservative free and contains no additives or chemical stabilizers. Prepare by adding 2 mL of dexmedetomidine (100 mcg/mL) to 48 mL of 0.9% sodium chloride injection for a total of 50 mL. The final concentration is 4 mcg/mL. The loading dose is 1 mcg/kg infused over 10 minutes followed by maintenance infusions of 0.2 to 0.7 mcg/kg/hr. It is approved for up to 24 hours use for sedation in critical care and for nonintubated patients requiring sedation for short-term surgical procedures. It is used for numerous off-label applications.

Pharmacokinetics

Dexmedetomidine exhibits a rapid distribution phase with a distribution half-life ($T_{½}$) of approximately 6 minutes; a terminal elimination half-life ($T_{½}$) of approximately 2 hours; and steady-state volume of distribution (Vss) of approximately 118 L. Clearance is estimated to be approximately 39 L/hr. The mean body weight associated with this clearance estimate was 72 kg. Dexmedetomidine exhibits linear kinetics in the dosage range of 0.2 to 0.7 mcg/kg/hr when administered by IV infusion for up to 24 hours. Target concentrations are usually in the range of 0.3 to 0.6 ng/mL. Protein binding to both albumin and α_1 acid glycoprotein is 94%.[204] Dexmedetomidine undergoes almost complete biotransformation with very little unchanged in urine and feces. Biotransformation involves both direct glucuronidation as well as cytochrome P450–mediated metabolism. There are no active metabolites. Similar kinetic data was noted in pediatric patients.[205,206] Onset of action with loading infusion is 10 to 20 minutes, and the duration of action after the infusion is stopped is 10 to 30 minutes.

Central Nervous System Effects. Dexmedetomidine produces a dose-dependent sedation that resembles natural sleep, unlike the classic GABA receptor agonists. Patients do not experience respiratory depression and are readily arousable.[207,208] An advantage of this type of sedation is that procedures requiring "wake up" tests can be more readily accomplished compared to usual anesthetic regimens.[209,210] Dexmedetomidine does not interfere with electrophysiologic monitoring allowing brain mapping during awake craniotomy and microelectrode recording during implantation of deep-brain stimulators.[211] Motor and somatosensory evoked potentials are maintained when added to a desflurane and remifentanil technique.[212] Decreases in the amplitude of motor evoked potentials may occur at high doses.[213] Bispectral index (BIS) values are decreased in a dose-dependent manner to a greater extent than with propofol.[214]

Dexmedetomidine does not change cerebral metabolism ($CMRO_2$). Cerebral blood flow (CBF) is decreased due to cerebral vasoconstriction. This suggests uncoupling between cerebral metabolism and flow due to decreases in central catecholamine turnover. Effects on intracranial pressure are not clinically significant.[215]

The central sympatholytic effects also result in an antishivering action, hypothermia, and a reduction in the neuroendocrine stress response to surgery.[199] A reduction in postoperative agitation and emergence delirium in children and adults is an increasingly used clinical action.[205] A neuroprotective effect has been proposed, but benefits in patients with head injuries remain to be clarified.[216] Reductions in the withdrawal symptoms from sedatives, opioids, and alcohol have been noted.[199] Analgesic- and anesthetic-sparing effects are well documented and are produced at both the brain and spinal cord level. Dexmedetomidine enhances the analgesic effects of nitrous oxide.[217]

Cardiovascular Effects. The main cardiovascular effects of dexmedetomidine are hypotension and bradycardia. This results from CNS alpha receptor stimulation and systemic vasodilation. Occasionally, transient hypertension is seen with rapid initial loading doses or administration of high maintenance doses due to vasoconstriction; however, dose-dependent hypotension is the norm. There is no direct effect on myocardial contractility. There is a reduction in myocardial oxygen demand, an antianginal effect.[199] Transient profound hypertension was noted when using glycopyrrolate to treat dexmedetomidine-induced bradycardia in children and caution is advised when coadministering these drugs.[205]

Respiratory Effects. A unique advantage of dexmedetomidine sedation is that respirations are maintained. Brain respiratory responsiveness to carbon dioxide is normal. Airway patency and reflexes are present or only slightly diminished. These properties allow for convenient use in out-of-operating room procedures and difficult airway situations. Dexmedetomidine completely blocked histamine-induced bronchoconstriction in dogs. It appears beneficial to decrease airway reactivity in patients with chronic obstructive pulmonary disease or asthma.[218] It improves tolerance, agitation, and weaning and lessens the time required for sedation in mechanically ventilated patients.[219,220]

Other Effects. Dexmedetomidine has a mild diuretic effect mediated via $alpha_2$ receptor stimulation. Additional beneficial actions include renal and gastroprotective and antiinflammatory effects. Dexmedetomidine is being widely used for many surgical and diagnostic procedures in both adults and children. Which clinical situations become established as the best places to use this unique drug is still evolving. Some key points for the clinical use of dexmedetomidine are noted in Box 9-10.

BOX 9-10

Key Points for Clinical Use of Dexmedetomidine

- Dexmedetomidine is an $alpha_2$ receptor agonist that results in central sympatholysis.
- Dexmedetomidine sedation allows for an arousable patient to ascertain neurologic status.
- Dexmedetomidine does not interfere with neurologic monitoring.
- Hypotension and bradycardia are the most frequent cardiovascular adverse effects.
- It is useful for procedural sedation.
- Respirations are maintained.
- Reduces postoperative agitation and emergence reactions.

SUMMARY

The availability of a variety of unique intravenous drugs that contain the necessary properties for use in induction has allowed the clinician to tailor the induction to fit the needs of the patient and surgeon. This characteristic has made it much easier to care for an increasingly diverse and complex patient population. Intravenous anesthetics can be chosen with consideration for the health status of the patient, the type of procedure to be performed, and the patient's susceptibility to possible adverse effects to produce the remarkably safe techniques and excellent outcomes achieved today.

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Local Anesthetics

◆ *John J. Nagelhout*

CHAPTER 10

Local anesthetics are drugs that reversibly block the conduction of electrical impulses along nerve fibers. Their ability to perform this function depends on various factors, including the nerve or nerves being blocked and the chemical structure and physicochemical properties of the local anesthetic. These drugs have always been used as a major component of clinical anesthesia and are increasingly being used to treat acute and chronic pain in new and innovative ways.

ANATOMY OF THE PERIPHERAL NERVE

To fully address the action of local anesthetics, a brief review of the anatomy and physiology of nerve fibers is appropriate. The axon, an extension of a centrally located neuron, is the functional unit of peripheral nerves. A cell membrane, or axolemma, and intracellular contents, or axoplasm, are the major components of the axon. Schwann cells, whose functions are support and insulation, surround each axon. In unmyelinated nerves, single Schwann cells cover several axons. Conversely, in larger nerves the Schwann cell sheath covers only one axon and has several concentric layers of *myelin*.

Between Schwann cells are periodic segments of nerve that do not contain myelin. These areas, known as *nodes of Ranvier*, are where conduction is propagated. Voltage-gated sodium channels (Na_v) are located in these nonmyelinated segments and are the primary site at which local anesthetics exert their action. Action potentials jump from node to node, and this phenomenon is known as *saltatory conduction*, which significantly facilitates conduction speed along the axon.[1,2] Myelinated nerves are larger, conduct impulses faster, and are more difficult to block with local anesthetics than are unmyelinated nerves[3,4] (Figure 10-1).

Peripheral nerves have structures containing bundles of axons called *fasciculi*. Three layers of connective tissue—the endoneurium, perineurium, and epineurium—also are components of the peripheral nerve.[4,5] The endoneurium, which is a delicate connective tissue composed of longitudinally arranged collagen, surrounds and embeds the axons in the fasciculi. The perineurium, which consists of layers of flattened, overlapping cells, binds a group of fascicles together. The epineurium, which surrounds the perineurium, is composed of areolar connective tissue that functionally holds the fascicles together to form the peripheral nerve.[5] These layers of connective tissue are important because they serve as barriers through which local anesthetics must diffuse if they are to exert their pharmacologic action (Figure 10-2).

NEURON ELECTROPHYSIOLOGY AND THE ACTION MECHANISM OF LOCAL ANESTHETICS

Electrophysiology

Measurement with an electrode placed in the axoplasm of a resting peripheral nerve demonstrates a negative membrane potential of −70 to −90 mV.[3,5] This voltage difference across the neuronal membrane at steady state is called the *resting membrane potential* (Figure 10-3). An ionic imbalance between the axoplasm and the extracellular fluid causes the electrical potential. Several physiologic mechanisms create the ionic gradient; the primary one is an active, energy-dependent process executed by a sodium-potassium pump (Na^+-K^+/ATPase) located in the axolemma.[6,7]

Although the membrane is relatively permeable to the outward diffusion of K^+, an intracellular-to-extracellular K^+ ratio of 150:5 mmol, or 30:1, exists. An important contributor to this concentration difference is the impermeability of the membrane to other cotransported ions such as Na^+.[7] In addition, the movement of K^+ out of the neuron leaves an excess of intracellular negatively charged organic ions. The negative charge results in an electrostatic counterforce that limits K^+ movement out of the neuron.

Two opposing forces influence K^+ movement into and out of the neuron. First, a concentration gradient pushes K^+ outward. Second, an electrostatic gradient, created by the impermeability of the membrane to cations, tends to keep the K^+ in the cell. The net effect of these counterforces is modest movement of K^+ out of the cell, and this movement creates an intracellular negative charge. The Nernst equation expresses the charge created by the K^+ concentration gradient[3]:

$$\text{Membrane potential} = -58 \log \frac{(K^+ 30 \text{ inside})}{(K^+ \text{ outside})}$$

Determination of the resting membrane potential is not as simple as the Nernst equation for K^+ indicates, because Na^+ and chloride (Cl^-) ions have a minor role in establishing the intracellular resting potential.[3]

When an electrical impulse is applied to a resting nerve, the membrane potential is reversed because of the intracellular movement of Na^+. This occurs because of the higher concentration of Na^+ outside the cell and the stimulation-induced increase in membrane permeability to this ion. The sudden influx of Na^+ that occurs in response to stimulation overrides the efflux of K^+ directed at maintaining the resting membrane potential. Once the process has reversed the membrane potential to 20 mV, an outward electrochemical gradient develops; this gradient resists the concentration-dependent, inward diffusion of Na^+.[5] This state of equilibrium causes the Na^+ channels to close. Shortly after Na^+ enters the cell, K^+ channels begin to open, and the ion rapidly diffuses out of the neuron, according to its concentration gradient. The active removal of intracellular Na^+ by the Na^+-K^+ pump and the passive diffusion of K^+ outward restore the resting membrane potential. During repolarization, three Na^+ ions leave the cell for each two K^+ ions that enter[8] (Figure 10-4).

The sequence of events that results in an action potential results from the passage of ions through pores, or "channels," located in the axolemma. These channels, which are composed of globular proteins, have transmural orientation to the phospholipid molecules that constitute the axolemma.[9] Although K^+ and

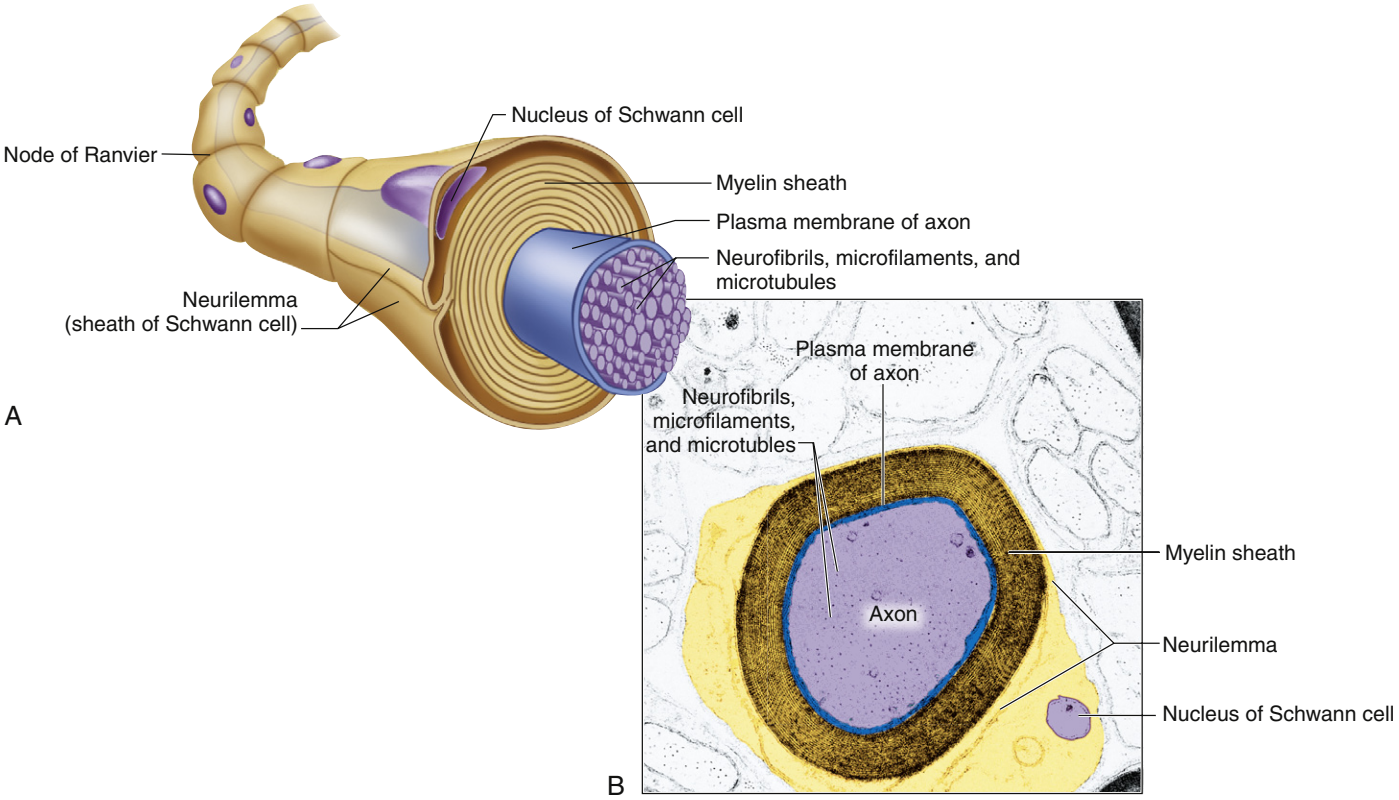

FIGURE **10-1** Myelinated axon. **A,** The diagram shows a cross section of an axon and its coverings formed by a Schwann cell: the myelin sheath and neurilemma. **B,** Transmission electron micrograph showing how the densely wrapped layers of the Schwann cell's plasma membrane form the fatty myelin sheath. (From Patton KT, Thibodeau GA. *Anatomy & Physiology*. 8th ed. St. Louis: Mosby; 2013:388.)

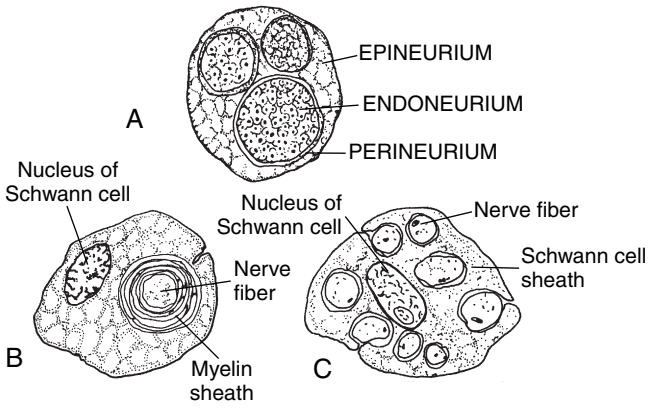

FIGURE **10-2** Transverse sections of a peripheral nerve **(A)** showing the outermost epineurium; the inner perineurium, which collects nerve axons in fascicles; and the endoneurium, which surrounds each myelinated fiber **(B),** and is encased in the multiple membranous wrappings of myelin formed by one Schwann cell, each of which stretches longitudinally over approximately 100 times the diameter of the axon. The narrow span of axon between these myelinated segments, the node of Ranvier, contains the ion channels that support action potentials. Nonmyelinated fibers **(C)** are enclosed in bundles of 5 to 10 axons by a chain of Schwann cells that tightly embrace each axon with but one layer of membrane. (From Miller RD. *Miller's Anesthesia*. Vol 1, 7th ed. Philadelphia: Churchill Livingstone; 2010:918.)

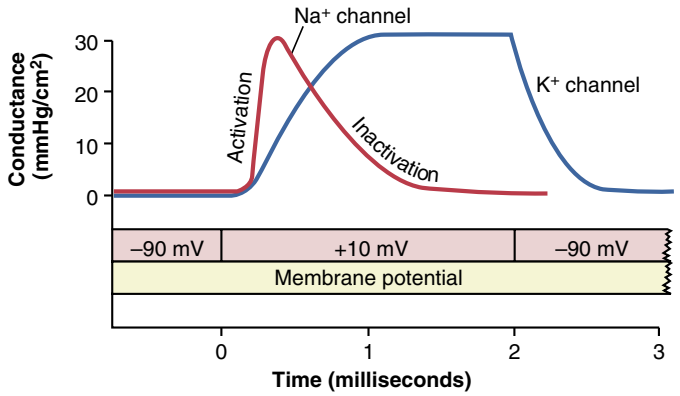

FIGURE **10-3** Typical changes in conductance of sodium and potassium ion channels when the membrane potential is suddenly increased from the normal resting value of −90 millivolts to a positive value of +10 millivolts for 2 milliseconds. This figure shows that the sodium channels open (activate) and then close (inactivate) before the end of the 2 milliseconds, whereas the potassium channels only open (activate), and the rate of opening is much slower than that of the sodium channels. (From Hall JE. *Guyton and Hall Textbook of Medical Physiology*. 12th ed. St. Louis: Saunders; 2011:62.)

calcium (Ca^{2+}) channels are important, the Na^+ channels are the most significant and best understood with respect to the initiation and propagation of the action potential.[3,10-14]

Mechanism of Action

As noted earlier, local anesthetics work by reversibly binding to the voltage-gated sodium channels (Na_v). Sodium channels have three functional states: resting (closed), open, and inactive. The resting state exists when the membrane is at its resting potential. When a nerve is stimulated, reversal of the membrane potential occurs until the threshold potential is reached. When this happens, a conformational change in the proteins that compose the channel occurs resulting in the open state. An inactive state, characterized by the return of the Na^+ channel to an impermeable state, follows the open state. This state, which prevents initiation of an action potential, lasts until the restoration of the resting membrane potential.[10] This three-state concept describes the changes in the Na_v that occur during depolarization and repolarization. Local anesthetics preferentially bind to both the open or inactivated states and not to the closed state. This is referred to as the guarded receptor or modulated receptor hypothesis of local anesthetic action. The open or inactive state may increase the affinity for binding, the physical access of the drug to the receptor, or both.[11,15] In addition, it has long been noted that local anesthetics work faster as the Na_v is repetitively depolarized. This is termed as *use-dependent* or *phasic block*. The more frequently the channel is depolarized, the more time it is available in the open and inactive states and thus available to local anesthetic blockade[16] (Figure 10-5).

Local anesthetics block the propagation of the action potential by binding reversibly to specific receptors within or adjacent to the internal opening of the Na_v channel.[17] Studies have indicated that these receptors, located on the intracellular side of the cell membrane, have a greater affinity for the charged or ionized form of the local anesthetics.[8,10,18] The uncharged or nonionized portion of the local anesthetic must first penetrate the cell membrane entering the axoplasm before they produce their effects. Figure 10-6 shows the penetration of local anesthetic into a nerve and subsequent access to the receptor. The sequence is as follows:

1. Almost all clinically useful local anesthetics (except benzocaine) are tertiary amines and when injected, will exist in both nonionized (lipid soluble) and ionized (water soluble) forms according to their particular pK_a (negative logarithm of the acid ionization constant) and the pH of the tissue or compartment they are in.
2. Local anesthetics must gain access to the interior of the neuron to reach their receptor. This occurs by the diffusion of the lipid soluble nonionized fraction across the cell membrane.
3. Once inside the neuron, a new equilibrium forms between ionized and nonionized fractions. The ionized fraction binds to the receptor on the inside of the Na_v.

Benzocaine is a secondary amine and thus is permanently nonionized or neutral. It penetrates the lipid bilayer and can directly inhibit the Na_v without entering the axoplasm first.[12]

Local anesthetics have additional effects on G-protein–coupled receptors affecting intracellular calcium signaling pathways. The inflammatory modulating action of local anesthetics may result from interruptions in these pathways. The antiinflammatory response to local anesthetics also occurs due to suppression of polymorphonuclear leukocyte priming, which prevents overactive inflammatory responses without impairing host defenses or suppressing normal inflammation.[16,19]

It must be noted that many questions remain as to the mechanism of the clinical effects of local anesthetics in different

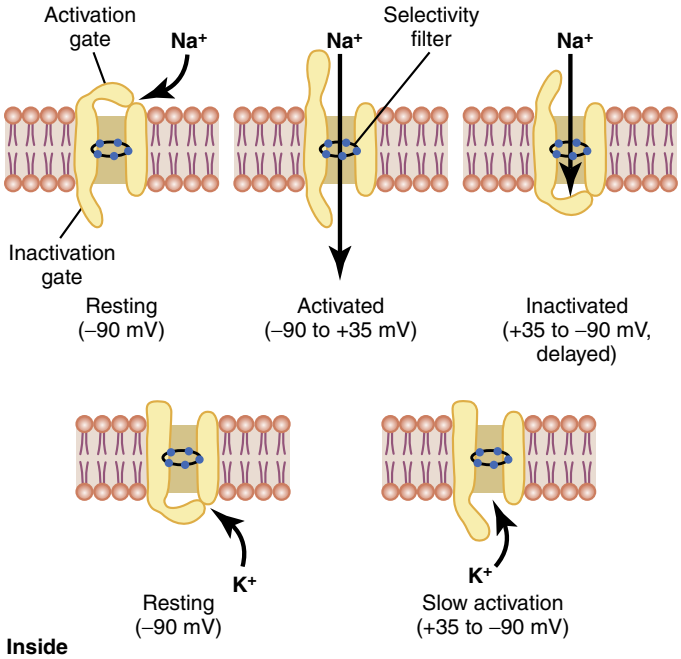

FIGURE 10-4 Characteristics of the voltage-gated sodium (*top*) and potassium (*bottom*) channels, showing successive activation and inactivation of the sodium channels and delayed activation of the potassium channels when the membrane potential is changed from the normal resting negative value to a positive value. (From Hall JE. *Guyton and Hall Textbook of Medical Physiology*. 12th ed. St. Louis: Saunders; 2011:61.)

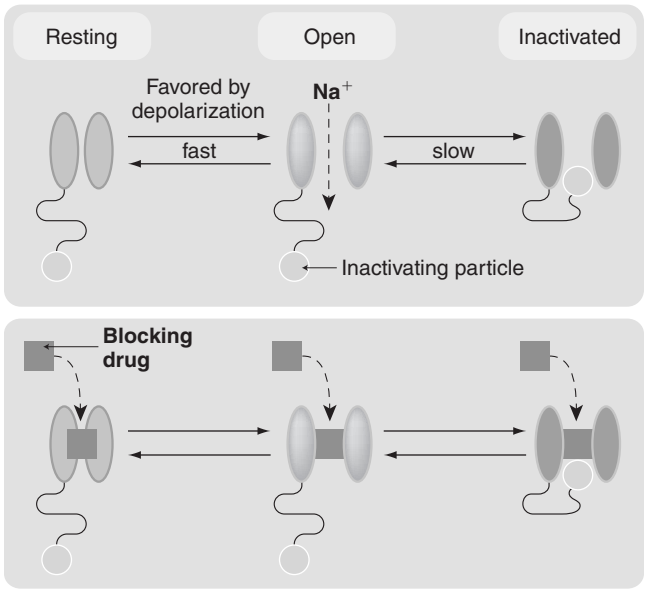

FIGURE 10-5 Resting, activated, and inactivated states of voltage-gated channels, exemplified by the sodium channel. Membrane depolarization causes a rapid transition from the resting (closed) state to the open state. The inactivating particle (part of the intracellular domain of the channel protein) is then able to block the channel. Blocking drugs (e.g., local anesthetics and antiepileptic drugs) often show preference for one of the three channel states, and thus affect the kinetic behavior of the channels, with implications for their clinical application.

types of nerve blocks. Different receptors may be involved in their action in peripheral nerves as opposed to spinal or epidural effects.[20]

Nerve Fiber Sensitivity and Differential Block

It has been observed that nerves functionally have different sensitivity or rates of effect when exposed to local anesthetics. For example, in most major nerve blocks, loss of autonomic function occurs first, followed in sequence by perception of superficial pain, touch, and temperature, motor function, and proprioception.[21] This phenomenon is termed *differential block*. Seen clinically, an excellent example of differential block occurs with the use of bupivacaine. When administered epidurally for labor pain, this local anesthetic spares motor function while providing adequate analgesia.[22,23]

Essential to the understanding of differential block is the concept that the diameter and myelination of nerve fibers influence the sensitivity to local anesthetics. For simplicity, nerve fibers are separated into three groups—A, B, and C—on the basis of diameter.[24,25]

The A fibers are further divided into four subgroups known as *alpha*, *beta*, *gamma*, and *delta fibers*. The alpha fibers are the largest in diameter (12 to 20 μm) and the most heavily myelinated; they have the fastest conduction velocity of all the fibers, including B and C fibers. Alpha fibers are responsible for motor functions and proprioception. The A beta (5-12 μm) and A gamma fibers (3-6 μm) have conduction velocities second only to A alpha fibers. The A beta fibers provide motor function, touch, and pressure sensation; the A gamma fibers innervate muscle spindles and are responsible for reflexes. The A delta fibers provide pain and temperature sensation. These fibers have a smaller diameter (1-5 μm) and slower conduction velocity than other A fibers. The beta, gamma, and delta fibers are all myelinated to a similar extent.[26]

B fibers have a similar diameter (less than 3 μm) to A delta fibers; however, they exhibit slower conduction velocity and less myelination than the A fibers. These fibers constitute the preganglionic autonomic nerves. The C fibers, which conduct pain and temperature impulses, are the smallest of all fibers (0.3-1.3 μm) and have the slowest speed of conduction. These are the only fibers that are unmyelinated.[8] Nerve fiber characteristics and local anesthetic sensitivity are summarized in Table 10-1.

It was first believed that nerve fiber diameter was the sole determinant of differential blockade.[27] This assumption came from the results of isolated in vitro studies performed only on myelinated nerves. Subsequent isolated studies on the small, unmyelinated C fibers revealed that they were more resistant to blockade than the larger A delta or B fibers.[8]

This apparent inconsistency can possibly be explained by the concept of conduction safety. This concept refers to the voltage change needed for the propagation of the action potential along the nerve. This voltage change is significantly greater than the action potential threshold and provides a safety factor for impulse conduction. Gissen et al.[28] defined this safety factor as the "ratio between the magnitude of the action potential and the magnitude of the critical membrane potential." Research has indicated that the margin of safety for transmission is greater in small, slow fibers than in large, fast fibers.

Lastly, differential block may be influenced by the rate of diffusion of local anesthetic molecules across multilayered lipoprotein membranes of the myelin sheath. For example, the clinical resistance to blockade observed in A fibers may be the result of a slower onset resulting from a greater diffusion barrier. As discussed in more detail later, diffusion can be influenced by such factors as the pK_a and the concentration of the local anesthetic, as well as the pH of the surrounding tissue and nerve fiber.[28]

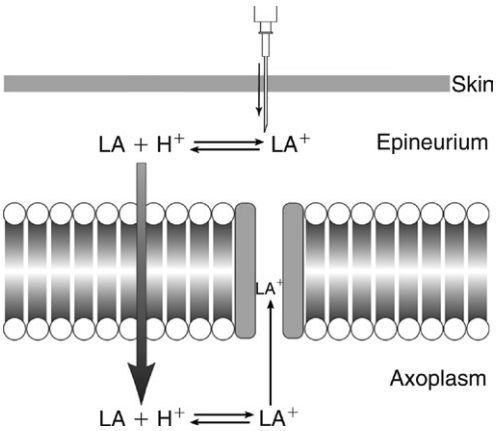

FIGURE **10-6** Schematic conceptualization of local anesthetic action. Equilibrium forms outside the nerve between the ionized and nonionized portions. The nonionized portion *(LA)*, which is lipid soluble, enters the nerve. Once inside the axoplasm, the drug re-equilibrates, and the ionized fraction *(LA^+)* attaches to the local anesthetic receptor on the inside of the sodium channel. *LA*, Nonionized form of the local anesthetic; *LA^+*, ionized form.

TABLE **10-1** Nerve Fiber Characteristics and Sensitivity to Local Anesthetics

Fiber Type	Function	Diameter (μm)	Myelination	Anesthetic Block Onset
Type A				
Alpha (A_α)	Proprioception, motor	12-20	Heavy	Last
Beta (A_β)	Touch, pressure	5-12	Heavy	Intermediate
Gamma (A_γ)	Muscle tone	3-6	Heavy	Intermediate
Delta (A_δ)	Pain, cold temperature, touch	1-5	Heavy	Intermediate
Type B				
	Preganglionic autonomic vasomotor	<3	Light	Early
Type C				
Sympathetic	Postganglionic vasomotor	0.3-1.3	None	Early
Dorsal root	Pain, warm and cold temperature, touch	0.4-1.2	None	Early

As the preceding discussion indicates, the concept of differential block is more complex than originally proposed. Future research will probably indicate that an isolated mechanism does not explain this phenomenon, but rather several factors interact to produce the effect.[22]

CHEMICAL STRUCTURE OF LOCAL ANESTHETICS

The local anesthetics used clinically for neural blockade are aminoesters or aminoamides and are similar in chemical structure. In general, these drugs have three characteristic segments: (1) an intermediate ester or amide carbon group separates (2) an unsaturated (aromatic) ring system from (3) an amine end (Figure 10-7). The aromatic ring provides lipophilic characteristics, whereas the tertiary/quaternary amine gives hydrophilicity to the molecule. The amine portion is able to become ionized in physiologic pH and thus hydrophilic.

Chemically, the major difference among local anesthetics is in their ester or an amide linkage that binds the aromatic ring to the amine group. This linkage is responsible for the classification of these drugs as either esters or amides. The type of linkage is important clinically because it has implications for metabolism, duration, and allergic potential (Figure 10-8). Box 10-1 lists the local anesthetics according to chemical class. The chemical structures are important in determining the pharmacologic effects of these drugs. Minor chemical alterations to drugs within these two "bond-related" groups can result in significant changes in drug potency, speed of onset, and duration of action and potential for producing differential block (Figure 10-9).[5,16,29] These changes are discussed in detail as the specific pharmacologic factors associated with local anesthetics are noted. Table 10-2 summarizes the clinical differences between the ester and amide local anesthetics.

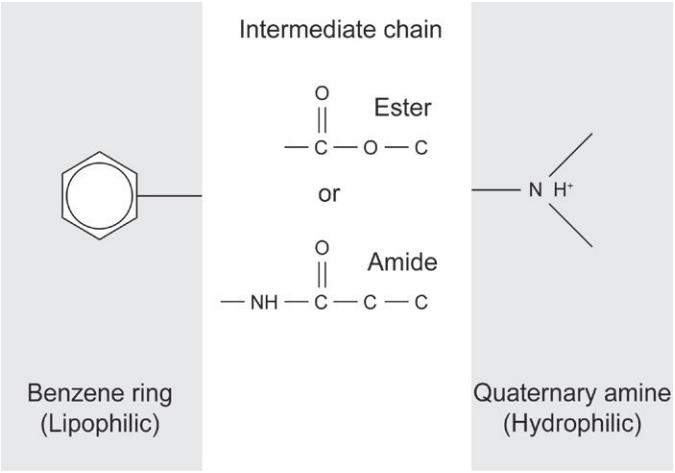

FIGURE **10-7** Core structure for local anesthetics, which includes a benzene ring and a quaternary amine separated by an intermediate carbon group. The bond between the benzene ring and the carbon group determines whether the drug is an amide or an ester.

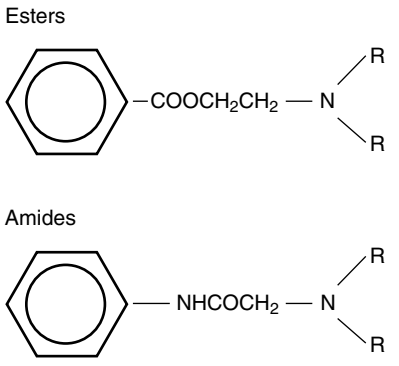

FIGURE **10-8** Representative chemical formula for ester and amide local anesthetic drugs.

PHARMACODYNAMICS AND PHARMACOKINETIC CONCEPTS

An important difference to note when describing the pharmacokinetics of local anesthetics is intuitive yet bears discussion. Unlike most medications, these agents are meant to remain localized in the area of injection or application. The higher the concentration (number of molecules) of drug injected that remain in the area of the nerve or nerves to be blocked, the faster the onset of action. If multiple nerves are being blocked, a greater intensity may also be evident. Therefore, systemic absorption away from the deposition site results in the offset and termination of drug effect, rather than the onset as with most other drugs. Factors that affect absorption, such as the vascularity and blood flow of the injection area, lipid and protein binding, and addition of vasoconstrictors, greatly influence duration of action. The same local anesthetic dose and concentration injected in different areas of the body, with or without added epinephrine, can result in vastly different durations of action. Absorption also influences toxicity. The slower a local anesthetic is systemically absorbed, the less likely that high blood levels and therefore central nervous system (CNS) or cardiac toxicity will result. Drug metabolism and elimination more readily "keep up" with absorption, ensuring that toxic blood levels are avoided. A conceptual kinetic depiction of the fate of an injected local anesthetic is given in Figure 10-10.

Potency

There is a strong relationship between the lipid solubility of local anesthetics and their potency.[28,29] This finding is understandable, considering that the axolemma and myelin sheath are composed primarily of lipids[29,30]; therefore, lipid-soluble drugs pass more readily through the nerve membrane. Larger, more lipid-soluble local anesthetics are relatively water insoluble, highly protein bound, and less readily washed out from nerves and surrounding tissues. They bind to Na_v channels with a higher affinity than agents with lower lipid solubility. Increased lipid solubility correlates with increased protein binding, increased potency, longer duration of action, and a higher tendency for severe cardiac toxicity.[12,29] It follows that fewer molecules or lower concentrations of these drugs are required for the production of blockade than if non–lipid-soluble anesthetics are used.[31] Changes in either the aromatic or amine moieties of the local anesthetic molecule can affect the lipid-water partition coefficient. In the amide series, for example, the addition of a butyl group to the amine end of mepivacaine leads to the formation of bupivacaine. Bupivacaine is 26-fold as lipid soluble and fourfold as potent as mepivacaine. In

BOX 10-1

Ester and Amide Local Anesthetics

Esters	Amides
Procaine	Lidocaine
Chloroprocaine	Mepivacaine
Tetracaine	Prilocaine
Cocaine	Bupivacaine
Benzocaine	Ropivacaine
	Articaine

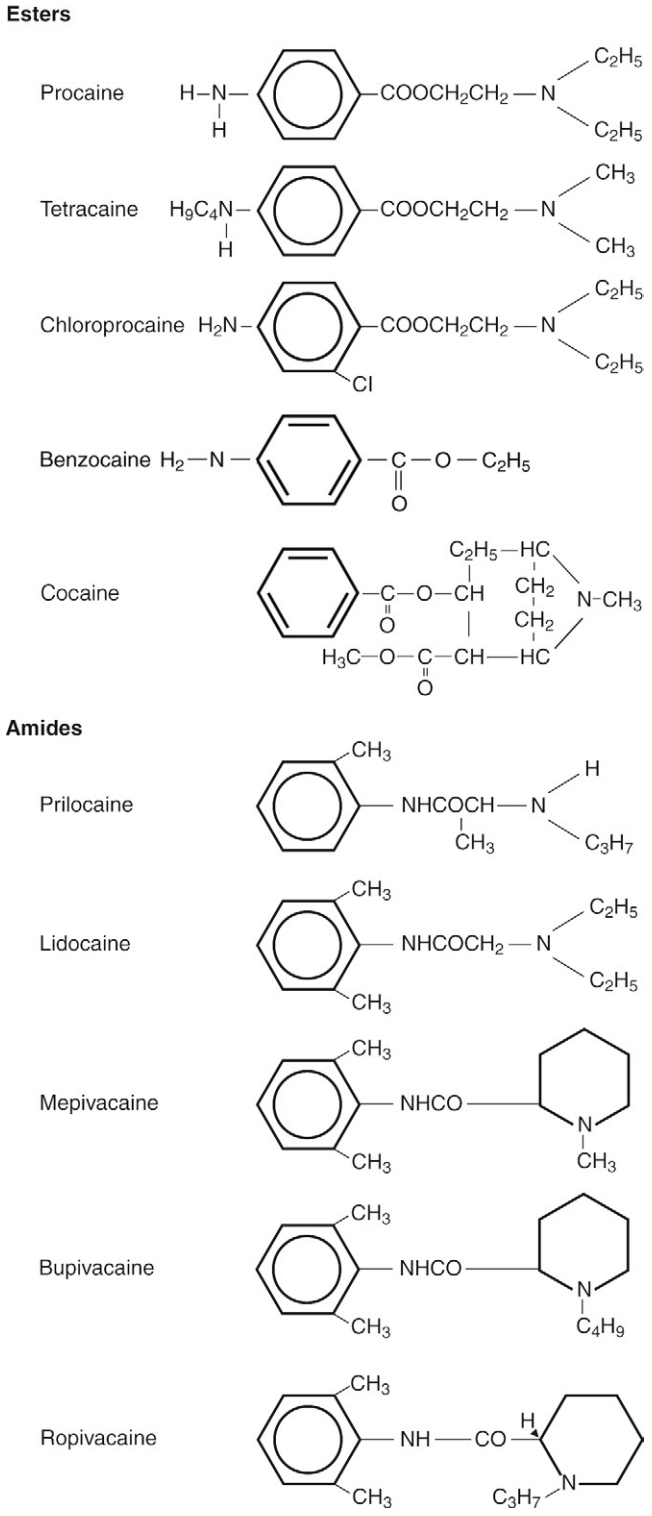

FIGURE **10-9** Chemical structure of the most commonly used local anesthetics. Note the chemical substitutions on the benzene ring and the amine end of the molecules.

TABLE 10-2 Clinical Differences Between the Ester and Amide Type Local Anesthetics

Esters	Amides
Ester metabolism is catalyzed by plasma and tissue cholinesterase via hydrolysis; occurs throughout the body and is rapid	Amides are metabolized in the liver by CYP1A2 and CYP3A4 and thus a significant blood level may develop with rapid absorption
Although local anesthetic allergy is uncommon, esters have a higher allergy potential, and if patients exhibit an allergy to any ester drug, all other esters should be avoided	Allergy to amides is extremely rare; there is no cross allergy among the amide class or between the ester and amide agents
Ester drugs tend to be shorter acting due to ready metabolism; tetracaine is the longest acting ester	Amides are longer acting because they are more lipophilic and protein bound and require transport to the liver for metabolism

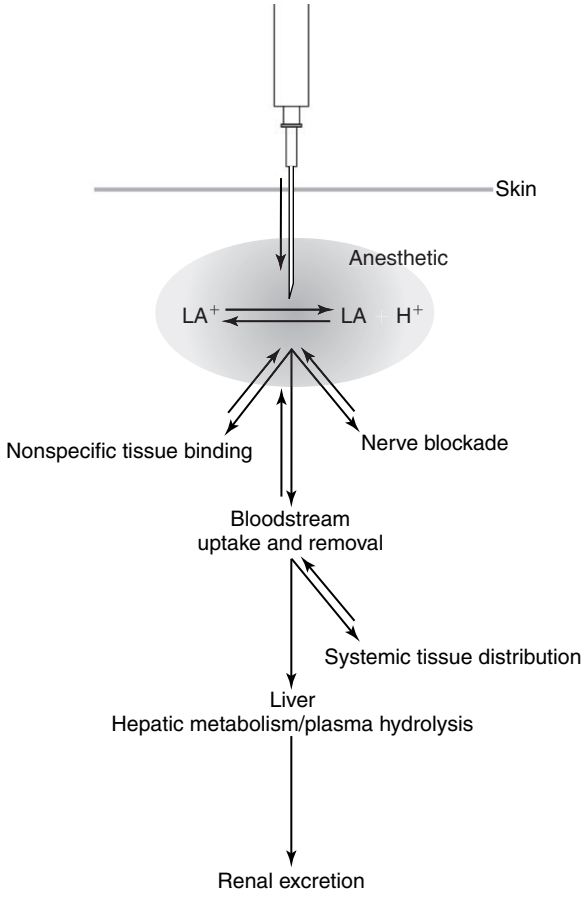

FIGURE **10-10** Representation of the fate of a local anesthetic injected into tissue.

the case of the esters, the addition of a butyl group to the aromatic end of procaine produces tetracaine, which is considerably more lipid soluble and potent than procaine.[16]

Factors other than lipid solubility can affect potency. For example, the potency of local anesthetics as demonstrated in isolated in vitro studies is not always the same as that observed in vivo. The discrepancy between in vitro and in vivo findings may be the result of many factors, including the vascular and tissue distribution properties of the drug.[32] For example, the results of in vitro studies show that lidocaine is twice as potent as prilocaine; however, clinical use indicates that they have similar potencies. This may be explained by the fact that lidocaine has greater vasodilating properties than prilocaine and therefore may be absorbed away more rapidly, leaving less drug available for interaction with the neuron.[33-35]

TABLE 10-3 Classification of Local Anesthetics Based on Onset, Duration of Action, and Potency

Characteristics	Drug (generic name)	Common Brand Name	Onset	Duration of Action (min)
Low potency, short duration of action	procaine	Novocaine	Slow	60-90
	chloroprocaine	Nesacaine	Fast	30-60
Intermediate potency, duration	mepivacaine	Carbocaine	Fast	120-240
	lidocaine	Xylocaine	Fast	90-120
High potency, long duration	tetracaine	Pontocaine	Slow	180-600
	bupivacaine	Marcaine, Sensorcaine	Slow	180-600
	ropivacaine	Naropin	Slow	180-600

Duration of Action

The duration of action of local anesthetics demonstrates a relationship to protein binding and lipid solubility.[29,36] In theory, drugs that have a high affinity for protein and lipids attach more firmly to these substances in the vicinity of the Na_v channel receptor. This means that the drug remains in the channel and surrounding areas for a longer time, producing prolonged conduction blockade.[29]

It appears therefore that there is a correlation between the degree of protein binding and duration of the local anesthetic. The addition of larger chemical radicals to the amide or aromatic end of the drugs results in greater protein binding. The duration is directly proportional to plasma protein binding, presumably because the local anesthetic receptor on the neural membrane is also composed of protein.[3,5,37] It has been posited that local anesthetics that have increased protein-binding properties (e.g., ropivacaine 94%, bupivacaine 97%) produce longer-duration anesthesia as a consequence of more efficient binding of the anesthetic to the Na_v channel.[38] For example, bupivacaine is more than 90% bound to plasma protein; however, its homologue, mepivacaine, is only 65% bound.[36] The duration of action of bupivacaine is significantly longer than for mepivacaine. Local anesthetics are weak bases and bind mainly to α_1-acid glycoprotein (AAG). Secondary binding to albumin also occurs.

As in the case of potency, the effect local anesthetics have on the vasculature at the injection site influences the duration of action. This is discussed in detail in the section on vasomotor action and absorption.

Onset of Action

As stated previously, local anesthetics must diffuse through the axolemma before they can interact with receptors. How readily they diffuse through the nerve membrane depends on their chemical structure, lipid solubility, and state of ionization. Of these, ionization is the most important, because the charged or ionized form of a drug does not penetrate membranes well.[30,32,37] In other words, the more ionized a local anesthetic, the slower it will penetrate a nerve.

Local anesthetics are bases. The pK_a of a drug is the pH at which 50% of the drug is in the charged, or ionized, and water soluble form while the remaining half is uncharged, or nonionized, and lipid soluble. A basic drug becomes predominantly ionized if it is placed in an environment with a pH that is significantly less than its pK_a. Therefore drugs that have a greater pK_a are ionized to a greater extent at body pH than those with a lower pK_a. For example, if lidocaine (pK_a 7.74) is placed in plasma (pH 7.4), 65% of the drug is ionized and 35% remains un-ionized. Similarly, if tetracaine (pK_a 8.6) is placed in plasma, 95% of the drug becomes ionized and 5% remains un-ionized.[29]

Because their ionization is less, local anesthetics with lower pK_a (7.6 to 7.8), such as lidocaine, mepivacaine, and prilocaine tend to have a more rapid onset of action than drugs with a greater pK_a (8.1 to 8.6), such as bupivacaine, tetracaine, and procaine. Chloroprocaine is one exception; it has a high pK_a but retains a rapid onset, probably because of the clinical use of high concentrations of the drug, which attenuates the ionization effect. In general, the closer the pK_a is to pH 7.4, the more rapid the onset. Some researchers downplay the role of pK_a on onset.[29]

The classification presented in Table 10-3 assists in the selection of an appropriate drug with respect to pharmacokinetic properties.[39]

Vasomotor Action and Absorption

All local anesthetics except cocaine, ropivacaine, and lidocaine produce relaxation of vascular smooth muscle.[33,40] The resultant vasodilation increases blood flow to the tissue in which the drug is deposited. This results in an increase in the drug's absorption, which limits its duration of action and increases the probability of toxic effects. It is interesting to note that ropivacaine and lidocaine are the only parenterally administered local anesthetics with mild vasoconstrictive properties.[40] Cocaine also has vasoconstrictive properties because of its ability to block reuptake of norepinephrine. It is used only topically.

All local anesthetics are not affected equally when epinephrine is added to the solution. There is a definite benefit in extending the duration of analgesic effects with both short- and intermediate-acting agents. The prolongation of the duration with long-acting drugs is less well defined.[40]

The speed of absorption and entry of the local anesthetic into the systemic circulation obviously has significant implications for toxicity. Absorption of drugs generally occurs in the following order of rapidity: interpleural blocks > intercostal > caudal > epidural > brachial plexus > sciatic-femoral and subcutaneous blocks.[16] Thus blood levels measured after an interpleural block will be higher with a greater potential for toxicity than with a subcutaneous block.

The total dose of local anesthetic, rather than the volume or concentration, linearly determines the peak plasma concentration.[41] For example, 400 mg of lidocaine yields the same peak plasma concentration regardless of whether 40 mL of a 1% or 80 mL of a 0.5% is injected.

Local anesthetic additives include α_2-adrenergic agonists, opioids, sodium bicarbonate, ketorolac, and hyaluronidase. These are variously added to increase the safety, quality, intensity, duration, and rate of onset of anesthesia, as well as reduce blood loss. $Alpha_2$-adrenergic agonists such as clonidine and dexmedetomidine have local anesthetic properties and can alter the nerve block characteristics.[42,43] The addition of 100 mcg of clonidine to a local

anesthetic solution prolongs the duration of the long-acting agents approximately 100 additional minutes with minimal side effects. The effect is produced by inhibition of the hyperpolarization-activated cation current (I_h current). This current normally restores nerves from the hyperpolarized state to resting potential. The effect is more pronounced in C-fibers (sensory) than Aδ (motor). That makes the effects mostly sensory specific. Cost has limited the routine use of clonidine.[40]

The addition of a vasoconstrictor (e.g., epinephrine) to local anesthetics can reduce the rate of vascular absorption, allowing more of the drug to stay in the local area where it was injected. The availability of the drug for neuronal uptake is increased, resulting in a longer and more profound block. Of importance, the slower rate of absorption also attenuates the peak plasma concentration of the drug, thereby reducing systemic toxicity. The magnitude of this effect depends on the drug, dose, and concentration of both the local anesthetic and the vasoconstrictor, as well as the site of injection.[7] For example, addition of epinephrine to mepivacaine prolongs the time to maximum arterial plasma drug concentration in all situations; however, adding epinephrine to a 2% solution used for an intercostal block has the greatest effect.[44]

Epinephrine does not prolong the duration of blockade to the same extent with all local anesthetics. For example, it prolongs the duration for local infiltration, peripheral nerve block, and epidural anesthesia with procaine, mepivacaine, and lidocaine.[30,45-48] Research indicates that adding epinephrine to lidocaine solutions increases the intensity and duration of block.[48] The early increase in intensity is not matched with an increase in intraneural lidocaine content at these early times, although the prolonged duration of block by epinephrine appears to correspond to an enlarged lidocaine content in a nerve at later times, as if a very slowly emptying "effector compartment" received a larger share of the dose. The increase in early analgesia without increased lidocaine content may be explained by a pharmacodynamic action of epinephrine that transiently enhances potency of lidocaine, but also by a pharmacokinetic effect that alters the distribution of the same net content of lidocaine within the nerve. In the case of prilocaine and bupivacaine, infiltration and peripheral nerve blocks are prolonged with epinephrine, whereas no significant effect occurs with epidural anesthesia.[49] The rationale for this discrepancy might be that epidural fat significantly absorbs ropivacaine and bupivacaine because of their high lipid solubility. These drugs are released slowly from the fat deposit, which could prolong the block.[47,49-51] This process overrides the effects of epinephrine on duration of action. In addition, the drug concentration can contribute to the differential effect seen with epinephrine. For example, epinephrine can prolong epidural blocks with 0.125% or 0.25% bupivacaine when used in patients in labor.[50,51] Conversely, epinephrine has less effect with the epidural administration of 0.5% or 0.75% bupivacaine.[52]

The addition of epinephrine does not attenuate the peak plasma level of all local anesthetics; for example, epinephrine significantly reduces the peak plasma concentration of lidocaine and mepivacaine, regardless of the site of administration. On the other hand, epinephrine does not significantly affect the peak plasma level of prilocaine or bupivacaine after epidural anesthesia. The lack of effect seen with prilocaine may be explained by its slower absorption and rapid tissue redistribution. In the case of bupivacaine, it may be explained by the significant lipid solubility and uptake in the epidural adipose tissue.[28] There is some controversy as to whether epinephrine may produce neurotoxicity when added to local anesthetics. Some clinicians only recommend its use for nerve blocks done without ultrasound guidance or where the needle tip and local anesthetic spread are not adequately visualized as a safety measure to detect intravascular injection.[40]

Studies that have compared vasoconstrictors conclude that epinephrine is superior to drugs such as phenylephrine and norepinephrine in producing vasoconstriction with local anesthetics.[53,54] The usual concentration of epinephrine used for this purpose is 1:200,000 or 5 mcg/mL.

Miscellaneous Factors That Influence Onset and Duration

Local anesthetics are basic drugs. As discussed previously, they have both water- and lipid-soluble properties. Factors that raise the pH of their environment increase their lipid solubility, and, conversely, lower pH environments result in increased water solubility. These changes to pH result in altered proportions of lipid- and water-soluble fractions of the drugs, which may have clinical consequences. At times, the term used for this phenomenon is *ion trapping*. Ion trapping results from changes in pH in relationship to the pK_a of the agent. Instances in which ion trapping may have clinical consequences are noted in Box 10-2.

Local anesthetics have been carbonated to speed onset. In isolated nerve preparations, carbonation gives a more rapid onset and greater intensity of block.[55] Diffusion of carbon dioxide through the nerve membrane can lower the intracellular pH. When local anesthetics accompany this process, they become more ionized within the neuron; this results in an increase in the concentration of the drug in the ionized form at the intracellular binding site.

Controversy exists concerning whether carbonation improves onset time in the in vivo situation.[56] Separate double-blind studies of lidocaine and bupivacaine have failed to yield positive results.[57] This inconsistency may exist because the injected carbon dioxide is rapidly buffered in vivo, so intracellular pH is not greatly affected.[56.57] This practice has been largely abandoned in modern clinical practice.

The addition of sodium bicarbonate to local anesthetics is widely used in epidural anesthesia to speed onset of sensory and motor block.[58-60] The effects of the addition of sodium bicarbonate to peripheral blocks is unclear.[40] In theory, the mechanism is that addition of bicarbonate increases the pH of the local anesthetic solution, resulting in the presence of more drug in the nonionized state. As stated previously, this form of the drug readily diffuses across the cell membranes and would therefore speed onset. Studies done with bupivacaine and lidocaine have indicated that this alteration does facilitate the onset and prolong duration of action.[58,59] Other researchers, however, have noted variable effects on onset and duration depending on whether epinephrine was contained in the solution.[60]

The major limitation to the addition of bicarbonate is the precipitation that can occur in the local anesthetic solution. It also should be noted that the amount of bicarbonate that can be added without precipitation depends on whether the epinephrine is commercially or "freshly" mixed.[58] Manufacturers acidify local anesthetic solutions to increase solubility and stability (the free base is more susceptible to photodegradation and aldehyde formation), which results in a longer shelf-life. For example, the pH range of plain lidocaine is 6.5 to 6.8, compared with 3.5 to 4.5 for preparations that contain epinephrine. The lower pH is used with epinephrine because of the instability of this compound in alkaline solutions.

Another benefit of alkalization is that it may result in less pain or stinging on injection. The mechanism of action for this effect could be more complex than just an increase in pH. It may be that the nociceptive nerve fibers may not be as sensitive to the

BOX **10-2**

Ion Trapping: Clinical Situations in Which Differences Between pK_a and pH May Affect Patient Response

- In the event of local anesthetic overdose, associated respiratory depression may occur, resulting in hypoxia and acidosis. The acidosis resulting from hypoxia may increase the ionized fraction of local anesthetic within the cerebral circulation, thereby decreasing the ability of the anesthetic to cross the blood-brain barrier, leave the brain, and reenter the systemic circulation. This phenomenon may prolong and enhance the central nervous system toxicity of local anesthetics.
- Local anesthetic accumulation in the fetal circulation is enhanced by the fact that fetal pH is lower than maternal pH, which may result in high fetal levels of local anesthetics.
- Local anesthetics injected into acidotic, infected tissues are rendered ineffective because of the loss of lipid solubility. The lipid solubility of local anesthetics is diminished in an acidotic environment because of an increased concentration of the ionized, water-soluble form of the drug. The loss of lipid solubility prevents absorption into the nerve, thereby preventing access to the site of action.
- Carbonation of local anesthetics speeds the onset and intensity of action of neural blockade. Carbon dioxide readily diffuses into the nerve, lowering the pH within the nerve. The lipid-soluble form of local anesthetic, after passing through the neuronal membrane, receives protons from the intraneuronal environment and ionizes. An increase in the ionized fraction within the neuron produces a higher concentration of the active form of the anesthetic available at the sodium channel, the site of action. This practice has been largely abandoned in modern clinical practice.
- Commercially available local anesthetics are prepared in a slightly acidic formulation that improves the stability of the drug by increasing the concentration of the ionized, water-soluble form of the drug. Addition of sodium bicarbonate to the local anesthetic mixture increases the pH of the solution, thereby increasing the concentration of the un-ionized, lipid-soluble form of the drug. Improving the lipid solubility of the local anesthetic improves diffusion of the local anesthetic through the neuronal membrane, leading to a more rapid onset of action. This seems to be most effective in epidural blocks and least effective in peripheral blocks.

un-ionized form of the drug. It also is possible that the un-ionized drug diffuses so rapidly through the tissue and axolemma that a sensory block occurs almost instantaneously.[61,62]

The addition of hyaluronidase to local anesthetics as a spreading factor facilitates the diffusion of the drugs in tissues. This additive accomplishes this effect via the hydrolysis of hyaluronic acid, which is a glycosaminoglycan found extensively in the interstitial matrix and basement membranes of tissue. Hyaluronic acid is the main component of interstitial gel, which inhibits the spread of substances through tissue.[63] It is has long been used in ophthalmic blocks to improve quality, speed onset, limit the acute increase in intraocular pressure with periocular injections, and reduce the incidence of postoperative strabismus.[64] Also, it has been suggested that hyaluronidase reduces hematoma size if a needle that is used with the regional technique punctures a major blood vessel. Other common uses are to facilitate the spread of fluids during hypodermoclysis and radiopaque agents in subcutaneous urography.[63] The addition of hyaluronidase can result in certain undesirable effects, such as the initiation of allergic reactions, a shortening of the duration of anesthetic action, and an increase in drug toxicity.[65-67]A new human recombinant product Hylenex is now available that may improve the safety profile.[68] Currently available hyaluronidase products are listed in Table 10-4. Recent off-label use for cosmetic applications, to reduce edema, epidural adhesions, and chronic lower back pain have led to an increased interest in this agent.[63]

Most current local anesthetics possess either a fast onset but intermediate duration or a slow onset and long duration. Clinicians frequently mix local anesthetics to obtain a more rapid onset and a longer duration of action. The use of intermediate-acting mepivacaine combined with long-acting bupivacaine for an ultrasound-guided interscalene block was recently reported.[69] Onset was not improved compared to bupivacaine alone, but duration was longer than mepivacaine alone. The duration was shorter than bupivacaine alone. Some clinicians have suggested that the use of combinations reduces the risk of toxicity; however, drug errors may increase when using more complex dosing schemes. In addition, the toxicity of local anesthetic combinations appears to be additive.[70-72] The authors suggest that the increased use of ultrasound-guided techniques allows for the use of lower doses and more precise deposition of drug, which may diminish the use of combined local anesthetics.[69]

TABLE **10-4** Available Formulations of Hyaluronidase

Drug	Source	Dosing
Vitrase	Lyophilized, ovine	A wide range of doses are used depending on the type of regional block and the goals; the dose can vary from 0.75 to 300 units/mL.
Amphadase	Bovine	
Hydase	Bovine	
Hylenex	Human (recombinant)	

Data from Dunn AL, et al. Hyaluronidase: a review of approved formulations, indications and off-label use in chronic pain management. *Expert Opin Biol Ther*. 2010;10(1):127-131; Adams L. Adjuvants to local anaesthesia in ophthalmic surgery. *Br J Ophthalmol*. 2011;95(10):1345-1349.

Distribution

The absorption or injection of local anesthetics into the systemic circulation results in rapid distribution throughout the body. Distribution results in a rapid decrease in the plasma concentration as the drug moves into highly perfused tissue. Rapid distribution into the brain and heart can be a concern because this can lead to systemic toxicity. A secondary, slower disappearance follows, which reflects a combination of distribution into tissues with a more limited blood supply, drug metabolism, and excretion.

Although local anesthetics are distributed throughout the body, their concentration varies in different tissues. Immediately after vascular uptake, more greatly perfused tissues, such as the brain, heart, and lungs, receive more of these drugs than do less perfused tissues. Once equilibration occurs, the local anesthetic leaves the highly perfused tissue and is deposited in tissue with less perfusion. As with many drugs, as they redistribute in the body over time, muscle tissue receives the greatest amount of local anesthetic from redistribution.

TABLE 10-5 Clearance Half-Life of Local Anesthetics

Drug	Clearance (L/min)	Half-Life (min)
Chloroprocaine	N/A	6
Procaine	N/A	6
Tetracaine	N/A	20
Cocaine	N/A	42
Prilocaine	2.84	90
Lidocaine	0.95	90
Mepivacaine	0.78	114
Bupivacaine	0.47	210
Ropivacaine	7.2	114

N/A, Not applicable. The ester compounds are rapidly broken down in the plasma and tissue so clearance is not a factor.
Adapted from: Malamed SF, ed. *Handbook of Local Anesthesia*. 6th ed. St. Louis: Mosby; 2013:27.

TABLE 10-6 Pharmacokinetics of Amide Local Anesthetics

Drug	Half-Life Alpha (min)	Half-Life Beta (min)	V_{dss} (L)	Clearance (L)
Prilocaine	0.5	90	261	2.84
Lidocaine	1	90	91	0.95
Mepivacaine	0.7	114	84	0.75
Bupivacaine	2.7	210	72	0.47
Ropivacaine	2.7	114	66.9	0.73

V_{dss}, Volume of distribution at steady state.

The distribution process varies significantly with different local anesthetics. For example, the disappearance rate of prilocaine is more rapid than that of mepivacaine or lidocaine. Ropivacaine also has a shorter half-life than bupivacaine. Distribution of the ester local anesthetics is similar to the amides; however, their rate of metabolism in plasma is very rapid, resulting in much lower and shorter duration systemic plasma concentrations.[16]

Metabolism

The metabolism of local anesthetics differs according to their chemical structure as either amides or esters. Plasma cholinesterase catalyzes the hydrolysis of ester local anesthetics. The hydrolysis occurs through the action of cholinesterase in plasma, red blood cells, and the liver.[73-75] The plasma half-lives of procaine and chloroprocaine are shorter than 1 minute. The rapid rate of clearance of these drugs significantly reduces the potential of toxicity. Conversely, hydrolysis of tetracaine is slower and it has limited clinical use (Table 10-5). Saturated, inhibited, or genetically atypical plasma cholinesterase can significantly prolong the plasma half-life of ester local anesthetics.[73,76] This would have little effect on duration of the ester agent because absorption away from the site of injection would occur as usual; however, this effect could theoretically increase the chance for systemic toxicity. For example, atypical plasma cholinesterase has been shown to significantly reduce the rate of procaine metabolism.[77]

Metabolism of the amide local anesthetics occurs primarily in the liver predominantly by microsomal cytochrome P-450 enzymes CYP1A2 and CYP3A4.[78] Table 10-6 presents pharmacokinetic data for the amide local anesthetics.[16]

Hepatic clearance is a function of the hepatic extraction ratio and hepatic blood flow and is the primary factor that determines the rate of elimination of amide local anesthetics. The hepatic extraction ratio is dependent on the ratio of free to protein-bound drug and represents the activity level specific to the liver for removing a drug from plasma. This ratio indicates the percentage of drug removed with each pass through the liver. The clearance of drugs that have higher hepatic extraction ratios depends on adequate hepatic blood flow. Hepatic enzyme activity is important when drugs with lower ratios, such as bupivacaine, are used.[79] Pathologic conditions that influence hepatic function may prolong the elimination half-life of these drugs by a reduction in hepatic blood flow, enzyme activity, or both. For example, lidocaine has a plasma half-life of 1.6 hours; however, in severe hepatic disease, its half-life is 4.9 hours. This probably results from both an enzymatic and a perfusion effect. Flow-limited clearance is affected by upper abdominal and laparoscopic surgery, inhalation anesthetics, hypovolemia, and congestive heart failure. Heart failure significantly reduces the rate of elimination of lidocaine because of a concomitant reduction in hepatic blood flow.[80] Clinically, hepatic dysfunction does not necessitate a reduction of dose for a single injection nerve block. Doses of amides used in continuous infusions or repeat blocks should be reduced 10% to 50%.[81]

Only 1% to 5% of the injected dose of local anesthetic is accounted for by unchanged renal and hepatic excretion. However, the inactive, more water-soluble metabolites of local anesthetics appear in the urine. Although renal dysfunction affects the clearance far less than does hepatic failure, it can result in the accumulation of potentially toxic metabolites.[82] It may also affect protein binding to both α_1-acid glycoprotein (AAG) and albumin. Some authors have suggested a 10% to 20% reduction in patients with severe renal disease.[83]

Pregnancy

The use of local anesthetics in pregnancy deserves some special pharmacokinetic and pharmacodynamic consideration. Clinical observations and studies both indicate that the spread and depth of spinal and epidural anesthesia are increased in pregnant women. Spread of neuraxial anesthesia increases during pregnancy due to decreases in thoracolumbar cerebral spinal fluid (CSF) volume and increased neural susceptibility to local anesthetic. At first this was thought to be the result of only mechanical factors produced by a gravid uterus. For example, mechanical factors result in dilation of epidural veins, which leads to narrowing of the epidural and subarachnoid space, thereby reducing the dose requirement.[84] However, hormonal changes appear to also play a role because there is a greater segmental spread of local anesthetics administered in the epidural space during the first trimester of pregnancy when little compression is evident.[85] A relationship appears to exist between the progesterone level in CSF and an increased segmental spread and sensitivity of nerves to these drugs. Studies performed on isolated nerves taken from pregnant animals demonstrate more sensitivity to local anesthetic block than in nonpregnant animals.[86,87]

LOCAL ANESTHETIC SYSTEMIC TOXICITY

Local anesthetic systemic toxicity (LAST) is a serious but rare consequence of regional anesthesia. It most commonly results from an inadvertent vascular injection or absorption of large amounts of drug from certain nerve blocks requiring large volume injections. It can also occasionally result from continuous infusion and accumulation of drug and metabolites over many days. The subsequent high systemic blood levels lead to LAST. Widespread

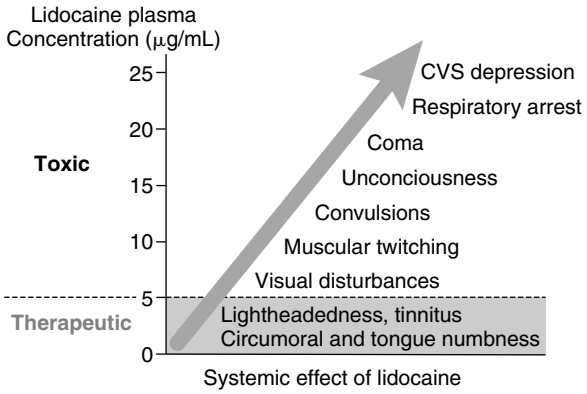

FIGURE **10-11** Classically reported sequence of clinical signs after increased central nervous system concentration of lidocaine.

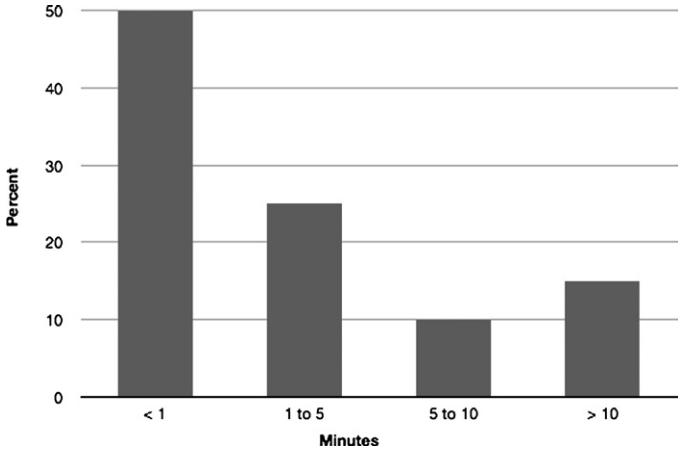

FIGURE **10-12** The timing for onset of signs of local anesthetic systemic toxicity after a single injection of local anesthetic (from a total of 77 incidents). (Data from Di Gregorio G, et al. Clinical presentation of local anesthetic systemic toxicity: a review of published cases, 1979 to 2009. *Reg Anesth Pain Med.* 2010;35[2]:181-187; Neal JM, et al. ASRA practice advisory on local anesthetic systemic toxicity. *Reg Anesth Pain Med.* 2010;35[2]:152-161; Mercado P, Weinberg GL Local anesthetic systemic toxicity: prevention and treatment. *Anesthesiol Clin.* 2011;29[2]:233-242.)

attention to this adverse effect is attributed to Albright, who wrote an editorial in 1979 outlining the risks of bupivacaine use in intravenous regional blocks.[88] Subsequently, 49 cases of cardiac toxicity from local anesthetics were reported to the Food and Drug Administration (FDA).[89] Worldwide concern followed with a renewed research and clinical interest and safety recommendations.[81] The American Society of Regional Anesthesia and Pain Medicine (ASRA), Panel on Local Anesthetic Systemic Toxicity has recently reevaluated the available research and clinical data from 1979 to 2009 and issued recommendations regarding prevention, diagnosis, and treatment of this complication. Many traditional concepts were reevaluated in light of new data, and practice advisories were formulated. Fortunately, the incidence is dropping as awareness, new practice techniques, and new drugs are instituted.[90]

Incidence and Clinical Presentation

Standard randomized controlled trials of LAST are obviously not ethical, so our knowledge is primarily derived from epidemiologic studies, case reports, and animal research. Data from animal and laboratory studies can vary widely depending on the model used, so comparisons as well as extrapolation to clinical situations can be difficult.

There has been a significant reduction in the incidence of LAST in the past 30 years.[91] The estimate of clinically important LAST is from 7.5 to 20 occurrences per 10,000 peripheral nerve blocks and approximately 4 per 10,000 epidurals.[81] This is a dramatic drop, for example, from the previously reported toxicity of 100 per 10,000 epidurals.[92]

As mentioned earlier, ASRA has evaluated data from 1979 to 2009 and identified 93 separate LAST events. The classic typical clinical presentation of LAST is a progression of subjective symptoms of CNS excitation such as agitation, tinnitus, circumoral numbness, blurred vision, and a metallic taste followed by muscle twitching, unconsciousness, and seizures and with very high drug levels, cardiac and respiratory arrest (Figure 10-11). The sequence occurs because the inhibitory pathways in the brain are affected first, leaving unopposed excitation. This is sometimes referred to as *disinhibition*. As the blood (therefore brain) levels increase, the more resistant excitatory pathways are inhibited, leading to unconsciousness and coma.[81] This was the presentation in about 60% of cases, although the types of CNS symptoms varied greatly. An atypical presentation was evident in about 40% of the patients. This was defined as LAST that is delayed for more than 5 minutes or with isolated cardiovascular symptoms alone. Most of the atypical presentations were for delayed symptoms.[90,91,93]

The most common regional block techniques associated with LAST were epidural (33%), axillary (17%), and interscalene (13%). Seventy-seven cases followed a single injection and 14 occurred with continuous infusion. Two cases involved both continuous infusions with a supplementary single injection. Of the continuous infusion cases, half were pediatric cases. Fifty-two events were related to bupivacaine (55%), 28 to ropivacaine (30%), 4 to levobupivacaine (4%), and 9 were attributed to other local anesthetics (11%). The patient characteristics were as follows: 63% female; 16% under 16 years old; 29% older than 60 years; 5 newborns receiving epidural anesthesia, and 37% of all patients had significant comorbidities such as diabetes, renal failure, or isovaleric acidemia.[93]

The timing of the onset of symptoms after a single injection varied from 30 seconds to 60 minutes (Figure 10-12). It is usually very rapid. In over half the cases, it happened in less than 50 seconds, and 75% of the cases occurred within 5 minutes of injection. The onset of symptoms following continuous infusion occurred hours or days after starting the drug.[93]

Central Nervous System and Cardiovascular Signs of Toxicity

The newly evaluated data point to a more varied presentation of toxicities. Symptoms of CNS toxicity occurred in 89% of cases either alone (45%) or together with significant cardiovascular symptoms (44%) (Figure 10-13). The spectrum of CNS signs of toxicity are given in Figure 10-14. It is interesting to note that the most frequent symptom was seizures (68%), whereas only 18% exhibited the typical prodromal symptoms. The spectrum of cardiovascular signs of toxicity are given in Figure 10-15. The most common involved various arrhythmias.[93]

Prevention of Local Anesthetic Systemic Toxicity

Adaption of suggested safety steps such as the use of test doses, incremental injection with frequent aspiration, and the use of pharmacologic markers such as epinephrine or fentanyl have lowered the incidence of LAST in recent years. Additional practices that have been suggested to improve safety include

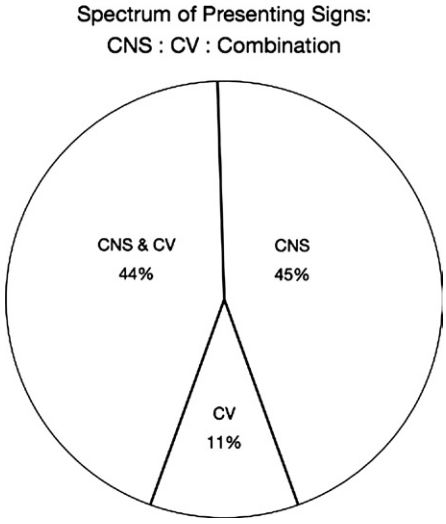

FIGURE **10-13** The frequency of symptoms and signs referable to cardiovascular (CV), central nervous system (CNS), or both is given for the 93 cases in this review. (Data from Di Gregorio G, et al. Clinical presentation of local anesthetic systemic toxicity: a review of published cases, 1979 to 2009. *Reg Anesth Pain Med* 2010;35[2]:181-187; Neal JM, et al. ASRA practice advisory on local anesthetic systemic toxicity. *Reg Anesth Pain Med.* 2010;35[2]:152-161; Mercado P, Weinberg GL. Local anesthetic systemic toxicity: prevention and treatment. *Anesthesiol Clin*. 2011;29[2]:233-242.)

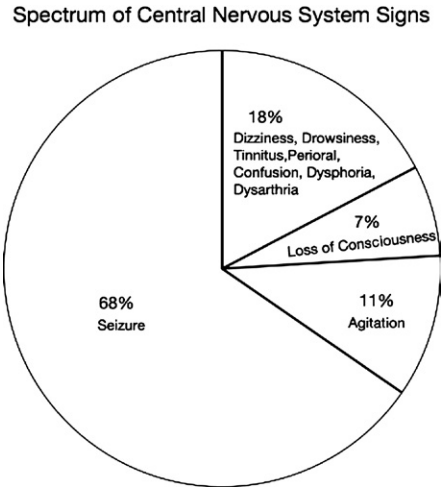

FIGURE **10-14** The distribution frequencies of all reported signs of central nervous system toxicity among published cases of local anesthetic systemic toxicity. Totals exceed 100% due to patients exhibiting more than one initial symptom. (Data from Di Gregorio G, et al. Clinical presentation of local anesthetic systemic toxicity: a review of published cases, 1979 to 2009. *Reg Anesth Pain Med.* 2010;35[2]:181-187; Neal JM, et al: ASRA practice advisory on local anesthetic systemic toxicity. *Reg Anesth Pain Med.* 2010;35[2]:152-161; Mercado P, Weinberg GL: Local anesthetic systemic toxicity: prevention and treatment. *Anesthesiol Clin*. 2011;29[2]:233-242.)

limiting the total dose of local anesthetic by restricting the use of 0.75% bupivacaine in obstetrics. The clinical principle in any regional technique is to use the lowest dose possible (the product of the concentration and volume) to produce a satisfactory block.[94] The use of generalized maximum recommended doses has been questioned.[83] Systemic blood levels of the same dose of anesthetic vary greatly depending on the area of blockade, technique, and specific drug. Blood levels are difficult to predict when dosing on a milligram per kilogram basis. Body weight as a guide should be used only in pediatric patients (Table 10-7). The use of ultrasound-guided techniques has the potential to further improve safety, although definitive studies are lacking to date.[95] The current ASRA recommendations for recognizing, preventing, and treatment of LAST are given in Box 10-3.[94] Further recommendations for preventing LAST are noted in Box 10-4.

Diagnosis and Treatment of Local Anesthetic Systemic Toxicity

Prompt recognition and treatment are essential to minimizing adverse outcomes of LAST. Airway management remains the primary intervention because preventing hypoxia and acidosis are essential first steps. As noted in Box 10-2, acidosis may enhance toxicity by ion trapping local anesthetic in the brain. Seizure suppression is essential to facilitate immediate airway control and prevent or reduce metabolic acidosis. Benzodiazepines are considered the drugs of choice because they are anticonvulsant without causing significant cardiac depression. When benzodiazepines are not available, small doses of propofol are appropriate. Succinylcholine may be useful to suppress intractable seizure-induced tonic-clonic muscle activity in spite of the lack of CNS effects. Cardiovascular support is essential to maintaining adequate coronary perfusion. The local anesthetics do not irreversibly damage the cardiac cells. Avoiding tissue hypoxia is essential in reversing the progression of toxic cardiac events.[96] Local anesthetic cardiotoxicity, especially with bupivacaine, involves both electrophysiologic disturbances and depression of contractility. The electrical disturbances appear to occur at lower doses and are more contributory to poor outcomes than contractile depression, but differences among specific local anesthetics exist.[97] Lipid emulsion therapy is recommended as a standard part of LAST resuscitation. There is some evidence that it is able to restore spontaneous circulation without the use of vasopressors. In fact, large doses of vasopressors may decrease the effectiveness of lipid emulsions.[98] Vasopressors may be required to maintain adequate blood pressure, but they can worsen local anesthetic-induced arrhythmias. Small doses of epinephrine, less than 1 mcg/kg, are recommended. Vasopressin should be avoided even though it is now part of Advanced Cardiac Life Support guidelines.[96]

As noted above, lipid emulsion therapy for LAST is the newest and most promising therapy that has emerged. Both laboratory and clinical use has shown it to be instrumental in facilitating successful recovery. The exact mechanisms for the beneficial effects is not clear. The mechanisms of action of lipid infusion can be broadly separated into intracellular (metabolic, signaling), intravascular (partitioning, sink), and membrane (channel) effects.

Six mechanistic actions may contribute to lipid resuscitation including: (1) capture of local anesthetic in the blood (lipid sink); (2) increased fatty acid uptake by mitochondria (metabolic effect); (3) interference with local anesthetic binding of sodium channels (membrane effect); (4) activation of Akt cascade A) serine/threonine protein kinase important in cell survival, proliferation, and migration, also called protein kinase B) leading to inhibition of GSK-3 which is glycogen synthase kinase (cytoprotection); (5) promotion of calcium entry via voltage-dependent calcium channels (ionotropic/inotropic effect); and (6) accelerated shunting (pharmacokinetic effects).[99–101] Lipid emulsion is also recommended in pregnant patients.[102] The recommendations for diagnosing LAST are given in Box 10-5.[90] Treatment recommendations are given in Box 10-6.[96]

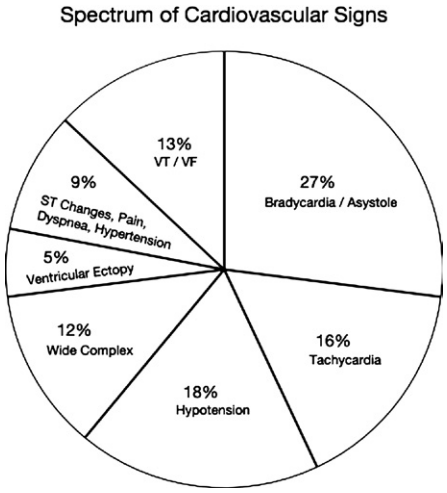

FIGURE **10-15** The distribution frequencies of all reported signs of cardiovascular toxicity during local anesthetic systemic toxicity. Totals exceed 100% due to patients exhibiting more than one initial symptom. (Data from Di Gregorio G, et al. Clinical presentation of local anesthetic systemic toxicity: a review of published cases, 1979 to 2009. *Reg Anesth Pain Med*. 2010;35[2]:181-187; Neal JM, et al. ASRA practice advisory on local anesthetic systemic toxicity. *Reg Anesth Pain Med*. 2010;35[2]:152-161; Mercado P, Weinberg GL. Local anesthetic systemic toxicity: prevention and treatment. *Anesthesiol Clin*. 2011;29[2]:233-242.)

Other Adverse Effects

Allergic Reactions

True allergic reactions to local anesthetics are rare, making up no more than 1% of reactions.[103] The frequency is decreasing with the lower use of the ester-type local anesthetics. Adverse reactions are most commonly due to anxiety, panic attacks, intravascular injection, vasovagal responses, or epinephrine. Local anesthetics can, however, produce allergic, hypersensitivity, and anaphylactic reactions. The use of ester local anesthetics is associated with a greater incidence of allergic reactions than the use of amides. This is likely because esters are derivatives of and metabolized to para-aminobenzoic acid (PABA), which is an allergenic compound.[104] Multidose vials also contain methyl and propylparaben as well as sulfites as preservatives. The parabens are additives in many cosmetics, lotions, and foods, and patients who are sensitized may exhibit cross-reactivity with the local anesthetics.[105] Preservative-free solutions are available. Cross-reactivity among the ester-type local anesthetics is high. Allergy to the amides remains largely anecdotal. Cross-reactivity within the amides as a class is extremely rare and between esters and amides is absent.[106] A thorough history of allergy may be difficult because many patients call all local anesthetic drugs "novocaine." They may not be aware of the specific agent administered. Clinicians use amides when possible because the incidence of allergy is extremely low, and they are not cross-reactive with other amides or esters. If a true allergy is suspected, referral to an allergist for skin testing and incremental dose challenges is necessary.[103,107,108]

Methemoglobinemia

Methemoglobinemia is a disorder characterized by high concentrations of methemoglobin (metHb) in the blood, which can lead to tissue hypoxia. The ferrous form of hemoglobin (Fe^{2+}) is oxidized to the ferric form (Fe^{3+}). Methemoglobin is an oxidized form of hemoglobin with reduced capacity to carry oxygen, which causes a shift to the left of the oxygen-hemoglobin dissociation curve. Normal methemoglobin levels are less than 1%. Signs and symptoms of developing methemoglobinemia include pale gray or blue-colored cyanosis, chocolate-colored blood, tachypnea, confusion, headache, dizziness, tachycardia, coma, and death. Decreasing oxygen saturation via pulse oximetry, which is unresponsive to oxygen

TABLE **10-7** Local Anesthetic Agents Used Commonly for Infiltrative Injection

Agent	Duration of Action	Maximum Dosage Guidelines (Total Cumulative Infiltrative Injection Dose per Procedure*)
Esters		
Procaine (Novocain)	Short (15-60 min)	7 mg/kg; not to exceed 350-600 mg
Chloroprocaine (Nesacaine)	Short (15-30 min)	Without epinephrine: 11 mg/kg; not to exceed 800 mg total dose With epinephrine: 14 mg/kg; not to exceed 1000 mg
Amides		
Lidocaine (Xylocaine)	Medium (30-60 min)	Without epinephrine: 4.5 mg/kg; not to exceed 300 mg
Lidocaine with epinephrine	Long (120-360 min)	With epinephrine: 7 mg/kg
Mepivacaine (Polocaine, Carbocaine)	Medium (45-90 min) Long (120-360 min with epinephrine)	7 mg/kg; not to exceed 400 mg
Bupivacaine (Marcaine)	Long (120-240 min)	Without epinephrine: 2.5 mg/kg; not to exceed 175 mg total dose
Bupivacaine with epinephrine	Long (180-420 min)	With epinephrine: Not to exceed 225 mg total dose
Prilocaine (Citanest)	Medium (30-90 min)	Body weight less than 70 kg: 8 mg/kg; not to exceed 500 mg Body weight less than 70 kg: 600 mg
Ropivacaine (Naropin)	Long (120-360 min)	5 mg; not to exceed 200 mg for minor nerve block

*Nondental use, administer by small incremental doses; administer the smallest dose and concentration required to achieve desired effect; avoid rapid injection.

BOX **10-3**

American Society of Regional Anesthesia and Pain Medicine Checklist for Managing Local Anesthetic Systemic Toxicity

For patients experiencing signs or symptoms of local anesthetic systemic toxicity (LAST), the pharmacologic treatment of LAST is different from other cardiac arrest scenarios.

- Get help.
- Initial focus:
  - *Airway management:* ventilate with 100% oxygen.
  - *Seizure suppression:* benzodiazepines are preferred.
  - *Basic and Advanced Cardiac Life Support (BLS/ACLS) will require adjustments of medications and perhaps prolonged effort.*
- Infuse 20% lipid emulsion (values in parenthesis are for a 70-kg patient).
  - Bolus 1.5 mL/kg (lean body mass) intravenously over 1 min (≈100 mL)
  - Continuous infusion at 0.25 mL/kg/min (≈18 mL/min; adjust by roller clamp)
  - Repeat bolus once or twice for persistent cardiovascular collapse.
  - Double the infusion rate of 0.5 mL/kg/min if blood pressure remains low.
  - Continue infusion for at least 10 min after attaining circulatory stability.
  - Recommended upper limit: approximately 10 mL/kg lipid emulsion over the first 30 min
- Avoid vasopressin, calcium channel blockers, β-blockers, or local anesthetic.
- Reduce individual epinephrine doses to less than 1 mcg/kg.
- Alert the nearest facility having cardiopulmonary bypass capability.
- Avoid propofol in patients having signs of cardiovascular instability.
- Post LAST events at www.lipidrescue.org and report use of lipid to www.lipidregistry.org.

Be Prepared

- We strongly advise that those using local anesthetics (LAs) in doses sufficient to produce systemic toxicity (LAST) establish a plan for managing this complication. Making a local anesthetic toxicity kit and posting instructions for its use are encouraged.

Risk Reduction (Be Sensible)

- Use the lowest dose of LA necessary to achieve the desired extent and duration of block.
- Local anesthetic blood levels are influenced by site of injection and dose. Factors that can increase the likelihood of LAST include advanced age, heart failure, ischemic heart disease, conduction abnormalities, metabolic (e.g., mitochondrial) disease, liver disease, low plasma protein concentration, metabolic or respiratory acidosis, and medications that inhibit sodium channels. Patients with severe cardiac dysfunction, particularly very low ejection fraction, are more sensitive to LAST and also more prone to receive "stacked" injections (with resulting elevated LA tissue concentrations) because of slowed circulation time.
- Consider using a pharmacologic marker and/or test dose, for example, epinephrine 5 mcg/mL of LA. Know the expected response, onset, duration, and limitations of a "test dose" in identifying intravascular injection.
- Aspirate the syringe prior to each injection while observing for blood.
- Inject incrementally, observing for signs and querying frequently for symptoms of toxicity between each injection.

Detection (Be Vigilant)

- Use standard American Society of Anesthesiologists (ASA) monitors.
- Monitor the patient during and after completing the injection, as clinical toxicity can be delayed up to 30 min or longer after tumescent procedures.
- Consider LAST in any patient with altered mental status, neurologic symptoms, or cardiovascular instability following a regional anesthetic.
- Central nervous system signs (may be subtle or absent):
  - Excitation (agitation, confusion, muscle twitching, seizure)
  - Depression (drowsiness, obtundation, coma, apnea)
  - Nonspecific (metallic taste, circumoral numbness, diplopia, tinnitus, dizziness)
- Cardiovascular signs (often the only manifestation of severe LAST):
- Initially may be hyperdynamic (hypertension, tachycardia, ventricular arrhythmias), then:
  - Progressive hypotension
  - Conduction block, bradycardia, or asystole
  - Ventricular arrhythmia (ventricular tachycardia, torsades de pointes, ventricular fibrillation)
- Sedative hypnotic drugs reduce seizure risk, but even light sedation may abolish the patient's ability to recognize or report symptoms of rising LA concentrations.

Treatment

- Timing of lipid infusion in LAST is controversial. The most conservative approach, waiting until after ACLS has proven unsuccessful, is unreasonable because early treatment can prevent cardiovascular collapse. Infusing lipid at the earliest sign of LAST can result in unnecessary treatment because only a fraction of patients will progress to severe toxicity. The most reasonable approach is to implement lipid therapy on the basis of clinical severity and rate of progression of LAST.
- There is laboratory evidence that epinephrine can impair resuscitation from LAST and reduce the efficacy of lipid rescue. Therefore it is recommended to avoid high doses of epinephrine and use smaller doses, for example, 1 mcg/kg for treating hypotension.
- Propofol should not be used when there are signs of cardiovascular instability. Propofol is a cardiovascular depressant with lipid content too low to provide benefit. Its use is discouraged when there is a risk of progression to cardiovascular collapse.
- Prolonged monitoring (up to 12 hr) is recommended after any signs of cardiac toxicity because cardiovascular depression due to LAs can persist or recur after treatment.

Data from Neal JM, et al. ASRA practice advisory on local anesthetic systemic toxicity. *Reg Anesth Pain Med.* 2010;35(2):152-161; Weinberg GL. Treatment of local anesthetic systemic toxicity (LAST). *Reg Anesth Pain Med.* 2010;35(2):188-193; Neal JM, et al. American Society of Regional Anesthesia and Pain Medicine checklist for managing local anesthetic systemic toxicity: 2012 version. *Reg Anesth Pain Med.* 2012;37(1):16-18.

BOX **10-4**

Recommendations for Preventing Local Anesthetic Systemic Toxicity (LAST)

- There is no single measure that can prevent LAST in clinical practice.
- Use the lowest effective dose of local anesthetic (dose = product of volume × concentration).
- Use incremental injection of local anesthetics—administer 3- to 5-mL aliquots, pausing 15 to 30 seconds between each injection.
  - When using a fixed needle approach, for example, landmark, paresthesia-seeking, or electrical stimulation, time between injections should encompass 1 circulation time (approximately 30-45 sec); however, this ideal may be balanced against the risk of needle movement between injections. Circulation time may be increased with lower extremity blocks. Use of larger dosing increments would dictate the need for longer intervals to reduce the cumulative dose from stacked injections before an event of LAST. Incremental injection may be less important with ultrasound guidance, given that frequent needle movement is often used with the technique.
- Aspirate the needle or catheter before each injection, recognizing that there is approximately 2% false-negative rate for this diagnostic intervention.
- When injecting potentially toxic doses of local anesthetic, use of an intravascular marker is recommended. Although epinephrine is an imperfect marker and its use is open to physician judgment, its benefits likely outweigh its risks in the majority of patients:
  - Intravascular injection of epinephrine 10 to 15 mcg/mL in adults produces a 10-beat or greater heart rate increase or a 15 or greater mmHg systolic blood pressure (SBP) increase in the absence of β blockade, active labor, advanced age, or general/neuraxial anesthesia.
  - Intravascular injection of epinephrine 0.5 mcg/kg in children produces a 15 or greater mmHg increase in SBP.
  - Appropriate subtoxic doses of local anesthetic can produce subjective symptoms of mild systemic toxicity (e.g., auditory changes, excitation, metallic taste) in unpremedicated patients.
  - Fentanyl 100 mcg produces sedation if injected intravascularly in laboring patients.
- Ultrasound guidance may reduce the frequency of intravascular injection, but actual reduction of LAST remains unproven in humans. Individual reports describe LAST despite the use of ultrasound-guided regional anesthesia. The overall effectiveness of ultrasound guidance in reducing the frequency of LAST remains to be determined.

Data from Mulroy MF, Hejtmanek MR. Prevention of local anesthetic systemic toxicity. *Reg Anesth Pain Med*. 2010;35(2):177-180; Neal JM, et al. ASRA practice advisory on local anesthetic systemic toxicity. *Reg Anesth Pain Med* 2010;35(2):152-161; Mercado P, Weinberg GL. Local anesthetic systemic toxicity: prevention and treatment. *Anesthesiol Clin*. 2011;29(2):233-242.

BOX **10-5**

Recommendations for Diagnosing Local Anesthetic Systemic Toxicity (LAST)

- Classic descriptions of LAST depict a progression of subjective symptoms of central nervous system (CNS) excitement (e.g., agitation, auditory changes, metallic taste, or abrupt onset of psychiatric symptoms) followed by seizures or CNS depression (e.g., drowsiness, coma, or respiratory arrest). Near the end of this continuum, initial signs of cardiac toxicity (e.g., hypertension, tachycardia, or ventricular arrhythmias) are supplanted by cardiac depression (e.g., bradycardia, conduction block, asystole, decreased contractility). However, there is substantial variation in this classic description, including the following:
  - Simultaneous presentation of CNS and cardiac toxicity
  - Cardiac toxicity without prodromal signs and symptoms of CNS toxicity

  Thus the practitioner must be vigilant for atypical or unexpected presentation of LAST.
- The timing of LAST presentation is variable. Immediate (less than 60 sec) presentation suggests intravascular injection of local anesthetic (LA) with direct access to the brain, whereas presentation that is delayed 1 to 5 minutes suggests intermittent or partial intravascular injection, delayed circulation time, or delayed tissue absorption. Because LAST can present more than 15 minutes after injection, patients who receive potentially toxic doses of LA should be closely monitored for at least 30 minutes after injection.
- Case reports associate LAST with underlying cardiac, neurologic, pulmonary, renal, hepatic, or metabolic disease. Heightened vigilance is warranted in these patients, particularly if they are at the extremes of age.
- The overall variability of LAST signs and symptoms, timing of onset, and association with various disease states suggests that practitioners should maintain a low threshold for considering the diagnosis of LAST in patients with atypical or unexpected presentation of CNS or cardiac signs and symptoms after receiving more than a minimal dose of LA.

Data from Di Gregorio G, et al. Clinical presentation of local anesthetic systemic toxicity: a review of published cases, 1979 to 2009. *Reg Anesth Pain Med*. 2010;35(2):181-187; Neal JM, et al. ASRA practice advisory on local anesthetic systemic toxicity. *Reg Anesth Pain Med*. 2010; 5(2):152-161; Mercado P, Weinberg GL. Local anesthetic systemic toxicity: prevention and treatment. *Anesthesiol Clin*. 2011;29(2):233-242.

BOX **10-6**

Recommendations for Treatment of Local Anesthetic Systemic Toxicity (LAST)

- If signs and symptoms of LAST occur, prompt and effective airway management is crucial to preventing hypoxia and acidosis, which are known to potentiate LAST.
- If seizures occur, they should be rapidly halted with benzodiazepines. If benzodiazepines are not readily available, small doses of propofol are acceptable. Future data may support the early use of lipid emulsion for treating seizures.
- Although propofol can stop seizures, large doses further depress cardiac function; propofol should be avoided when there are signs of cardiovascular compromise. If seizures persist despite benzodiazepines, small doses of succinylcholine or similar neuromuscular blocker should be considered to minimize acidosis and hypoxemia.
- If cardiac arrest occurs, we recommend standard advance cardiac life support with the following modifications:
  - If epinephrine is used, small initial doses (10- to 100-mcg boluses in adults) are preferred.
  - Vasopressin is not recommended.
  - Avoid calcium channel blockers and beta-adrenergic receptor blockers.
  - If ventricular arrhythmias develop, amiodarone is preferred; treatment with local anesthetics (lidocaine or procainamide) is not recommended.
- Lipid emulsion therapy:
  - Consider administering at the first signs of LAST, after airway management.
  - Dosing
    - 1.5 mL/kg 20% lipid emulsion bolus.
    - Infusion of 0.25 mL/kg per minute, continued for at least 10 minutes after circulatory stability is attained.
    - If circulatory stability is not attained, consider giving another bolus and increasing infusion to 0.5 mL/kg per minute.
    - Approximately 10 mL/kg lipid emulsion over 30 minutes is recommended as the upper limit for initial dosing.
- Propofol is not a substitute for lipid emulsion.
- Failure to respond to lipid emulsion and vasopressor therapy should prompt institution of cardiopulmonary bypass. Because there can be considerable lag in beginning cardiopulmonary bypass, it is reasonable to notify the closest facility capable of providing it when cardiovascular compromise is first identified during an episode of LAST.

Data from Neal JM, et al. ASRA practice advisory on local anesthetic systemic toxicity. *Reg Anesth Pain Med*. 2010;35(2):152-161; Weinberg GL. Treatment of local anesthetic systemic toxicity (LAST). *Reg Anesth Pain Med*. 2010;35(2):188-193; Mercado P, Weinberg GL. Local anesthetic systemic toxicity: prevention and treatment. *Anesthesiol Clin*. 2011;29(2):233-242.

supplementation, may occur. It can be diagnosed by CO-oximetry, laboratory testing, or implied by symptoms.[109-111] Two local anesthetics, benzocaine and prilocaine, can produce this adverse effect.

Benzocaine and benzocaine-containing mixtures are widely used for topical anesthesia. The FDA has issued two safety bulletins warning of benzocaine-induced methemoglobinemia.[112] In a 2006 communication, the FDA reported 247 cases of methemoglobinemia from benzocaine sprays including three deaths. Since then the number of cases has risen to 319. The development of methemoglobinemia does not seem to be dose related. Symptoms appear within minutes up to 2 hours after benzocaine use. Benzocaine sprays are marketed as different brand names such as Cetacaine, Hurricaine, Exactacain, and Topex. A 2011 safety bulletin warned of serious adverse events associated with over-the-counter benzocaine gels, sprays, and liquids. They are applied to the throat and gums for pain relief. The cases were primarily in children less than 2 years old. Benzocaine gels and liquids are marketed under the names Anbesol, Hurricaine, Ora-Jel, Baby Ora-Jel, Orabase, and some store brands. Benzocaine should not be used in children under 2 years old.

Prilocaine can produce methemoglobinemia because of one of its metabolites, o-toluidine, which oxidizes hemoglobin to methemoglobin. The tendency of prilocaine to produce methemoglobin is dose related. Current recommendations are that prilocaine should not be used in children younger than 6 months old, in pregnant women, or in patients taking other oxidizing drugs. The dose should be limited to 2.5 mg/kg.[113,114] Treatment of methemoglobinemia consists of methylene blue 1 to 2 mg /kg IV.

Local Tissue Toxicity

Past formulations of chloroprocaine were reported to produce prolonged cauda equina syndrome when large doses were given by inadvertent intrathecal injection.[16,115-117] The neurotoxicity was due to a combination of large intrathecal doses, low pH, and the preservative sodium metabisulfite. This problem disappeared with the introduction of preservative-free chloroprocaine.

Lidocaine has been associated with cauda equina syndrome when used for continuous spinal anesthesia, and it is no longer used in this anesthetic technique in the United States.[118,119] Single dose spinal administration of lidocaine has also been implicated in transient neurologic syndrome (TNS), which results in back and lower extremity pain for up to 5 days postoperatively. No permanent problems occur. Symptoms include a burning, aching, cramplike, and radiating pain in the anterior and posterior aspect of the thighs. Pain radiates to the lower extremities, and lower back pain is common. Other anesthetics have been implicated, but it is much more prevalent following spinal lidocaine.[120] Surgical positioning may be a factor as well.[121] The exact mechanism is unclear. Newer techniques and agents other than lidocaine are being used now, and this has diminished this problem as a clinical issue.[122] Treatment is supportive and should include nonsteroidal antiinflammatory agents when possible.

CLINICAL USE OF LOCAL ANESTHETICS

Topical Anesthesia

Anesthesia with a number of diverse topical formulations is used for a variety of clinical applications. These include decreasing the pain of venipuncture, circumcision, dressing changes, dentistry, minor surgical procedures, laser procedures, and multiple injection regional blocks. Some available products are listed in Table 10-8 and described below.[123,124]

Cocaine

Cocaine is derived from the coca plant and is the only naturally occurring local anesthetic. Other unique properties include the

TABLE 10-8 Topical Anesthesia Products

Product	Composition	Time to Efficacy	Occlusion	Potential
TAC	0.5% tetracaine, 1:2000 epinephrine, and 11.8% cocaine	30 min	No	Seizures; cardiac arrest
LET	0.5% tetracaine, 1:2000 epinephrine, and 4% lidocaine	15-30 min	No	None
Topicaine	4% lidocaine	30 min	No	Contact dermatitis
EMLA	2.5% lidocaine and 2.5% prilocaine	30 min to 2 hr	Yes	Contact dermatitis; methemoglobinemia
LMX 4/5	4% or 5% liposomal lidocaine	15-40 min	No	None
BLT	20% benzocaine, 6% lidocaine, and 4% tetracaine	15-30 min	No	None

Data from Kaweski S. Plastic Surgery Educational Foundation Technology Assessment Committee: topical anesthetic creams. *Plast Reconstr Surg.* 2008;121(6):2161-2165.
BLT, benzocaine, lidocaine, tetracaine; *EMLA*, eutectic mixture of local anesthetics; *LET*, lidocaine, epinephrine, and tetracaine; *LMX*, lidocaine mixture; *TAC*, tetracaine, epinephrine, and cocaine.

ability to block the monoamine transporter in adrenergic neurons. The neuronal transporter is responsible for the termination of the action of catecholamines. This catecholamine reuptake blockade results in significant vasoconstriction. This action in the CNS also accounts for cocaine's analeptic actions. It is used primarily for topical anesthesia of the nose and throat. A maximum of 5 mL of 4% solution or 200 mg should be used. It is frequently administered with other epinephrine-containing preparations so arrhythmias, hypertension, and tachycardia may occur. Caution is advised for possible drug interactions in patients taking other catecholamine-enhancing drugs such as tricyclic antidepressants or monoamine oxidase inhibitors.[125,126]

Eutectic Mixture of Local Anesthetics

Eutectic mixture of local anesthetics (EMLA) is a mixture of lidocaine and prilocaine that is applied to the skin as either a cream or patch. A eutectic mixture of chemicals has a lower melting point and solidifies at a lower temperature when combined. Pharmacokinetic studies indicate that satisfactory dermal analgesia is achieved 1 hour after application with an occlusive dressing; maximal analgesia occurs 2 to 3 hours after application.[123] When EMLA is applied to areas of abnormal skin (e.g., where psoriasis or eczema is present), absorption is faster, plasma levels are higher, and the duration of anesthesia is shorter. Systemic absorption of lidocaine and prilocaine is dependent on the duration and surface area of application. Toxicity is more likely to occur in infants and small children than in adults. Guidelines for the use of EMLA are given in Table 10-9.

TABLE 10-9 Guidelines for Application of EMLA

Age and Body Weight Requirement	Maximum Total Dose of EMLA	Maximum Application Area
0-3 months or less than 5 kg	1 g	10 cm^2
3-12 months and more than 5 kg	2 g	20 cm^2
1-6 years and less than 10 kg	10 g	100 cm^2
7-12 years and more than 20 kg	20 g	200 cm^2

Data from Kaweski S. Plastic Surgery Educational Foundation Technology Assessment Committee: topical anesthetic creams. *Plast Reconstr Surg.* 2008;121(6):2161-2165.
EMLA, Eutectic mixture of local anesthetics.

Tetracaine, Epinephrine, and Cocaine

Three available agents—tetracaine, epinephrine, and cocaine (TAC)—have been combined for use on traumatic lacerations. The relative concentration of each component is as follows: tetracaine 1%, epinephrine 1:200, and cocaine 4%. This combination has been as effective as infiltration of local anesthetics for the closure of certain types of laceration. Tetracaine and cocaine can produce excellent topical anesthesia, and cocaine and epinephrine result in vasoconstriction at the site of application. TAC is much more expensive to administer than lidocaine. The drug combination in TAC can produce significant toxicity.[123]

Local Wound Infiltration

Pain can be effectively alleviated with local anesthetics; however, their clinical usefulness is limited by their relatively short duration of action. Even long-acting local anesthetics such as bupivacaine and ropivacaine have durations less than 8 to 16 hours. Wound infiltration prior to closing is a common practice for immediate short-term postoperative pain relief. Direct application of local anesthetic and opiate drugs via continuous infusion indwelling catheters provides long-term analgesia. Wound catheters are commonly placed in the subcutaneous, fascial, intraarticular, pleural, and periosteal areas. Local anesthetic systemic toxicity has not been reported.[127,128] Problems associated with the use of indwelling catheters are blockage or breakage, migration away from the intended area, and infection. Chondrotoxicity when intraarticular bupivacaine is used in high concentrations for long periods has been reported.[129]

Sustained Release of Local Anesthetics

A sustained-release formulation of the local anesthetic bupivacaine that does not require an indwelling catheter to achieve a long duration of action is available. Bupivacaine extended-release liposome injection, Exparel, consists of bupivacaine encapsulated in DepoFoam. It provides continuous and extended postsurgical analgesia for up to 72 hours.[130]

Tumescent Anesthesia

Tumescent local anesthesia (TLA) involves the use of lidocaine, sodium bicarbonate, and epinephrine diluted in normal saline.[131,132] Very dilute solutions of lidocaine 0.1% or less are used so that large volumes may be infiltrated subcutaneously. The volume of tumescent anesthesia solution used is determined by

the achievement of palpable tumescence (uniform swelling) of the surgical field. The maximum dose of lidocaine in TLA can approach 50 mg/kg. Peak serum levels occur 12 hours postinfiltration, and complete elimination is usually within 36 hours. Strict adherence to liposuction guidelines has minimized adverse reactions from this technique. Specific regional anesthetic techniques and blocks are discussed in detail in Chapters 44 and 45.

SUMMARY

Local anesthetic techniques are becoming more commonplace in outpatient procedures, obstetrics, and pain services. A thorough understanding of the pharmacologic properties of local anesthetics is essential in order to administer and manage local, topical, and regional anesthesia appropriately. The selection of a drug with an appropriate dose, concentration, time to onset, and duration of action for a selected regional technique are critical for a clinically successful block. A thorough evaluation of the data on local anesthetic systemic toxicity has led to new insights into the clinical presentation, prevention, and treatment of this adverse event. Lipid resuscitation is expected to offer a new and efficacious approach to clinical management of this problem. Continued efforts to develop new drugs and formulations of existing agents will broaden our ability to address pain management needs.

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Opioid Agonists and Antagonists

◆ *John J. Nagelhout*

CHAPTER 11

In the past, opium was used as a topical, intravenous, and inhaled analgesic. One of the earliest uses of opium is found in Greek literature dating from 300 BCE. Opium sponges, referred to as *soporific sponges*, were used for the control of pain as early as the fourteenth century. An attempt to administer opioids by the intravenous route was attributed to Elscholtz in 1665, approximately 200 years before the invention of the syringe and needle. The first attempt to administer an opium vapor by inhalation was documented in 1778. It was not until 1853, when the syringe and needle were introduced into clinical practice by Wood, that an accurate dose of opioid could be administered intravenously.

In 1803, Sertürner reported the isolation of a pure substance from opium that he named *morphine*, after Morpheus, the Greek god of dreams. Other opium alkaloids were soon discovered—codeine by Robiquet in 1832 and papaverine by Merck in 1848. Abuse of opium and isolated alkaloids led to the synthetic production of potent analgesics. The goal of synthetic manufacture of analgesics was the creation of potent analgesics that would have high specificity for receptors, were not addictive, and were free of side effects. Synthetic production led to the development of opioid agonists, partial agonists, agonists-antagonists, and antagonists.[1,2]

OPIOIDS

Opioid is a term used to refer to a group of drugs, both naturally occurring and synthetically produced, that possess opium- or morphine-like properties. Opioids exert their effects by mimicking naturally occurring endogenous opioid peptides or endorphins. *Narcotic* is derived from the Greek word *narkōtikos*, "benumbing," and refers to potent morphine-like analgesics with the potential to produce stupor, insensibility, and dependence. The term *narcotic* is not useful in a pharmacologic or clinical discussion because of its legal connotations.

Several systems of classification are used to describe opioids. One common method divides the opioids into four categories: agonists, partial agonists, agonists-antagonists, and antagonists (Table 11-1). Another system of categorization is based on the chemical derivation of the opioids and divides them into naturally occurring, semisynthetic, and synthetic compounds, with each group having subgroups (Box 11-1).[3] Other classification systems describe the drugs as either weak or strong or hydrophilic and lipophilic.

The term *opioid* is derived from the word *opium* (from *opos*, Greek for "sap"), an extract from the poppy plant *Papaver somniferum*. The properties of opium are attributable to the 20 different isolated alkaloids, and the alkaloids are divided chemically into two types: phenanthrene (from which morphine and codeine are derived) and benzylisoquinoline (from which papaverine, a nonanalgesic drug, is derived). Modification of the morphine molecule with retention of the five-ring structure results in the semisynthetic drugs heroin and hydromorphone. When the furan ring is removed from morphine, the resulting four-ring synthetic opioid levorphanol is formed. The phenylpiperidines (e.g., fentanyl) and the diphenylheptane derivatives (e.g., methadone) all have only two of the original five rings of the basic morphine molecular structure. A close relationship exists between the stereochemical structure and potency of opioids, with the *levo*-isomers being the most potent. All opioids, despite the diverse molecular structures, share an *N*-methylpiperidine moiety, which seems to confer analgesic activity.[1] Figure 11-1 illustrates the structures of the commonly used opioids.

Opioid drugs produce pharmacologic activity by binding to opiate receptors primarily located in the central nervous system (CNS), supraspinal and spinal; and several peripheral sites. These include the gastrointestinal (GI) system, vasculature, lung, heart, and immune systems. Supraspinal analgesia occurs through activation of opioid receptors in the medulla, midbrain, and other areas, which causes inhibition of neurons involved in pain pathways. Spinal analgesia occurs by activation of presynaptic opioid receptors, which leads to decreased calcium influx and decreased release of neurotransmitters involved in nociception. Clinically, supraspinal and spinal opioid analgesic mechanisms are synergistic.[3] This explains why opioids such as fentanyl and sufentanil produce more profound analgesia when delivered epidurally than when delivered systemically, despite the similar blood concentrations measured with both routes of administration.[1,4]

Opiate Receptors

Opiate receptors are from the rhodopsin family of G-protein–coupled receptors (GPCRs). They have been DNA and amino acid sequenced and cloned. The discovery of opioid receptors can be traced back to the 1950s, when pharmaceutical companies were involved in research in anticipation of the development of an effective nonaddictive analgesic. In 1973, the examination of vertebrate species led to the discovery of three opiate receptor classes that mediate analgesia.[5] Questions emerged as to why the receptors existed, and further research led to the hypothesis that the receptors possess endogenous functions.

After the discovery of opiate receptors in the early 1970s, the search began for endogenous substances that were their agonists. In 1975, three such agonists were identified: enkephalins, endorphins, and dynorphins.[5] Each group is derived from a distinct precursor polypeptide and has a characteristic anatomic distribution. By the early 1980s, three precursor molecules to these agonists were identified and named after the active fragments: proenkephalin, proadrenocorticotropic hormone (ACTH)–endorphin (now called *proopiomelanocortin*), and prodynorphin.[1,5] Opioid peptides share the common amino-terminal sequence of Try-Gly-Gly-Phe-(Met or Leu), which has been labeled the *opioid motif* or *message* and is necessary for interaction at the receptor site. The peptide selectivity resides in the carboxy-terminal extension, providing

TABLE 11-1 Opioid Agonists, Partial Agonists, Agonists-Antagonists, and Antagonists at Sites of Activity

Opioid	Mu	Kappa	Delta
Morphine	Agonist	Agonist	Agonist
Meperidine	Agonist	Agonist	Agonist
Fentanyl	Agonist	Agonist	Agonist
Sufentanil	Agonist	Agonist	Agonist
Alfentanil	Agonist	Agonist	Agonist
Remifentanil	Agonist	Agonist	Agonist
Butorphanol	Antagonist	Partial agonist	Agonist
Nalbuphine	Antagonist	Partial agonist	Agonist
Naloxone	Antagonist	Antagonist	Antagonist
Naltrexone	Antagonist	Antagonist	Antagonist
Nalmefene	Antagonist	Antagonist	Antagonist

BOX 11-1

Classification of Opioids Based on Derivation of Drug

Naturally Occurring Opium Alkaloids

Phenanthrene Derivatives
- Morphine
- Codeine
- Thebaine

Benzylisoquinoline Derivatives
- Papaverine

Semisynthetic Derivatives of Opium Alkaloids

Morphine Derivatives
- Oxymorphone
- Hydromorphone
- Heroin
- Naloxone
- Naltrexone
- Methylnaltrexone

Thebaine Derivatives
- Buprenorphine
- Oxycodone

Synthetic Opioids

Morphinans
- Levorphanol
- Nalbuphine
- Dextromethorphan

Phenylheptylamines
- Methadone

Piperidines

Anilinopiperidine
- Meperidine

Phenylpiperidines
- Alfentanil
- Fentanyl
- Sufentanil
- Remifentanil

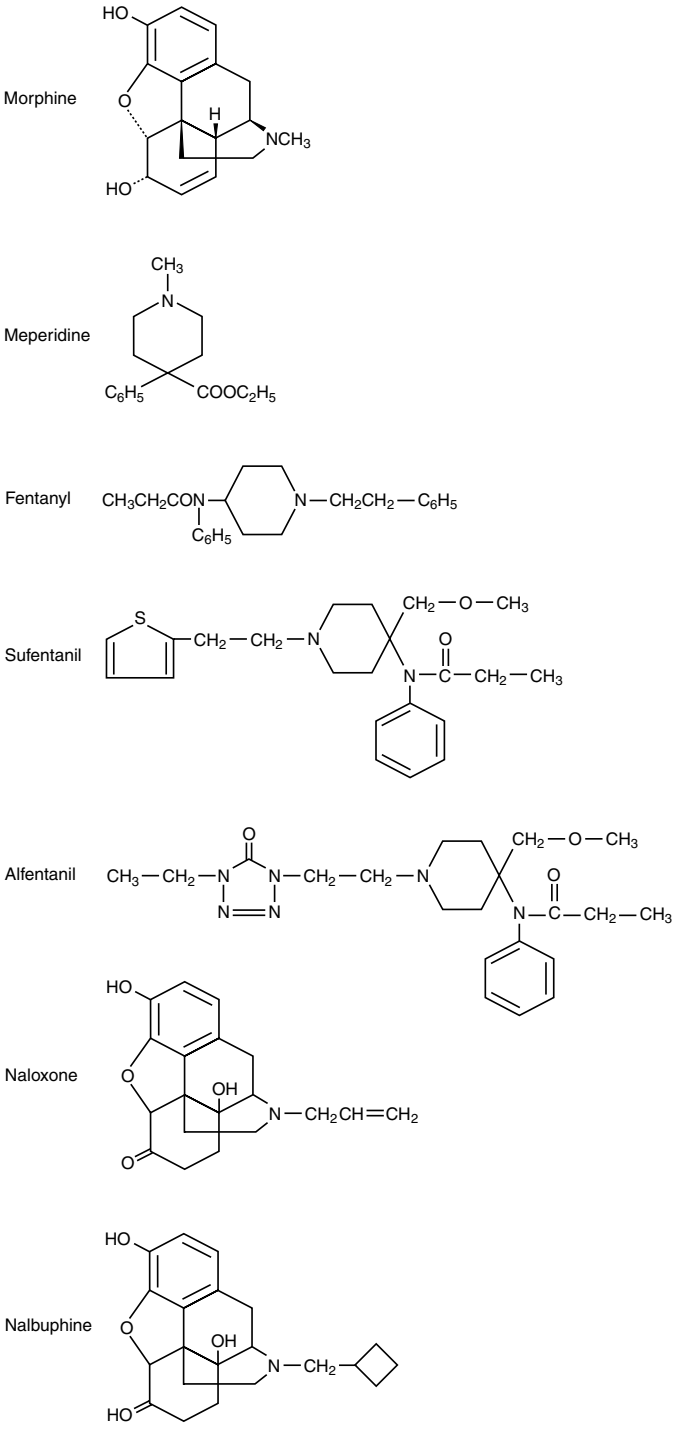

FIGURE 11-1 Selected opioid agonists and antagonists used as anesthesia adjunct drugs.

the *address*.[1] Since then an additional precursor pronociceptin that results in nociceptin has been identified. Endomorphin 1 and 2, which are highly selective agonists at μ receptors, have been identified, but the precursor's molecule has not yet been defined.[3] In 1975, Hughes and Kosterlitz[6] identified the first endogenous substance with opioid activity.

Martin et al.[7] were the first to provide evidence for opiate receptor subtypes (Table 11-2). Their findings provided evidence for the existence of three opiate receptors: mu (μ), kappa (κ), and sigma, named after their respective agonists—morphine, ketocyclazocine, and SK&F 10047. The sigma receptor was later determined not to be an opiate receptor. A delta (δ) receptor was subsequently identified. Each major opioid receptor has a unique anatomic distribution in the brain, spinal cord, and periphery.[8] The three receptor subtypes share 55% to 58% sequence homologies. Their diversity is greatest in their extracellular loops.[1] A fourth receptor has been cloned and named opiate receptor like (ORL1) or the nociceptin orphanin FQ peptide receptor (NOP). Because this receptor family awaits further clarification as to its role in pain signaling and does not display opioid pharmacology, discussion of this category is not included here.

Stimulation of the mu receptor produces supraspinal analgesia, euphoria, and a decrease in ventilation and most of the classic clinical actions of the opioid agonists. Kappa receptor stimulation produces spinal analgesia, sedation, and miosis. Currently, kappa-opioid drugs are being investigated for antiinflammatory actions that reduce disease severity of arthritis and other inflammatory diseases.[9-11] The delta receptor is responsible for spinal analgesia,

TABLE 11-2 Actions Produced at Each Opioid Receptor Subtype

Effects	Mu (μ) Receptor	Kappa (κ) Receptor	Delta (δ) Receptor
IUPHAR name	**MOP**	**KOP**	**DOP**
Analgesia	Supraspinal Spinal	Supraspinal, spinal	Supraspinal, spinal; modulates mu-receptor activity
Cardiovascular	Bradycardia		
Respiratory	Depression	Possible depression	Depression
Central nervous system	Euphoria, sedation, prolactin release, mild hypothermia, catalepsy, indifference to environmental stimulus	Sedation, dysphoria, psychomimetic reactions (hallucinations, delirium)	
Pupil	Miosis	Miosis	
Gastrointestinal	Inhibition of peristalsis, nausea, vomiting		
Genitourinary	Urinary retention	Diuresis (inhibition of vasopressin release)	Urinary retention
Pruritus	Yes		Yes
Physical dependence	Yes	Low abuse potential	Yes
Antishivering		Yes	

IUPHAR, International Union of Basic and Clinical Pharmacology; *MOP*, mu opiate peptide; *KOP*, kappa opiate peptide; *DOP*, delta opiate peptide.

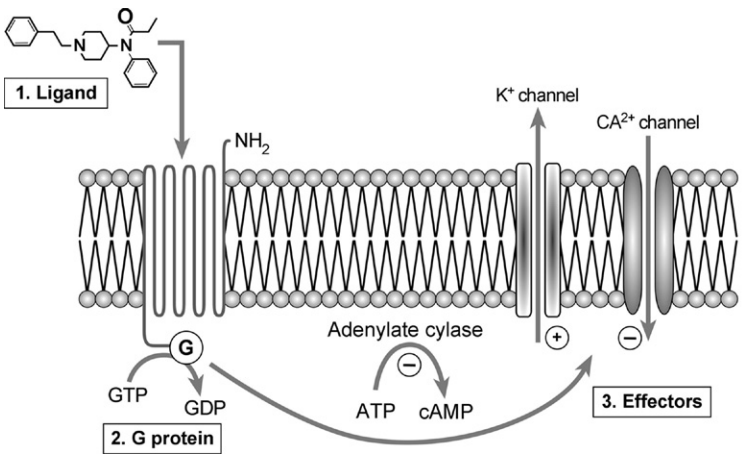

FIGURE **11-2** Mechanism of opioid drugs. *(1)* Opioid agonist such as fentanyl binds to a opiate receptor. *(2)* A G protein is activated that produces a conformational change in the intracellular effectors such as cAMP, potassium, and calcium. *(3)* This results in a decrease in cAMP, K^+, and CA^{2+}, preventing neuropeptide release and excitation of the neuron. *cAMP*, Cyclic adenosine monophosphate.

responds to enkephalins, and serves to modulate activity of the mu receptors.[3] Various subtypes of each of the three opiate receptors have been proposed but have not been well defined.[8]

At the cellular level, endogenous peptides and exogenous opioids produce effects by altering patterns of interneuronal communications. Receptor binding initiates a series of biochemical changes that result in cellular hyperpolarization and inhibition of neurotransmitter release, effects mediated by second messengers. Opioid receptors are GPCRs and inhibit the activity of adenylate cyclase inside of cells. This results in a decrease in intracellular cyclic adenosine monophosphate (cAMP), which decreases conductance of the voltage-gated calcium channels and opens potassium channels, resulting in decreased neuronal activity. This leads to a decrease in neuronal excitation and an inhibition of neurotransmitter or neuropeptide release.[3] The mechanism of action of opioid drugs is shown in Figure 11-2. The endogenous ligands for opioid receptors are noted in Table 11-3.

Pharmacokinetics

Pharmacodynamic and pharmacokinetic considerations must be combined to reach an ideal analgesic clinical state. Surgical requirements for analgesic drugs are much different than nonoperative uses. These differences include a much higher analgesic requirement, the coadministration of potent anesthetic and sedative drugs and the ability to support respirations so that respiratory depression is not an issue until the patient emerges from anesthesia.

In anesthesia, opioids are most commonly administered by the parenteral, intrathecal, and epidural routes. They may also be given by oral, nasal, intramuscular, and transdermal administration. Physiochemical properties of opioids influence their pharmacokinetics. To reach effector sites in the CNS, opioids must cross biologic membranes from the blood to receptors on neural cell membranes. The ability of opioids to cross the blood-brain and placental barriers depends on molecular size, ionization, lipid

solubility, and protein binding. The physicochemical characteristics, pharmacokinetic variables, and partition coefficients (octanol and water as a measure of lipid solubility) for several of the commonly used opioid analgesics are summarized in Table 11-4.

The wide variation in dosing of the opioids in anesthesia depending on the patient and surgical situation leads to vastly different durations even with the same drug. Fentanyl, for example, can last 30 minutes to 18 to 24 hours, depending on how and how much is given. The pharmacokinetic parameters are important, but the context of how they are used in clinical practice is a major factor in the ultimate patient response.

Opioids are modestly absorbed orally. Some opioids undergo extensive first-pass metabolism in the liver, greatly reducing their bioavailability and therapeutic efficacy after oral dosing. Orally administered morphine has limited absorption from the GI tract. Drugs with greater lipophilicity are better absorbed through nasal and buccal mucosa and the skin.

When small doses of the opioids are used, the effects are usually terminated by redistribution rather than metabolism. Larger or multiple doses or continuous infusions are much more dependent on metabolism for offset.[12] Like most drugs, opioids are usually metabolized in the liver to more polar and less active or inactive compounds by both phase 1 and phase 2 processes. Some opioids, such as morphine, have active metabolites such as morphine 6 glucuronide, that can prolong the therapeutic effects of the parent compound. The meperidine metabolite, normeperidine, is neurotoxic and may accumulate in the elderly or in patients with decreased renal or hepatic function. This has led to a decline in its use. It is avoided in the elderly or patients with renal or hepatic dysfunction and where chronic use may be needed.[1] The opioid drugs are metabolized by the usual cytochrome enzymes including CYP3A4, CYP2D6, and CYP2B6.[13-15] Remifentanil was designed with an ester group in its structure and is metabolized by hydrolysis in the plasma and tissues by non-specific esterases. Remifentanil has a low volume of distribution and a large clearance, which results in a short half-life of approximately 10 minutes. Opioids and their metabolites are excreted primarily by the kidneys and secondarily by the biliary system and GI tract.[16] Clinicians become very adept in the art of administering opioids by bolus, incremental injection, or infusion to maximize analgesia during surgery as needed yet allowing for safe and rapid recovery and residual postoperative analgesia.

TABLE 11-3 Endogenous Opioid Ligands and Their Precursors

Precursor	Endogenous Peptide
Proopiomelanocortin	β-Endorphin α, β, and γ MSH ACTH
Proenkephalin	Met-enkephalin Leu-enkephalin
Prodynorphin	Dynorphin A Dynorphin B Neodynorphin
Pronociceptin/orphanin FQ	Nociceptin
Proendomorphin*	Endomorphin-1 Endomorphin-2

*Presumed to exist, awaiting discovery.

ACTH, Adrenocorticotropic hormone; *MSH*, melanocyte-stimulating hormone.

Pharmacogenetics

The wide variations in dosing and patient responses have both pharmacodynamic and pharmacokinetic causes. Pharmacogenetics appears to be an important factor as well. Opioids have a narrow therapeutic index, calling for a fine balance between optimizing pain control and sedative effects (without respiratory depression) and recognizing great variability from patient to patient in response and dose requirements. Genetic factors regulating their pharmacokinetics (metabolizing enzymes, transporters) and pharmacodynamics (receptors and signal transduction) contribute to this variability and to the possibility of adverse drug effects, toxicity, or therapeutic failure of pharmacotherapy. Significant variation in conversion of the prodrug codeine into the active metabolite morphine has been noted. Polymorphisms in CYP2D6 are responsible for the wide variations among different populations.[17]

The clinical use of opioids involves knowledge regarding patient characteristics, their perception, severity and likely duration of pain, lifestyle variables such as smoking habits and alcohol intake, and opioid drug and dosing regimen selection.[17] Other factors affecting pharmacokinetics and pharmacodynamics of opioids include age, body weight, renal failure, hepatic failure, cardiopulmonary bypass, acid-base changes, and hemorrhagic shock.

In adults, advancing age requires lower opioid doses for the treatment of postsurgical pain. Also, in relatively similar patient groups, dosage requirements vary. Aubrun et al.[18] reported that in more than 3000 patients, morphine dosage requirements for postoperative hip replacement therapy varied almost 40-fold. Large

TABLE 11-4 Physicochemical Characteristics and Pharmacokinetics

Opioids	pK_a	Percent Nonionized	Protein Binding (%)	V_c (L/kg)	V_d (L/kg)	Clearance (mL/min/kg)	Elimination Half-Life (hr)	Partition Coefficient (Octanol/Water)
Morphine	7.9	23	35	0.23	2.8	15.5	1.7-3.3	1
Meperidine	8.5	7	70	0.6	2.6	22.7	3-5	21
Methadone	9.3	N/A	85	0.15	3.4	1.6	23	115
Fentanyl	8.4	8.5	84	0.85	4	13	2-4	820
Sufentanil	8	20	93	0.1	2	12	2-3	1750
Alfentanil	6.5	89	92	0.12	0.6	5	1-2	130
Remifentanil	7.26	58	93	0.1-0.2	0.39	41	0.1-0.3	N/A
Butorphanol	8.6	17	80	0.1	5	38.6	2.65	140
Nalbuphine	8.71	N/A	N/A	0.45	4.8	23.1	3.7	N/A

N/A, Not applicable; V_c, volume of distribution central compartment; V_d, volume of distribution.

variabilities have been reported in cancer patients receiving morphine via various routes.[17] Variability is contributed to by inherent pain sensitivity, tolerance, and other factors, including pharmacogenetics influencing the clinical pharmacology of opioids.[19]

Clinical Effects of Opioids

The common clinical effects of opioid agonists are listed in Box 11-2.

Central Nervous System Effects: Analgesia, Sedation, and Euphoria

Opiate analgesia results from actions in the CNS, spinal cord, and peripheral sites (Table 11-5). They are most effective for visceral continuous dull pain; however, at high doses they will relieve any pain. They are less effective against neuropathic pain that requires chronic multimodal therapy.[20] The sedative and euphoric actions contribute to the feeling of well-being in awake patients. The analgesic effects of opioids come from their ability to (1) directly inhibit the ascending transmission of nociception information from the spinal cord dorsal horn and (2) activate pain control pathways that descend from the midbrain, via the rostral ventromedial medulla to the spinal cord dorsal horn.[1] The effect of opioids on electroencephalographic and evoked-potential activity is minimal; therefore neurophysiologic monitoring can be conducted during opioid anesthetic techniques. The opiates can increase intracranial pressure if respiratory depression–induced hypercarbia occurs. They have variable effects on cerebral vascular tone depending on the background anesthetic present. Possible untoward CNS effects when the opioids are used in neurosurgery are easily managed by controlling ventilation and maintaining adequate blood pressures.[21] The comparative potency of the opioid agonists that are used in anesthesia is as follows: sufentanil > fentanyl = remifentanil > alfentanil.

The sedative and euphoric effects of the opiates vary depending on the agent. Patients will exhibit sedation and euphoria that is different with mu versus kappa agonists. Dysphoria can occur and appears more prominent with drugs that have strong kappa receptor effects or when opioids are taken in the absence of pain. Physical and psychological dependence occur with repeat administration as evidenced by physical withdrawal with abstinence and drug-seeking behaviors.[1,22] The opiates are not anesthetics, so awareness under anesthesia is a concern when even high doses of opiates are used.[23,24] Both acute and chronic tolerance occur with the opiates. Cross-tolerance among mu agonists will occur. Usually a decrease in duration is noted first, followed eventually by a decrease in effect. The mechanism of tolerance is complex and does not appear to be due to a change in receptor number. Receptor internalization, activation of *N*-methyl-D-aspartate (NMDA) receptors, second messenger changes, and G-protein uncoupling may all play a role. Hyperalgesia that can result from chronic administration may be related to these same mechanisms.[1,22]

Respiratory Depression

All opiate agonists produce a dose-dependent depression of respirations via effects on mu and delta receptors in the respiratory centers in the brainstem. They reduce the responsiveness of the respiratory centers to increasing carbon dioxide and decreasing oxygen. It requires higher partial pressure of carbon dioxide (pCO_2) levels to maintain normal respiration. Stated in pharmacologic terms, they produce a shift to the right in the CO_2 response curve for respiration. Respiratory rate is affected first, and a classic "narcotized" patient will take slow deep breaths. As doses increase, apnea is produced. Because both analgesia and respiratory depression are mediated via the same receptors, reversal of respiratory depression with antagonists such as naloxone also reverses analgesia. The goal of most clinical anesthetics is to leave some residual analgesia without respiratory depression upon emergence to address postoperative pain.[1]

Miosis

Miosis, or pinpoint pupils, is a prominent action of opioids and is usually present under general anesthesia as a result of the high doses of high potency opiates used. Tolerance does not develop to this effect. It is produced by effects in the pupillary reflex arc. Opiate depression of inhibitory gamma-aminobutyric acid (GABA) interneurons leads to stimulation of the Edinger Westphal nucleus, which sends a parasympathetic signal via the ciliary ganglion to the oculomotor nerve to constrict the pupil.[1] Clinicians note the degree of miosis as somewhat indicative of the presence of opiates.

Antitussive Effects

The opiates produce cough suppression via a depressant effect on the cough center in the medulla. Protective glottal reflexes are not

BOX 11-2

Common Clinical Effects of Opioid Agonists

Acute	Chronic
Analgesia	Tolerance
Respiratory depression	Physical dependence
Sedation	Constipation
Euphoria	
Dysphoria	
Vasodilation	
Bradycardia	
Cough suppression	
Miosis	
Nausea and vomiting	
Skeletal muscle rigidity	
Smooth muscle spasm	
Constipation	
Urinary retention	
Biliary spasm	
Pruritus, rash	
Antishivering (meperidine only)	
Histamine release	
Hormonal effects	

TABLE 11-5 Opioid-Mediated Analgesia in the Central Nervous System

Central Nervous System Location	Opioid Receptor
Supraspinal	
Periaqueductal gray area	Mu = kappa > delta
Raphe nuclei	Mu = kappa > delta
Caudal linear	Kappa
Dorsal	Kappa > mu
Median	Mu > kappa
Magnus	Mu > kappa
Pallidus	Delta
Gigantocellular reticular	Mu = kappa = delta
Spinal	
Spinal cord	Mu = delta = kappa
Dorsal root ganglia	Mu = delta = kappa

affected. Although they all produce this effect, codeine and heroin are especially good suppressants. D-isomers such as dextromethorphan are also effective. Anesthetic use of opiates can assist the patient in tolerating airway devices and ventilators.

Nausea and Vomiting

The emetic effect of the opioids is complex. They elicit nausea and vomiting by stimulating the chemoreceptor trigger zone in the area postrema of the medulla. A vestibular component is also probable because the incidence is much higher in ambulatory patients. Nausea and vomiting are rare in the preoperative area and operating room where patients are recumbent. A separate action with higher repeat doses can have an antiemetic effect by depressing the vomiting center. Clinically, when opiates are used as part of the anesthetic plan, there is an increased incidence of postoperative nausea and vomiting.[25] The effect is less frequent with repeat doses although individual patient response is highly variable. Figure 11-3 depicts the centers in the brain involved with nausea and vomiting and the types of receptors involved.

Cardiac Effects

The usual result of anesthetic use of opioids in healthy patients is bradycardia with little effect on blood pressure. Bradycardia results from medullary vagal stimulation.[1] All opioids induce some degree of dose-dependent peripheral vasodilation. Myocardial contractility, baroreceptor function, and autonomic responsiveness is not affected. Opiate anesthesia is often used in patients with cardiovascular compromise because of this minimal depression. Much of the hypotension produced by morphine, codeine, and meperidine is attributed to histamine release, which is absent with fentanyl, sufentanil, alfentanil, and remifentanil. $Histamine_1$ and $histamine_2$ antagonists, when combined, block the cardiovascular effects of vasodilation, tachycardia, and hypotension that results.[12]

Opioids usually produce an antidiuretic effect. Opioids that are agonists at kappa receptors can cause diuresis. They decrease tone at the bladder detrusor muscle and constrict the urinary sphincter. This results in urinary retention. Urinary retention is a common side effect with intrathecal and epidural opioid administration.

Muscle Rigidity

Opioids have no major effects on nerve conduction at the neuromuscular junction or at the skeletal muscle membrane. A generalized hypertonus of skeletal muscle can be produced by large intravenous doses of most opioid agonists. Although morphine can produce rigidity, the problem is most often associated with fentanyl, alfentanil, sufentanil, and remifentanil. The difficulty is caused in part by loss of chest-wall compliance and by constriction of pharyngeal and laryngeal muscles. It becomes very difficult to ventilate the patient unless the rigidity is reversed. It is commonly referred to as *tight chest* or *truncal rigidity*. This effect most often occurs during anesthesia induction when high doses of potent opiates are administered rapidly. Remifentanil, which is administered by infusion, may be especially prone to producing this effect. Administration of nitrous oxide also increases the frequency.[26] Opioid-induced muscle rigidity is thought to be mediated by central mu receptors interacting with dopamine and GABA pathways. This rigidity is easily reduced or eliminated by the administration of muscle relaxants or naloxone.[27]

Pruritus

Opiates frequently produce a rash, itching, and a feeling of warmth in the "blush" area of the face, upper chest, and arms. This occurs

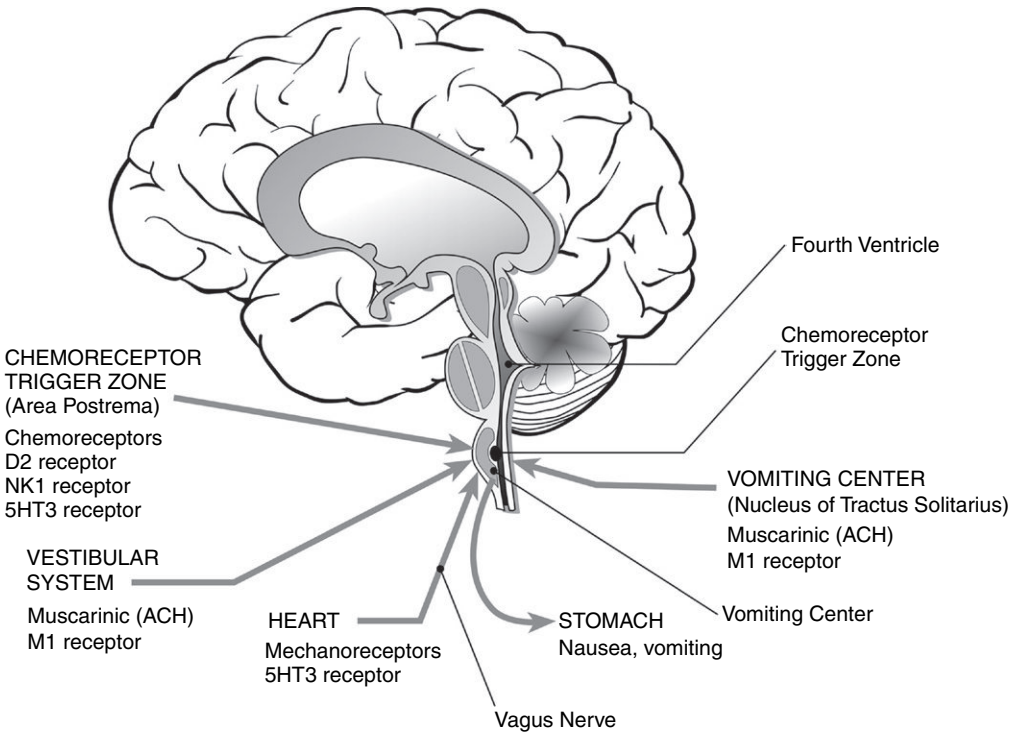

FIGURE **11-3** The vomiting center and chemoreceptor trigger zone are shown. Inputs from sites outside the central nervous system are noted. Type and location of various receptors involved in nausea and vomiting are given. Anti-emetic drugs act on these receptor targets. *D2*, Dopamine receptors; *NK1*, neurokinin; *5HT3*, serotonin; *M1*, muscarinic; *ACH*, acetylcholine.

with both histamine and nonhistamine-releasing drugs and is especially prominent with neuraxial administration. The mechanism appears to be through central mu receptors and not local histamine release.[28] Pruritus can be treated with antagonists such as naloxone or naltrexone; however, they also decrease analgesia. Nalbuphine, droperidol, antihistamines, and ondansetron may also be effective. Many clinical pain services have established protocols to treat this problem.[29,30]

Gastrointestinal Effects

Opioids have multiple effects on the gastrointestinal (GI) function. They decrease gastric motility and intestinal propulsive activity, prolong gastric emptying time, and reduce secretory activity throughout the GI system. This leads to the common problems of opiate-induced constipation and postoperative ileus. Alvimopan (Entereg) and methylnaltrexone (Relistor) are both locally acting opiate receptor antagonists approved for use in treating these GI side effects.[31,32]

Opioids produce a dose-dependent increase in biliary duct pressure and sphincter of Oddi tone via opioid receptor-mediated mechanisms. They also increase urinary sphincter tone. This has led to a few clinical concerns. The use of opiates for the treatment of biliary or renal colic may be compromised by this action. Meperidine, which produces this effect the least among opiate agonists or nonsteroidal antiinflammatory drugs (NSAIDs), is considered the agent of choice for this situation.[33] In anesthesia, the use of opiates during surgery may produce false positive cholangiograms. The clinical relevance of this effect is questionable because the opiates are used routinely without problems.

Endocrine Effects

Opiates reduce the stress response to surgery and have an immunosuppressant effect.[3] Endocrinologic effects of opioids include the release of vasopressin and inhibition of the stress-induced release of corticotropin and gonadotropins from the pituitary. Release of thyrotropin from the adrenohypophysis is also inhibited. Basal metabolic rate and temperature may also be decreased in patients receiving chronic opioids, although animal data indicate that acute administration either systemically or intrathecally can increase temperature. Opioids slightly decrease body temperature by resetting the equilibrium point of temperature regulation in the hypothalamus.[1]

Neuraxial Effects

The epidural and intrathecal routes have become common for the administration of pain medication. Opioids delivered by epidural or subarachnoid routes behave differently in onset, duration, and side effects than the same drugs given systemically. Pain that is unresponsive to systemic opioids may respond to the same drugs given centrally, reducing some side effects while increasing the incidence of others. Systemic opioids suppress nociception in lamina II and V cells of the dorsal horn of the spinal cord, leaving lamina IV and VI cells, which mediate nonnociceptive information, relatively unaffected.[34]

Spinal administration of opioids is a selective and potent means of producing analgesia. Intrathecal administration allows injection of the opioids directly into the cerebrospinal fluid (CSF), a more efficient method of delivering the drug to the spinal cord opiate receptors. The analgesic response is the result of activity at spinal opiate receptors, especially kappa receptors in the substantia gelatinosa, lamina II of the dorsal horn.[34] Opioids can be given with local anesthetics or other adjuncts intraoperatively at the initiation of spinal anesthesia or postoperatively for pain control.[35] Side effects with spinal administration are similar to those described previously with systemic administration, except that pruritus and urinary retention occur with much greater frequency. Less lipid-soluble agents such as morphine and hydromorphone produce a delayed ventilatory depression, the result of migration of opioid via the CSF to the midbrain vestibular centers.

Respiratory depression is the most common serious complication associated with intrathecally and epidurally administered opioids. Two different levels of respiratory depression can occur after neuraxial morphine administration. An early phase observed soon after administration reflects rapid systemic absorption and is similar to parenteral dosing. A later, more insidious depression that occurs over a period of 8 to 12 hours has been related to rostral flow of CSF and delivery of morphine to the brainstem respiratory center.[36] Awareness of delayed respiratory depression has resulted in increased monitoring of patients and dose reductions, thereby greatly reducing the incidence of serious respiratory depression to that seen with patient-controlled analgesia (PCA) opioids.

Generalized pruritus has been observed with neuraxial morphine and to a lesser extent with other opioids. Mild itching, usually involving the face or chest, is common; however, the intensity of itching can become so annoying that it interferes with sleep. Pruritus is commonly seen with opioids such as fentanyl and sufentanil that do not release histamine. Pruritus can be treated with antihistamines or with opiate receptor antagonists. The incidence of postoperative nausea and vomiting increases for patients treated with neuraxial opioids. Nausea may result either from the rostral spread of the drug in the spinal fluid to the brainstem or vascular uptake and delivery to the chemoreceptor trigger zone in the area postrema of the medulla.

Urinary retention after spinal opioid analgesia has been related to inhibition of sacral parasympathetic outflow, which results in relaxation of the bladder detrusor muscle and an inability to relax the sphincter.[34]

Opioids with a higher lipid solubility (see Table 11-4) tend to be rapidly absorbed into the spinal tissues after central administration, resulting in a faster onset of action. However, higher lipid solubility is associated with a small area of distribution of the drug along the length of the spinal cord and therefore a more limited area of analgesia.[4] Higher lipid solubility is also associated with faster clearance of the drug out of the epidural and intrathecal space, resulting in a shorter duration of action and higher blood concentrations of the opioid.[34,36] Spinal opioids are advantageous in selective analgesia, which occurs in the absence of motor and sympathetic blockade.

Epidural anesthesia and analgesia have been successfully used in obstetric patients and surgical patients. Epidural doses of opioids, however, are much higher than doses of opioids for intrathecal use. Small portions of epidural opioids cross the dura, enter the CSF, and penetrate spinal tissue in amounts proportional to their lipid solubility. The remaining drug is absorbed by the vasculature, producing plasma levels comparable to those after intramuscular injections and providing supraspinal analgesia.[36] Neuraxial administration of opioids is a selective and potent means of producing analgesia in many surgical and obstetric procedures.[37] Table 11-6 gives neuraxial opioid dosages.[34,36]

Opioid Techniques and Delivery

In clinical practice, opioids are used to relieve pain during monitored anesthesia care and regional anesthesia and as a component of balanced anesthesia, as well as a primary component of general anesthesia. The inclusion of opioids reduces pain and anxiety, decreases somatic and autonomic responses to airway

TABLE 11-6 Doses of Neuraxial Opioids*

Opioid	Single Dose	Infusion Rate
Epidural		
Morphine	2-5 mg	0.1-1 mg/hr
Meperidine	25-50 mg	5-20 mg/hr
Methadone	5 mg	0.3-0.5 mg/hr
Fentanyl	50-100 mcg	25-100 mcg/hr
Sufentanil	25-50 mcg	10-50 mcg/hr
Butorphanol	2-4 mg	0.2-0.4 mg/hr
Subarachnoid		
Morphine	0.25-0.3 mg	
Meperidine	10 mg	
Fentanyl	10-20 mcg	
Sufentanil	5-10 mcg	

*Doses adjusted for age and level of regional injection.

manipulation, improves hemodynamic stability, lowers requirements for inhaled anesthetic agents, and provides postoperative analgesia.[38]

The most common method of administering opioids in the practice of anesthesia is intermittent bolus injection, which although effective for many procedures, produces wide swings in drug plasma concentration. Intermittent periods of deep and light anesthesia are produced. Continuous opioid infusion results in plasma concentration that can be maintained more accurately and consistently. Continuous infusion of opioids is associated with hemodynamic stability, reduces the total necessary dose of opioids, and decreases the need for opioid reversal agents.

Continuous intravenous administration involves the infusion of a loading dose that "fills" the volume of distribution, followed by continuous drug replacement that keeps the volume of distribution "filled" as the drug is eliminated.[39]

$$\text{Loading dose (mcg/kg)} = V_d \text{ (mL/kg)} \times C_p \text{ (mcg/mL)}$$

$$\text{Maintenance infusion (mcg/kg/min)} = \text{Cl (mL/kg/min)}$$

where V_d is volume of distribution, C_p is plasma concentration, and Cl is drug clearance. See Table 11-4 for the V_d and Cl of various opioids.

The rate of continuous infusion does not remain constant, but rather is adjusted to meet the patient's needs and to control varying surgical stimuli. The volume of distribution is decreased for patients with hypovolemia and trauma and for geriatric patients. Factors such as enzyme induction, hepatic failure, and adjunctive drug use are also considered. Table 11-7 provides dose ranges for continuous infusions.

Continuous intravenous infusion can be administered by gravity flow with a manual control device (e.g., Buretrol), an infusion pump, or a syringe pump. Syringe pumps are advantageous because they are programmed to administer drug in units of micrograms per kilogram per minute. Some advantages of continuous infusion techniques are listed in Box 11-3.

Nonparenteral routes of opioid delivery are also used. Fentanyl is the prototypic opioid for transdermal application. Transdermal administration of fentanyl does not require cooperation from the patient; also, first-phase hepatic metabolism is not a factor, and the route does not produce discomfort. Currently available formulations permit delivery of 25 to 100 mcg per hour for 24 to 72

TABLE 11-7 Infusion Rates*

Opioid	Induction (mcg/kg)	Maintenance (mcg/kg/min)
Fentanyl	5-10	0.01-0.05
Sufentanil	1-30	0.005-0.015
Alfentanil	8-100	0.5-3
Remifentanil	0.5-1	0.05-2

*Doses will vary depending on coadministered drugs, patient characteristics, and surgical procedure.

BOX 11-3
Advantages of Continuous Opioid Infusion

- Hemodynamic stability
- Decreased side effects
- Reduced need for opioid-reversal agents
- Reduced use of vasopressor drugs
- Suppression of cortisol and vasopressin response to cardiopulmonary bypass: stress-free anesthesia
- Reduced total dosage of opioids
- Decreased recovery time

hours. The transdermal fentanyl patch provides a relatively constant plasma concentration for 72 hours. It is not currently recommended for use in managing postoperative pain.

Oral transmucosal fentanyl citrate is occasionally used for providing analgesia in children. Its primary use is for treating breakthrough pain in cancer patients.[40] Fentanyl is dissolved in a sucrose solution and shaped into a lozenge. The transmucosal route is effective, owing to the characteristics of the oral mucosa. The oral mucosa is thinner than the skin and is supplied by numerous blood and lymphatic vessels. The opioid administered transmucosally is also absorbed directly into the systemic circulation without passing through the liver. A high incidence of pruritus is a problematic side effect with transmucosal administration.

The Food and Drug Administration has approved a nasal spray formulation of fentanyl (Lazanda) for management of breakthrough pain in adult cancer patients who are already receiving and are tolerant to opioid therapy. Nasal administration of sufentanil preoperatively in the pediatric patient has also been studied. The children remained calm, and some experienced somewhat decreased ventilatory compliance. Recovery room time was not increased, and the highest incidence of nausea and vomiting occurred in the group that received the highest dose of sufentanil. Nasal butorphanol is currently available and is widely used in the management of migraine headaches. Table 11-8 compares dosages for various routes of opioid administration.[41]

INDIVIDUAL OPIOIDS

Agonists

Naturally Occurring Opioids

Morphine. Morphine, the prototype for opioid agonists, is the most abundant alkaloid in raw opium. The primary therapeutic use of morphine is the abatement of moderate to severe pain. Morphine can be administered via the intramuscular, intravenous, subcutaneous, oral, intrathecal, and epidural routes. Effects of intravenous morphine on the time course

TABLE 11-8 Opioid Dose Comparisons

Opioid	Route	Onset	Peak	Duration of Action	Half-Life
Morphine	PO	60 min	30-60 min	4-5 hr	Neonates 4.5-13 hr
	IM	30-60 min	30-60 min	4-5 hr	Adults 3-5 hr
	IV	20 min	30-60 min	4-5 hr	
	Epidural	60-90 min	30-60 min	8-24 hr	
Codeine	PO	30-60 min	60-90 min	4-6 hr	2.5-3.5 hr
	IM	10-30 min	30-60 min	4-6 hr	2.5-3.5 hr
Hydromorphone	IV	15-30 min	30-90 min	4-5 hr	1-3 hr
Oxycodone	PO	10-15 min	30-60 min	4-5 hr	3.2-4.5 hr
Methadone	PO	30-60 min	30-60 min	6-8 hr	15-30 hr
	IV	5-10 min	15-20 min	4-6 hr	15-30 hr
Meperidine	PO	10-15 min	30-60 min	2-4 hr	2.5-4 hr
	IM	10-15 min	30-60 min	2-4 hr	2.5-4 hr
	IV	5 min	30-60 min	2-4 hr	2.5-4 hr
Alfentanil	IV	Immediate	Immediate		1.5 hr
Fentanyl	Transmucosal	5-15 min	20-30 min	Related to blood levels	6.6 hr
	IM	7-15 min	20-30 min	1-2 hr	2-4 hr
	IV	2-5 min	20-30 min	0.5-1 hr	2-4 hr
	Epidural	20-30 min		2-3 hr	2-4 hr
Remifentanil	IV	1 min	1 min	5-10 min	9 min
Sufentanil	IV	1-3 min		Dose dependent	6 hr
Tramadol	PO	60 min	120 min	9 hr	2-3 hr
Buprenorphine	IM	10-30 min	60 min	6 hr	2-3 hr
	IV	10-30 min	60 min	6 hr	2.5-4 hr
Butorphanol	IM	10-15 min	30-60 min	3-4 hr	2.5-4 hr
	IV	Immediate	30-60 min	3-4 hr	2.6-2.8 hr
Dezocine	IM	15-30 min	60 min	4-6 hr	2.6-2.8 hr
	IV	15-30 min	60 min	4-6 hr	3.5-5 hr
Nalbuphine	IM		30 min		3.5-5 hr
	IV		1-3 min		2-3 hr
Pentazocine	PO	15-30 min		4-5 hr	2-3 hr
	IM	15-30 min		2-3 hr	2-3 hr
	IV	2-3 min		2-3 hr	Neonates 1.2-3 hr
Naloxone	IM	5 min	5-15 min	20-60 min	Adults 1-1.5 hr
	IV	2 min	5-15 min	20-60 min	10.8 hr
Nalmefene	IM	5-15 min	120 min	8 hr	10.8 hr
	IV	2 min	2-3 min	8 hr	6-10 hr
Naltrexone	PO	45-60 min	60 min	24-72 hr	

IM, Intramuscularly; *IV*, intravenously; *PO*, by mouth.

of sedation and analgesia occur with sedation first, followed by analgesia.[42] Morphine-induced sedation, therefore, should not be considered as an indicator of appropriate analgesia. When given intrathecally, morphine has the longest duration of action of the specific opioids. Morphine is among the least lipophilic of the opioids, resulting in slow penetration of biologic membranes, less accumulation in lipid membranes or fatty tissues, and slower onset.

Morphine undergoes phase 2 glucuronide conjugation in the liver at both the 3 position (which produces morphine-3-glucuronide, M3G) and the 6 position (which produces morphine-6-glucuronide, M6G), in a 2:1 ratio.[43] As a result of the active metabolite, M6G, morphine appears to produce a more prolonged effect, often excessive sedation, in the patient with renal failure. Within the CNS, M6G metabolite is more potent than the parent drug, whereas M3G metabolite is inactive.[43,44] The greater hydrophilicity of M6G than the parent drug normally impedes its passage into the CNS. However, after chronic administration or in patients with renal failure, M6G at a high blood level can enter the CNS.

Morphine produces a nonimmunologic release of histamine from tissue mast cells, resulting in local itching, redness, or hives near the site of intravenous injection or generalized flushing. When sufficient histamine is released, the patient may exhibit signs of decreased systemic vascular resistance, hypotension, and tachycardia. Localized histamine release after a morphine injection is not uncommon. Morphine is primarily used for preoperative or postoperative pain relief. The delayed onset and peak effects and large patient variability make it less useful for intraoperative use than fentanyl and its analogs.

Codeine. Considered a weak opioid, codeine is generally not used for treatment of severe pain. Approximately 10% of the administered dose of codeine is O-demethylated to morphine, which accounts for most of its analgesic activity.[37] It has good antitussive activity, but on a weight basis, codeine is a less potent antitussive than morphine. Combinations of codeine with acetaminophen remain very popular as prescribed analgesics.

Semisynthetic Opioids

Hydromorphone. Derived from morphine in the 1920s, hydromorphone has a pharmacokinetic profile similar to that of morphine but it is more potent. Hydromorphone is absorbed from the oral, rectal, and parenteral sites. Because of its lipid solubility, it is sometimes used instead of morphine for epidural or spinal administration when a wide area of analgesia is needed.[45] Studies performed on parenteral hydromorphone relative to morphine tend to demonstrate similar analgesia and side-effect profiles. Because of the lack of any known active metabolites, it is often recommended for patients with renal failure.[1] It is available in high potency and sustained release preparations.

Synthetic Opioids

Methadone. Introduced in the 1940s, methadone is used primarily for relief of chronic pain, treatment of opioid abstinence syndromes, and treatment of heroin addiction. Compared to other common opioids, it is well absorbed orally and produces less euphoria. Supplied as a racemic mixture of two optical isomers, most of methadone's activity comes from the *l*-isomer. Unlike most opioids, it has a long half-life, allowing less frequent dosing. It has a prolonged effect in part due to extensive protein binding (90%) with slow release and a lower intrinsic ability of the liver to metabolize it. It also has the advantage of a high bioavailability and no active metabolites. Disadvantages include accumulation and a longer time to reach steady state than other opioids.[46]

Meperidine. Meperidine is a synthetic mu-receptor agonist. It is structurally similar to atropine and has an atropine-like antispasmodic effect. After demethylation in the liver, meperidine is partially metabolized to normeperidine, which is half as analgesic as meperidine but lowers the seizure threshold and induces CNS excitability. Normeperidine's elimination half-life is significantly longer than that of meperidine. With accumulation of normeperidine, subjects may experience a CNS excitation characterized by tremors, muscle twitches, and seizures. Because of accumulation of normeperidine, limitations on its use should be considered in patients with renal failure and for chronic use in cancer patients who may require high doses. There is a significant drug interaction that can occur between meperidine and the first-generation monoamine oxidase (MAO)-inhibiting drugs isocarboxazid (Marplan, others), phenelzine (Nardil, others), and tranylcypromine (Parnate, others). Hyperthermia, seizures, and death have been reported.[47,48]

Meperidine is effective in reducing shivering from diverse causes, including general and epidural anesthesia.[49] This appears to result from kappa receptor stimulation. It reduces or eliminates visible shivering, as well as the accompanying increase in oxygen consumption.[22] Anesthetic uses of meperidine have declined in recent years due to the availability of safer, more convenient techniques.

Alfentanil. After bolus injection, alfentanil has a more rapid onset of action and shorter duration than fentanyl, even though it is less lipid soluble. The high nonionized fraction (90%) of alfentanil at physiologic pH and its small volume of distribution increase the amount of drug available for binding in the brain. Although alfentanil is effective epidurally, the duration of analgesia is short, and for this reason, it has never achieved popularity. Alfentanil is metabolized in the liver by oxidative *N*-dealkylation and *O*-demethylation in the cytochrome P-450 system, and the inactive metabolites are excreted in the urine. Alfentanil has great patient-to-patient variability, as seen in the original studies, in which a high coefficient of variation was reported. Erythromycin has been shown to prolong the metabolism of alfentanil and interact with alfentanil to produce clinical symptoms of prolonged respiratory depression and sedation. Its popularity in current practice is limited.

Fentanyl. Fentanyl is the most widely used opioid analgesic in anesthesia. A single administered dose of fentanyl has a short duration of action (approximately 20 to 40 minutes). It produces a profound dose-dependent analgesia, ventilatory depression, and sedation. The action of a single dose of fentanyl is terminated by redistribution. The high lipid solubility of fentanyl allows for rapid tissue uptake.[12] Fentanyl and its derivatives all undergo significant first-pass uptake in the lungs with temporary accumulation before release. When fentanyl is given in multiple doses or as a continuous infusion, the termination of action reflects elimination but not redistribution. Clearance of fentanyl is dependent on hepatic blood flow. Fentanyl is metabolized by *N*-dealkylation and hydroxylation to inactive metabolites that are eliminated in urine and bile. Fentanyl elimination is prolonged in the elderly and the neonate.

Initially used intravenously during surgery, fentanyl has many other uses. It is administered for intrathecal, epidural, and postoperative patient-controlled analgesia (PCA) intravenous use. Fentanyl transdermal patches deliver 75 to 100 mcg/hr, resulting in peak plasma concentrations in approximately 18 hours because a subcutaneous depot of drug must be saturated before the drug is consistently absorbed into the bloodstream.[12] The dose remains stable during the presence of the patch. After removal, the decline in blood concentration follows an apparent 17-hour half-life; the true elimination half-life of fentanyl remains at approximately 3 hours, but continued absorption from the subcutaneous depot during elimination makes it appear longer.

Transmucosal fentanyl (Fentanyl Oralet) was initially developed in the form of a lollipop as an adjunct to pediatric anesthesia. A similar fentanyl product is available in higher strengths and is used for relief of breakthrough cancer pain. The pharmacokinetics of this form are dose related, with an apparent elimination half-life of approximately 6 hours. Not all opioids are absorbed sublingually. Hydromorphone, oxycodone, and heroin are minimally absorbed, whereas absorption for morphine is 18%; fentanyl, 51%; and methadone, 34%.[50]

Remifentanil. Remifentanil use in anesthesia has increased tremendously in recent years as new applications are being discovered for its unique profile.[51,52] Its rapid onset and ultra-short duration, titratability, and simple metabolism make it very convenient for many modern clinical perioperative situations. Remifentanil is a moderately lipophilic, piperidine-derived opioid with an ester link. The addition of the ester group allows the drug to be easily and rapidly metabolized by blood and tissue esterases. Kinetic studies indicate that the drug has a small volume of distribution (V_d 0.39 ± 0.25) and an elimination half-life of 8 to 20 minutes. It is metabolized by hydrolysis catalyzed by general esterase enzymes to a less active compound. It is not dependent on cholinesterase enzyme for metabolism and therefore is not influenced by quantitative or qualitative changes in cholinesterase. Succinylcholine metabolism does not influence remifentanil breakdown.

Because of the potential for respiratory depression and muscle rigidity, bolus dosing in the preoperative or postoperative care unit is not recommended. Due to its unique metabolic pathway, remifentanil has a short duration of action, a precise and rapid titratable effect because of rapid onset, and noncumulative effects and results in rapid recovery after discontinuation of its administration by infusion. However, because of the rapidity of emergence from remifentanil anesthesia, it is important to develop and start a plan for alternative analgesic therapy in the postoperative period.[53]

The commercial preparation of remifentanil is a water-soluble, lyophilized powder that contains a free base and glycine as a vehicle

to buffer the solution. Because of potential glycine neurotoxicity, remifentanil should not be administered epidurally or intrathecally.[1]

Sufentanil. Sufentanil is the most potent of the phenylpiperidines and is used for situations in which profound analgesia is required such as in cardiac or other major surgical procedures. The patients are usually in-hospital patients requiring significant analgesia and postoperative care. Sufentanil is a mu agonist that produces effective analgesia via both the intravenous and intrathecal routes. It has a high lipophilicity and potency and a shorter elimination half-life than fentanyl. Hepatic clearance of sufentanil approaches liver blood flow. Sufentanil metabolism involves *O*-demethylation and *N*-dealkylation, with minimal amounts being excreted unchanged in the urine.

The effects of age on the distribution and elimination of sufentanil are reflected in a decrease in the initial volume of distribution for the elderly. The reduced volume of distribution of sufentanil in elderly patients is associated with increased respiratory depression.

Tramadol. Tramadol is a synthetic codeine analog that is a weak mu opioid receptor agonist, with analgesic effects produced by inhibition of norepinephrine and serotonin neuronal reuptake as well as presynaptic stimulation of 5-hydroxytryptamine release.[1] Tramadol is a racemic mixture; the (+) enantiomer binds to the mu receptor and inhibits serotonin uptake, whereas the (−) enantiomer inhibits norepinephrine uptake and stimulates α_2-adrenergic receptors. It has an elimination half-life of 5 to 6 hours and is an effective analgesic for the treatment of mild to moderate pain. Tramadol can cause seizures and possibly exacerbate them in patients with predisposing factors. Tramadol-induced analgesia is not entirely reversed by naloxone, but tramadol respiratory depression can be reversed. In overdose situations, most of the toxicity is related to the amine uptake inhibition rather than to opioid effects.[1]

Partial Agonists and Agonists-Antagonists

Buprenorphine. Buprenorphine, a synthetic derivative, is a potent partial agonist opioid that binds mainly to the mu receptors.[54] Its slow dissociation from the receptor is a result of its long duration of action (approximately 8 hours). Its high affinity for the mu receptor accounts for the reduced ability of naloxone to reverse the effects of buprenorphine. Clinically significant respiratory depression can occur with therapeutic doses. Buprenorphine exhibits a ceiling effect in which an increase in the dose does not increase respiratory depression; this is believed to result from the fact that the drug's antagonistic effects become more apparent at higher doses. It also has minimal effect on GI motility and smooth muscle sphincter tone. A transdermal system of buprenorphine was developed for treatment of moderate to severe cancer pain.[55] Administered transdermally, it provides analgesia and has a low incidence of adverse events.

Butorphanol. Butorphanol, a highly lipophilic opioid, acts as an agonist at the kappa receptors and as a weak antagonist at mu receptors. It is more potent than morphine in the production of analgesia. It produces respiratory depression, but its ceiling effect is below that of mu agonists. Intranasal butorphanol is used for the treatment of migraine headaches and postoperative pain. Butorphanol has also been studied for epidural use, although it tends to produce significant sedation. It has been shown to be effective in the treatment of postoperative shivering, but the mechanism of this effect is unknown.

Nalbuphine. Nalbuphine has the ability to reverse respiratory depression that results from opioid use and to maintain analgesia. Nalbuphine acts as both an agonist and an antagonist at the opioid receptors. Nalbuphine's analgesic response is equal to that of morphine. Nalbuphine provides an agonist effect at the kappa receptors and an antagonist effect at the mu receptors. A ceiling effect for respiratory depression and difficulty with reversal with naloxone has been demonstrated with both nalbuphine and butorphanol.[56] Nalbuphine has been used to antagonize pruritus induced by epidural and intrathecal morphine. Nalbuphine effectively antagonizes fentanyl-induced respiratory depression, maintains analgesia, and does not produce adverse circulatory changes.

Antagonists

Naloxone. Naloxone, an oxymorphone derivative, is a pure opioid antagonist. Naloxone blocks the opioid receptor sites and reverses respiratory depression and opioid analgesia. The reversal of respiratory depression and analgesia occurs as a result of competitive antagonism at the mu, kappa, and delta receptors. The duration of action of naloxone is less than that of most opioid agonists, allowing the return of respiratory depression in some patients treated with naloxone. Naloxone is effective only when it is administered intravenously or intramuscularly.

Naloxone may antagonize intrinsic analgesic systems, as evidenced by its ability to blunt the placebo effect and inhibit the analgesia of electroacupuncture. Studies have demonstrated that naloxone's effect on reversing the effects of morphine is in fact titratable. Administration of low doses of naloxone can reverse the side effects of epidural opioids while preserving some of the analgesic effects.

The effects of naloxone use range from discomfort to pulmonary edema to sudden death. Pulmonary edema after naloxone administration has been observed in patients with a documented history of cardiovascular disease. Prough et al.[57] reported two cases of acute onset of pulmonary edema in young male patients who received either 100 or 200 mcg of naloxone. The report discusses the ability of naloxone to inhibit endogenous pain suppression pathways and to allow unopposed noradrenergic transmission from medullary centers that can produce neurogenic pulmonary edema. Neurogenic pulmonary edema results from an increase in catecholamine levels in healthy patients, as well as in patients with a history of cardiovascular disease. Cautious titration of naloxone is of paramount importance. Andree[58] reported two cases of sudden death after naloxone administration. This study suggests that naloxone produces increases in blood catecholamine levels that predispose patients to ventricular fibrillation and subsequent cardiac arrest.

Nalmefene. Structurally similar to naloxone, nalmefene (Revex) is a long-acting parenteral opioid antagonist. It has an elimination half-life of approximately 10 hours (compared with naloxone's half-life of 1 hour) and duration of action of 8 hours when it is given in the usual doses.[59] The clinical effects of nalmefene are similar to those of naloxone.

Reversal of postoperative respiratory depression is accomplished with the administration of nalmefene 0.1 to 0.5 mcg/kg titrated at 2- to 5-minute intervals. In acute opioid overdose, it is recommended that 0.5 to 1.6 mcg be given intravenously. Administration of doses higher than 1.6 mcg does not elicit additional effects and is not recommended. As with all antagonists, slow titration of small doses may minimize side effects. As with naloxone, nalmefene should not be administered to opioid-dependent patients.[60]

Naltrexone. As a synthetic congener of oxymorphone, naltrexone has antagonist and receptor-binding properties similar to those of naloxone but higher oral efficacy and longer duration of action. Its activity is the result of both the parent drug and its 6-beta metabolite. The parent and metabolite have half-lives of 6 and 13 hours, respectively. Naltrexone has a duration of action of approximately 24 hours. An extended release formulation is routinely used in alcohol withdrawal programs.[61]

Naltrexone is administered to patients addicted to opioids so that the euphoric effects of opioids can be prevented. When doses greater than 100 mg are administered to the opioid-addicted patient, plasma concentrations are reached within 2 hours, and the agent's half-life is approximately 10 hours. Naltrexone produces an active metabolite with a half-life even longer than that of naltrexone.[1]

Non-Narcotic Analgesics

The nonsteroidal antiinflammatory drugs (NSAIDs) and acetaminophen (paracetamol outside the United States) are primarily used in anesthesia as postoperative pain medications. Aspirin is used as an antiplatelet drug for cardiac patients and is rarely given as an analgesic. They are effective for mild to moderate pain. Acetaminophen, ibuprofen, and ketorolac are available as intravenous preparations and are used for select intraoperative and postoperative applications. The mechanism of both the NSAIDs and acetaminophen is inhibition of the cyclooxygenase enzyme, which prevents the production of prostaglandins and thromboxanes. Some important differences exist. The NSAIDs are analgesic, antipyretic, and antiinflammatory, whereas acetaminophen is analgesic and antipyretic but only minimally antiinflammatory. In anesthetic uses more than one or two doses are rarely given so many of the adverse effects of chronic administration are not a concern.[62,63]

Ketorolac. Ketorolac (Toradol) is an intravenous NSAID that has been used for many years in anesthesia. It is very effective for mild to moderate pain. It can be administered via both intramuscular and intravenous routes. The primary advantages over the opioids are the very low incidence of nausea and vomiting and lack of respiratory depression. It is frequently given near the end of surgical procedures such as laparoscopy to provide postoperative analgesia. It is also used for minor procedures where avoiding opioids is desirable. The usual dose is 30 to 60 mg either intramuscularly (IM) or intravenously (IV). The onset is 30 minutes and the duration of action is 4 to 6 hours.[62] It should not be used in atopic or asthmatic patients, in the elderly, or in patients with renal or GI dysfunction or bleeding disorders. Some clinicians feel that bone healing is delayed by the NSAIDs and do not use them in orthopedic procedures.[64] Bleeding may also be a problem in intracranial surgery.[65]

Ibuprofen. An intravenous formulation of ibuprofen (Caldolor) is available as an analgesic and antipyretic. Its clinical effects are similar to ketorolac. The usual dose is 400 to 800 mg IV over 30 minutes. Onset is 30 minutes and duration is 4 to 6 hours.[66,67] Contraindications and precautions are similar to ketorolac.

Acetaminophen. Acetaminophen (Ofirmev) is available as an IV analgesic and antipyretic drug for use in both adults and children over 2 years old. It also has a significant opiate sparing effect. Acetaminophen does not exhibit the significant gastrointestinal and cardiovascular side effects associated with nonsteroidal antiinflammatory drugs. The dose in patients over 13 years old is 1000 mg infused over 15 minutes. The dose in children is 15 mg/kg. Onset is approximately 10 minutes with a peak effect in 1 hour. The duration of action is 4 to 6 hours.[68,69] Side effects are rare. Hepatotoxicity is a concern with acetaminophen but not expected with doses less than 4000 mg/day.

SUMMARY

Opioids are a group of drugs that bind to receptor sites in the CNS, supraspinal and spinal, and at peripheral sites, producing morphine-like effects. Opioid analgesia results from the inhibition of nociceptive reflexes and the release of neurotransmitters. Because of their multiplicity of sites and mechanisms of action, opioids are a uniquely valued means for analgesia and anesthesia. Opioids are used for preoperative medication, as induction agents, as maintenance anesthetics, and for treatment of postoperative pain. The newer methods of opioid delivery have been growing in popularity. Opioids provide the anesthesia practitioner with a multitude of delivery modalities.

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CHAPTER 12

Neuromuscular Blocking Agents, Reversal Agents, and Their Monitoring

◆ *John J. Nagelhout*

The neuromuscular blocking drugs (NMBDs) are an integral part of anesthesia practice. They allow for easy airway and operative field manipulation, which is essential in today's sophisticated and complex surgical environment. As with many other types of anesthetic drug components, no single agent or agents are ideal in all situations. For example, the development of a rapid onset, ultrashort-acting nondepolarizing replacement for succinylcholine has eluded researchers for decades. In addition, reversal of the NMBDs is too complex, and residual paralysis in the postanesthesia care unit (PACU) remains a problem. Despite these challenges, our knowledge regarding the safe use of these drugs in anesthesia continually evolves. This chapter updates the clinician with the latest information and concepts on the use of these drugs in modern clinical practice.

HISTORY

In the nineteenth century, Claude Bernard, a famous French physiologist and philosopher, carried out experiments with curare, then in use by the Amazonian Indians of South America.[1] He noted that animals the Indians hunted for food were paralyzed by arrows poisoned with curare and subsequently died of asphyxiation.[2] Bernard's experiments with the poison the Indians tipped their arrows with formed the basis for our ideas of the neuromuscular junction, neuromuscular transmission, and neuromuscular pharmacology.[3] Indeed, curare had been used since 1857 as an anticonvulsant treatment in tetany and other types of spastic disorders.[4]

Laewen also described the use of curare in anesthetized humans in a German report in 1912.[3] For readers who are interested in historical aspects of this topic, a fascinating and more complete report of the earliest work of these and other researchers, beginning as early as the year 1548, is available in an outstanding review article by Bisset.[5]

In 1936 Dale and colleagues found that acetylcholine (ACh) was the chemical neurotransmitter that activated the postjunctional muscle membrane receptors after excitation of the nerve terminal.[5] This finding contradicted the once widely held theory that direct electrical transmission from the nerve to the muscle occurs.[6] This discovery provided the impetus for further research concerning pharmacologic agents that could either enhance the action of ACh or prevent it, thereby causing a temporary and reversible state of therapeutic paralysis.

Griffith and Johnson[7] of Montreal, Canada, are universally acknowledged as the persons responsible for the introduction of neuromuscular blockers into anesthetic practice. Their groundbreaking report laid the foundations for other studies that followed. Within a year of their study, Cullen reported on the use of curare in 131 general anesthetic procedures. His only report of an adverse reaction dealt with a 44-year-old woman who experienced "complete paralysis and severe salivation," accompanied by muscular twitching.[4]

Despite initial successes with the neuromuscular blockers, an early study nearly doomed their use before they became widely accepted. Henry Beecher and Donald Todd, two physicians in the anesthesia department of Harvard Medical School, reviewed 599,548 anesthetic procedures administered at 10 institutions between 1948 and 1952. As part of this review, they examined the death rate in patients receiving *curares* (the term by which they described any neuromuscular blocking agent, including tubocurarine chloride, decamethonium bromide, succinylcholine chloride, gallamine triethiodide, and dimethyl-tubocurarine [*d*-tubocurarine] iodide). Beecher and Todd[8] found that the overall death rate for persons treated with neuromuscular blockers was 1:370, compared with a death rate of 1:2100 in patients who did not receive these agents.

After reviewing the conditions of the patients; the educational background and training of the practitioners who administered the anesthetic (e.g., physician, nurse anesthetist, or physician-in-training); the size of the institution; the sexes, races, and ages of the patients; and numerous other combinations of these factors, the investigators reached the following conclusions:

> *[I]n our judgment the situation is one where neither experience of individual nor experience of institution appears to protect. This adds up to evidence that neither mistakes nor preventable error of any kind are involved in the main, but rather the inherent toxicity of the "curares" themselves.*[8]

In the litigious environment of modern anesthetic practice, such a statement may have ended the administration of these agents. It would certainly have slowed their development. The positive attributes of the agents, however, were discussed later in the same paper, as Beecher and Todd added this caveat:

> *Having presented the foregoing evidence and comment, one can ask what, then, is to be done about these agents? Are they to be banned as a practical solution of the problem? We believe not. These data strongly suggest that great caution in the use of muscle relaxants should be exercised, that the agents available at present be considered as on trial, and that they be employed only when there are clear advantages to be gained by their use, that they not be employed for trivial purposes or as a corrective for generally inadequate anesthesia.*[8]

Beecher and Todd's admonition still echoes through the halls of anesthetic practice today. Although the safety and efficacy of neuromuscular blocking agents have markedly increased, the sage advice is still germane for the practitioner: Neuromuscular blocking agents, like all anesthetic agents, are best used where and when they are indicated. Nevertheless, as one leg of the anesthetic objectives that includes anesthesia, analgesia, amnesia, and muscle relaxation, neuromuscular blockade has become an integral part of most modern anesthetic techniques. A broad spectrum of these agents now exists, although no single agent has all of what would be the ideal properties. Their individual pharmacokinetic and pharmacodynamic attributes enable the anesthetist to tailor

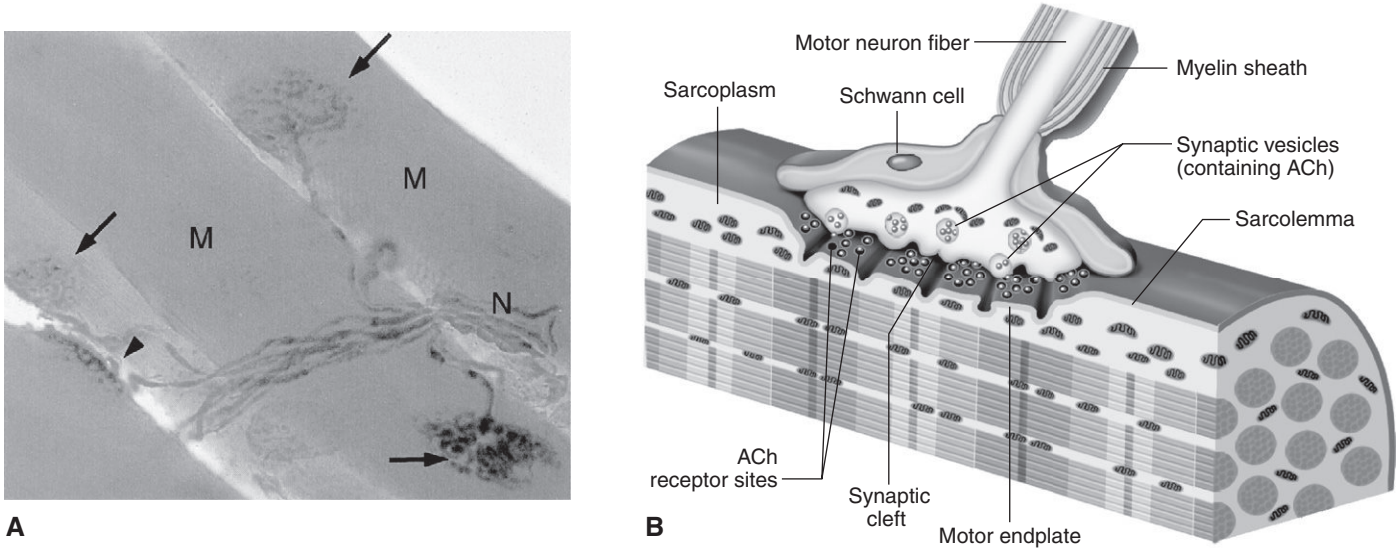


FIGURE **12-1** Neuromuscular junction (NMJ). **A,** Micrograph showing four neuromuscular junctions (NMJs). Three are surface views (*arrows*) and one is a side view (*arrowhead*). *N*, Nerve fibers; M, muscle fibers. **B,** This sketch shows a side view of the NMJ. Note how the distal end of a motor neuron fiber forms a synapse, or "chemical junction," with an adjacent muscle fiber. Neurotransmitter molecules (specifically, acetylcholine, or ACh) are released from the neuron's synaptic vesicles and diffuse across the synaptic cleft. There they stimulate receptors in the motor endplate region of the sarcolemma. (From Patton KT, Thibodeau GA. *Anatomy & Physiology*. 8th ed. St Louis: Mosby; 2013:353.)

the use of the agent to the physiologic needs of the patient and the requirements of the surgeon.

MONITORING OF NEUROMUSCULAR BLOCKADE

Monitoring of neuromuscular blockade should be the standard during most anesthetics when a relaxant is administered. Combining objective data from nerve monitoring with clinical signs of paralysis offers obvious advantages when dosing relaxants intraoperatively and assessing postoperative recovery. An important anesthetic discussion has been taking place on the gap between the scientific knowledge on effective monitoring and use of muscle relaxants in anesthesia and actual current clinical practice.[9-12] Expert consensus strongly recommends the routine monitoring of neuromuscular block in the perioperative period as a safety issue. They feel this guides intraoperative relaxant dosing by avoiding over-paralysis and helps reduce the incidence of residual weakness in the postanesthesia care unit (PACU). A recent extensive survey of clinicians in the United States[13] and Europe indicate that many practitioners are not using these monitors in everyday practice.[14-16] Several explanations are given: the current quantitative monitors are cumbersome and difficult to use, qualitative monitoring is unreliable, residual paralysis is not a problem in their practice, and clinical signs can be used to assess paralysis in most patients, among others. Survey respondents felt that the incidence of residual paralysis in their practice was usually less than 1%. Objective studies estimate the incidence at about 35%.[13] The discrepancy may exist because most patients recover safely in spite of residual paralysis and their problem is not noticed. Many patients may have had some difficulty or discomfort but manage to compensate until full recovery occurs and do not need specific interventions. There is no question however, that residual paralysis in the PACU represents a significant potential hazard for airway complications and aspiration. A complete discussion of neuromuscular blockade reversal is later in this chapter.

The response to a peripheral nerve monitor indirectly infers the relaxation of musculature. The neuromuscular monitor is an electrical device that delivers a series of electric shocks or impulses to the patient through electrodes applied to the skin near a nerve. There are several methods for monitoring neuromuscular blockade intensity, including acceleromyography (AMG), electromyography (EMG), phonomyography (PMG), mechanomyography (MMG), and kinemyography (KMG). Visual and tactile response to evoked electrical stimulus as assessed by the clinician, or *qualitative* monitoring, is the most common method. On activation of the stimulator, various predictable muscle contraction patterns are visible in the presence and absence of neuromuscular blockers. *Quantitative* monitoring where the stimulator is coupled with a displacement transducer as a movement measuring device and a number value is displayed is preferred but less common. Quantitative monitoring can be accomplished with MMG, AMG, KMG, or EMG.[9]

Depolarization and contraction of a muscle are caused by an action potential traveling along the course of a nerve. As the impulse reaches the motor endplate, acetylcholine (ACh) is released across the synaptic cleft. It subsequently travels toward the receptor sites on the muscle membrane, resulting in depolarization and subsequent contraction of the muscle.[2] The stimulator elicits the same activity, which makes it useful for the monitoring of neuromuscular blockade (Figure 12-1).

The proper administration of neuromuscular blocking agents (NMBAs) is essential for patient safety and efficient perioperative workflow. Inadequate doses of NMBAs may result in complications during surgical procedures because of unexpected patient movement and a less than ideal operative field. In contrast, overdosage may result in residual paralysis in the postoperative period, increasing morbidity and the need for labor-intensive interventions (e.g., mechanical ventilation).

Contraction of the adductor muscle of the thumb via stimulation of the ulnar nerve is the preferred site for determining the level of neuromuscular blockade. It is usually accessible and convenient.

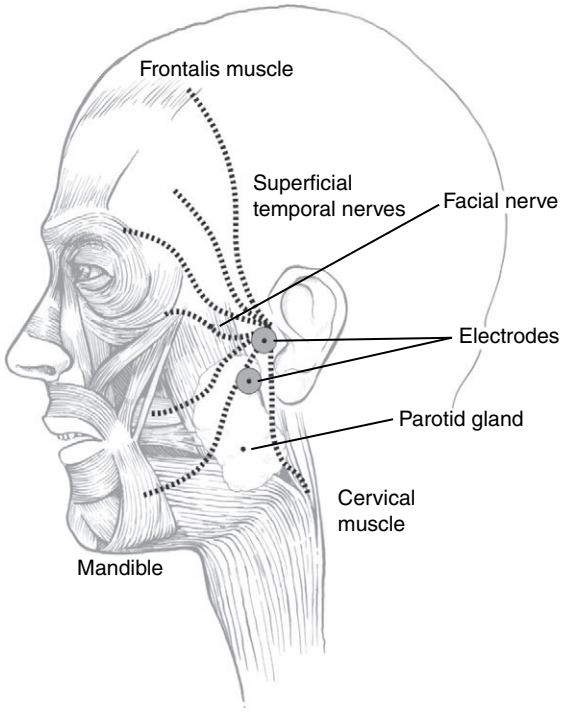


FIGURE **12-2** Facial neuromuscular blockade testing.

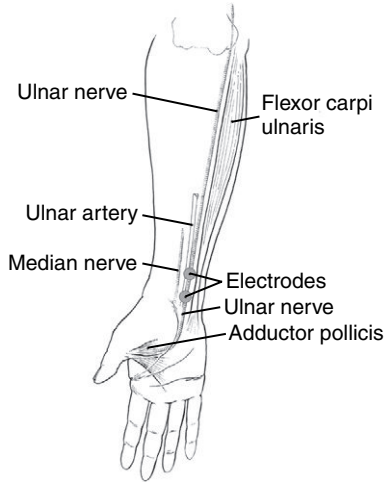


FIGURE **12-3** Ulnar neuromuscular blockade testing.

Disposable electrodes are applied over the ulnar nerve. The distal electrode is placed over the proximal flexor crease of the wrist, and the other electrode is placed over and parallel to the carpi ulnaris tendon. On stimulation of these electrodes with the monitoring device, adduction of the thumb is visible. When access to the arm and hand is not practical, other monitoring sites include the nerves of the foot and the facial nerve. Facial nerve monitoring generally involves stimulation of the temporal branch of the facial nerve that supplies the orbicularis oculi muscle around the eye or the orbicular muscle that contracts the lip.[10] The facial and ulnar nerves sites are shown in Figures 12-2 and 12-3, respectively. Table 12-1 gives a comparison of the ulnar and facial nerve monitoring sites.

A few contrasting factors involving blood flow versus muscle sensitivity must be considered when assessing paralysis and interpreting responses from the ulnar nerve or face. During onset of a relaxant, the muscle group sensitivity exhibits the following pattern: The eye muscles are the most sensitive and are the first group to be affected, followed by the extremities, the trunk of the body with the neck and chest first, then abdominal muscles, and lastly the diaphragm. During recovery, muscle function returns in the opposite pattern with the diaphragm first and the eye muscles last. Blood flow, however, is greater to the head, neck, and diaphragm so more of the drug is distributed to these areas upon initial distribution and onset.

Due to these conflicting influences, the facial nerves should be used when assessing relaxant onset. Blood, thus drug, distribution to the facial muscles mirrors distribution in the larynx and diaphragm where relaxation is required for intubation and airway manipulation. Recovery is best measured in the hand. The hand muscles are more sensitive to relaxant than the diaphragm, so if recovery is evident in the hand, the larynx and diaphragm will be recovered as well.[17]

TABLE 12-1 A Comparison of Neuromuscular Monitoring Sites

Monitoring Site	Response	Comments
Ulnar nerve innervation of the adductor pollicis	Thumb adduction	Usually have easy access Best site to measure recovery
Facial nerve	Eyelid movement	Easily accessed when arm is not available Best site to measure onset

Tests of Neuromuscular Function

There are five clinical tests of neuromuscular function: single twitch, train-of-four (TOF), double-burst stimulation (DBS), tetanus, and posttetanic count (PTC). The TOF, DBS, and tetanic stimulation are the most commonly used.[18] The ability to evaluate muscle function with each mode of stimulation varies (Table 12-2).

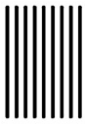
A brief explanation of the concept of *fade* is required to understand the responses to nerve monitoring. The inability to sustain a response, known as fade, to repetitive nerve stimulation is seen in several of the clinically used monitoring tests. This is a sign of drug-induced muscle paralysis. Fade occurs because the nondepolarizing drugs block presynaptic acetylcholine receptors in addition to their classic antagonist effect at postsynaptic ACh neuromuscular junction sites. The function of presynaptic ACh receptors is to facilitate the release of ACh from the nerve terminal via a positive feedback mechanism. During high impulse rates of nerve stimulation this positive feedback mechanism prevents the decrease (fade) of transmitter release. The facilitated ACh release associated with this positive feedback mechanism is blocked by the relaxants.[19] This inhibition is detected as fade during the use of the monitoring tests as described below.

Single Twitch

The first (and simplest) type of stimulation is a single twitch at 0.1 to 1 hertz (Hz) for 0.1 to 0.2 milliseconds (ms). These impulses can be delivered automatically every second, every 10 seconds, or manually, depending on the sophistication of the neurostimulating apparatus.

Unless you have a comparison twitch response before any relaxant is given, this test simply indicates whether 100% paralysis is present. If the patient's muscle moves when stimulated, less than

TABLE 12-2 Common Neuromuscular Monitoring Tests

Monitoring Test	Definition	Comments	Stimulation Characteristics
Single twitch	A single supramaximal electrical stimulus ranging from 0.1-1.0 Hz	Requires baseline before drug administration; generally used as a qualitative rather than quantitative assessment	
Train-of-four	A series of four twitches at 2 Hz every ½ second for 2 sec	Reflects blockade from 70%-100%; useful during onset, maintenance, and emergence Train-of-four ratio is determined by comparing T_1-T_4	
Double-burst simulation	Two short bursts of 50 Hz tetanus separated by 0.75 sec	Similar to train-of-four; useful during onset, maintenance, and emergence; may be easier to detect fade than with train-of-four; tactile evaluation	
Tetanus	Generally consists of rapid delivery of a 30-, 50-, or 100-Hz stimulus for 5 sec	Should be used sparingly for deep block assessment; painful	
Posttetanic count	50-Hz tetanus for 5 sec, a 3-sec pause, then single twitches of 1 Hz	Used only when train-of-four and double-burst stimulation is absent; count of less than eight indicates deep block, and prolonged recovery is likely	

100% muscle paralysis exists. If no movement is detected, 100% paralysis is present.

Train-of-Four

The second and most widely used means of stimulation is the train-of-four (TOF), which delivers four separate stimuli every 0.5 second at a frequency of 2 (Hz) for 2 seconds.[20] A comparison is made of the four stimulated responses. Each of the four twitch responses are referred to as T_1 through T_4, respectively. Upon the onset of paralysis with a nondepolarizing relaxant, there is a progressive diminution of the twitch responses with visible fade. Fade refers to the fact that each of the successive twitch responses from T_1 through T_4 is smaller. When partial paralysis is present yet all four twitch responses can be elicited, with fade from T_1 through T_4, an assessment can be made regarding the size of T_4 compared to T_1. This T_4:T_1 ratio is referred to as the *train-of-four ratio*, or TOFR. Train-of-four testing can aid in approximating the degree or percent of paralysis present. It is most sensitive between 70% and 100% paralysis. The fourth twitch (T_4) disappears first, which represents a block of 75% to 80%. Progressive disappearance of the third twitch (T_4 and T_3 absent) indicates 80% to 85% block. When three twitches are abolished (T_4, T_3, and T_2 are absent), 90% to 95% neuromuscular blockade is present. When 100% paralysis is achieved, no responses can be elicited. Figure 12-4 correlates the responses to TOF stimulation with the approximate degree of paralysis present. Intraoperatively, the ideal degree of paralysis necessary for any procedure with sufficient anesthetic depth is 85% to 95%. That correlates with 1 to 2 twitch responses present upon TOF stimulation. Avoiding total 100% paralysis intraoperatively ensures a successful operative procedure while avoiding overdosing of the relaxant. Less total relaxant administered lessens the chances of residual paralysis upon reversal.[20]

A representative assessment of the TOF test during onset and recovery of a nondepolarizing relaxant is shown in Figures 12-5 and 12-6, respectively.

Double-Burst Stimulation

Double-burst stimulation was conceptualized as an analog to TOF with some improvements. It consists of two short bursts of a 50-Hz tetanus separated by 0.75 seconds. The use of DBS seems to improve the ability to detect residual paralysis during recovery. The suggestion is that DBS relies on the direct comparison of the muscle contraction in response to two rapidly sequential minitetanic bursts rather than the indirect comparison of the fourth twitch with the first twitch as in the TOFR. It is thought that the comparison of the fourth to the first twitches when assessing the TOFR is hindered by the second and third twitches that provide no useful information. Evaluating two rather than four twitch responses facilitates detection of fade. Tactile evaluation is suggested to improve the ability to detect fade. Responses are similar to the TOF. Fade of the second impulse is comparable to a TOFR of less than 0.6 and indicates significant paralysis.[17] A comparison is shown in Figure 12-7.[18,21,22]

Tetanus

Tetanus consists of continuous electrical stimulation for 5 seconds at 50 or 100 Hz. The 100-Hz current is more reliable for detecting fade but is not always specific.[17,23] If the muscle contraction produced is sustained for the entire 5 seconds of stimulation without fade, significant paralysis is unlikely. If fade is present, clinically significant block remains.[18,24] The higher intensity of stimulation produced by tetanic frequencies as compared to TOF, DBS, or a single twitch makes it useful when other tests such as TOF or DBS are equivocal. The test is painful and should not be repeated too often to avoid muscle fatigue.

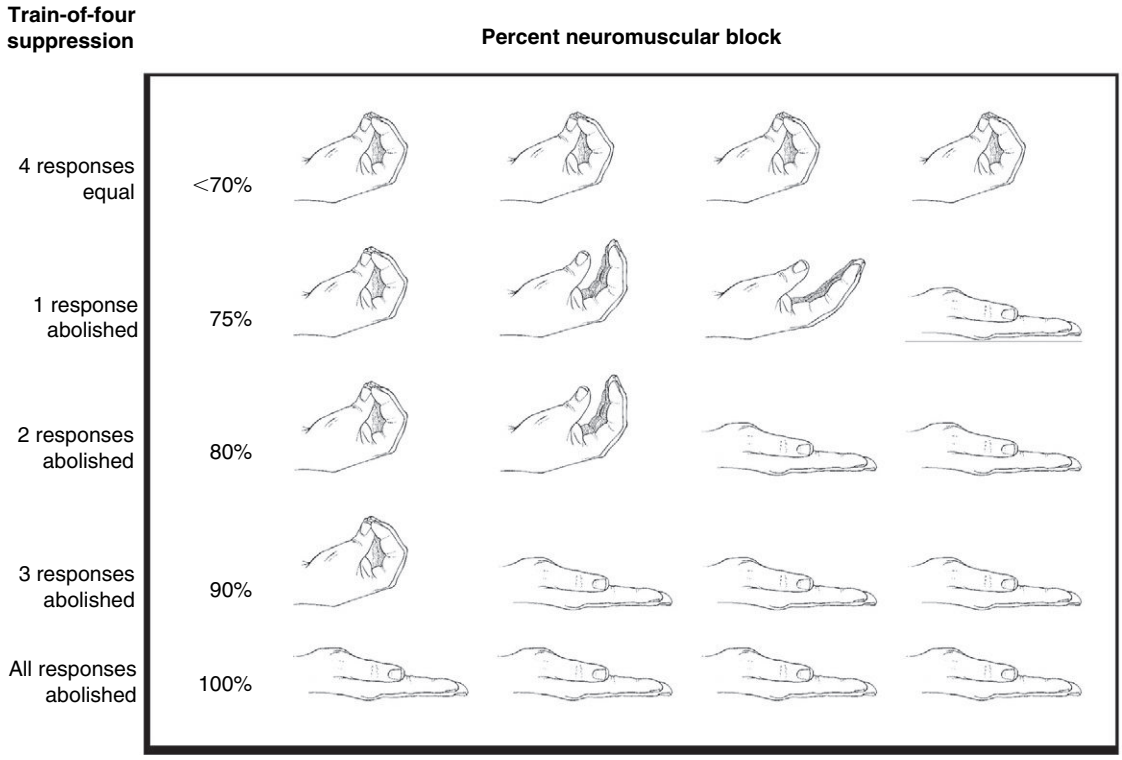


FIGURE **12-4** Train-of-four test.

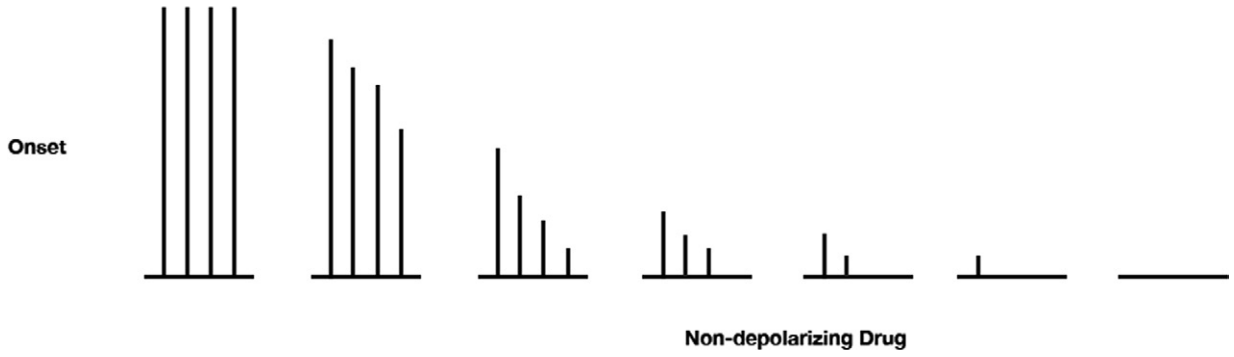


FIGURE **12-5** Characteristic train-of-four response during onset of a nondepolarizing muscle relaxant.

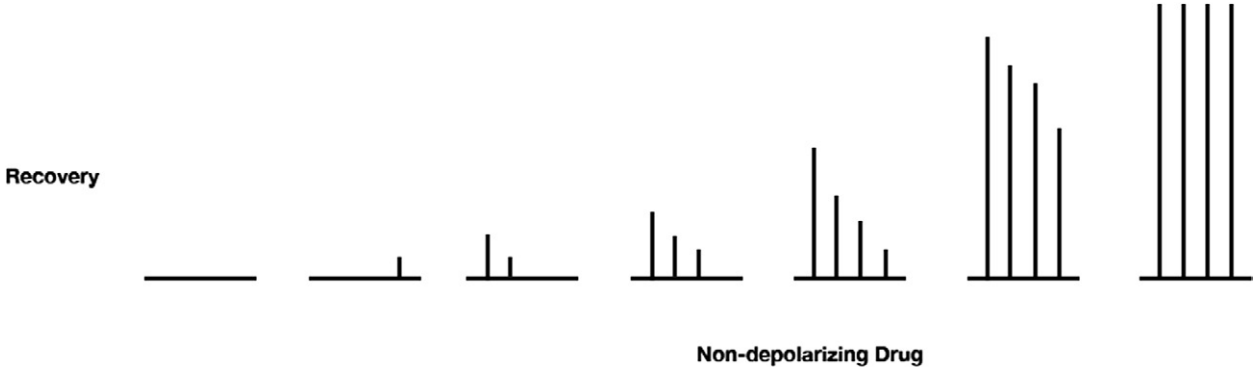


FIGURE **12-6** Characteristic train-of-four response during recovery from a nondepolarizing muscle relaxant.

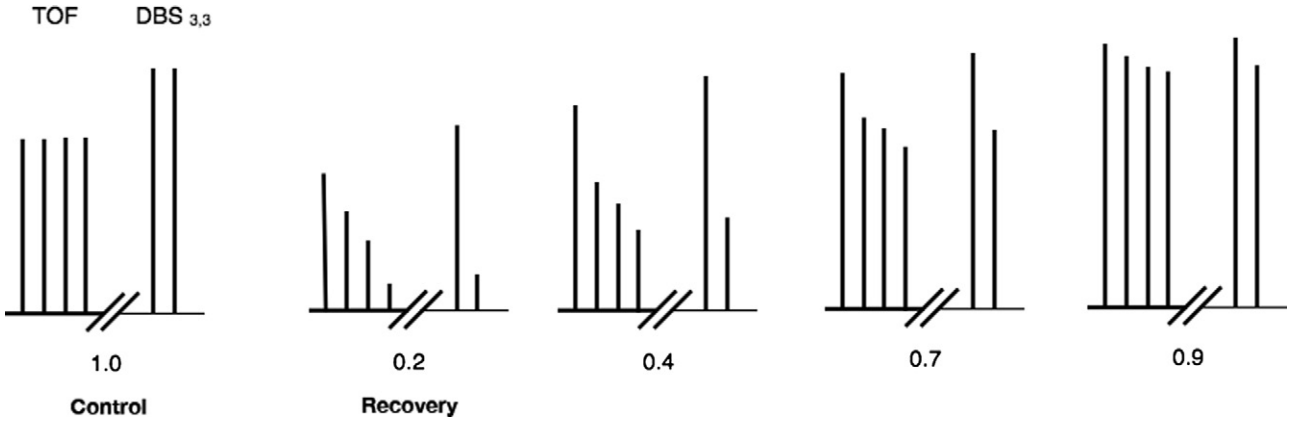


FIGURE **12-7** A comparison of responses to double-burst and train-of-four stimulation during recovery from a nondepolarizing muscle relaxant.

BOX **12-1**

Commonly Used Neuromuscular Terminology

- *Onset time:* Time from drug administration to maximum effect
- *Clinical duration:* Time from drug administration to 25% recovery of the twitch response
- *Total duration of action:* Time from drug administration to 90% recovery of twitch response
- *Recovery index:* Time from 25% to 75% recovery of the twitch response
- *Train-of-four ratio:* Compares the fourth twitch of a TOF with the first twitch; when the fourth twitch is 90% of the first, recovery is indicated

TOF, Train-of-four.

Posttetanic Count

The posttetanic count (PTC) is rarely used clinically but will be described for completeness. It is only performed when there is no response to any of the commonly used tests due to presence of 100% paralysis. Because you are already aware that the patient is completely paralyzed, the value of the PTC is to attempt to give a rough time estimate as to when recovery may occur. The PTC mode involves the use of a 50-Hz tetanic stimulation for 5 seconds, followed in 3 seconds by a series of single 1-Hz twitch stimulations.[22] An understanding of the phenomenon of posttetanic potentiation (also referred to as posttetanic stimulation or facilitation) is necessary to comprehend the PTC test. When the 50-Hz tetanus is applied, there is no response because the patient is completely blocked. Application of the 50-Hz tetanus, however, transiently mobilizes excesses of acetylcholine so that after a 3-second pause, you are able to produce a short series of single-twitch responses. Because they only occur after a tetanic stimulation and not before, this single-twitch response is termed *posttetanic potentiation*. This extra acetylcholine will in effect "transiently reverse" the relaxant by competing for the receptor at the local monitoring site. This augmented response will only last several seconds until the excess acetylcholine dissipates. The number of twitches elicited is counted. The higher the count, the less intense the block. The usual count is between 0 (deep block) and 8 (less intense block where TOF response should return). With rocuronium, for example, neostigmine reversal of an intense block where the PTC was 1 to 2 takes more than 50 minutes.[25] At a PTC of 6 to 8, reversal should occur in less than 10 minutes.

Neuromuscular monitoring terminology and tests are summarized in Box 12-1, Figure 12-2, and Table 12-3. Some key points related to successful use of tests of neuromuscular transmission are given in Box 12-2.[26]

DEPOLARIZING AGENTS

Succinylcholine Chloride

Succinylcholine chloride (Anectine, Quelicin, and others) is very familiar to every clinician, having been a standard for several decades of practice. Although its widespread use in clinical anesthesia represents the standard of care for a variety of situations, opinions regarding its use remain divided because of some of its untoward effects.

Stephen Thesleff at the Karolinska Institute in Stockholm was one of the pioneers who introduced the drug into clinical practice to induce neuromuscular paralysis in humans. Initial description of the neuromuscular blocking properties of succinylcholine is credited to Daniel Bovet. (Bovet was awarded the Nobel Prize for Physiology and Medicine in 1957 for his discovery of synthetic compounds that act on the vascular system and skeletal muscle.)[27] The first use of succinylcholine in the United States occurred in 1952. Foldes et al.[28] described this agent in the following manner:

> *Compared to other muscle relaxants used in anesthesiology, succinylcholine possesses several advantages, the outstanding one, in our experience, being its easy controllability, which permitted almost instantaneous changes in degree of muscular relaxation. With succinylcholine, both increasing and decreasing muscular relaxation took less than a minute.*[28]

The disadvantages of succinylcholine have been well recorded through years of clinical experience. It has no action in the ganglionic nicotinic receptors but may cause bradycardia by an action on cardiac cholinergic muscarinic receptors.[29,30] Prolonged neuromuscular blockade can result from excessive doses of succinylcholine in patients with atypical, inhibited, or deficient levels of plasma cholinesterases.[3,29]

Succinylcholine is the only remaining depolarizing muscle relaxant licensed for use in the United States. Remembering the composition of the drug is helpful in better understanding its effects and side effects. Succinylcholine results from the joining of two ACh molecules and is represented by the chemical formula $C_{14}H_{30}N_2O_4$. Although succinylcholine mimics the action of ACh by depolarizing the motor endplate, its degradation is distinct. In contrast with the degradation of ACh by acetylcholinesterase (AChE), succinylcholine is hydrolyzed by plasma cholinesterase (pseudocholinesterase). The popularity of this muscle relaxant is

TABLE 12-3 Key Points Related to Tests of Neuromuscular Transmission and Reversal

Test	Acceptable Clinical Result to Suggest Normal Function	Approximate Percent of Receptors Occupied When Response Returns to Normal Value	Comments, Advantages, and Disadvantages
Tidal volume	At least 5 mL/kg	80	Necessary, but insensitive as an indicator of neuromuscular function
Single-twitch strength	Qualitatively as strong as baseline	75-80	Uncomfortable; need to know twitch strength before relaxant administration; insensitive as an indicator of recovery, but useful as a gauge of deep neuromuscular blockade
Train-of-four (TOF)	No palpable fade	70-75	Uncomfortable, but more sensitive as indicator of recovery than single twitch; used as a gauge of depth of block by counting the number of responses perceptible
Sustained tetanus at 50 Hz for 5 sec	At least 20 mL/kg	70	Very uncomfortable, but a reliable indicator of adequate recovery
Vital capacity	At least 20 mL/kg	70	Requires patient cooperation, but is the goal for achievement of full clinical recovery
Double-burst stimulation	No palpable fade	60-70	Uncomfortable, but more sensitive than TOF as an indicator of peripheral function; no perceptible fade indicates TOF of at least recovery of 60%
Inspiratory force	At least −40 cm H_2O	50	Difficult to perform with endotracheal intubation, but a reliable gauge of normal diaphragmatic function
Head lift	Must be performed unaided with patient supine and sustained for 5 sec	50	Requires patient cooperation, but remains the standard test of normal clinical function
Hand grip	Sustained at a level qualitatively similar to preinduction	50	Sustained strong grip, though also requires patient cooperation; is another good gauge of normal function
Sustained bite	Sustained jaw clench on tongue blade	50	Very reliable with patient cooperation; corresponds with TOF of 85%

Modified from Miller RD. Neuromuscular blocking drugs. In: Miller Rd, Pardo M: *Basics of Anesthesia*. 6th ed. Philadelphia: Saunders; 2011:158.

BOX 12-2

General Guidelines for Successful Neuromuscular Monitoring

- Objective (quantitative) monitoring of neuromuscular function should be used when possible.
- Peripheral nerve stimulator units should display the delivered current output, which should be at least 30 mA.
- During onset, paralysis begins with the eye muscles, followed by the extremities, trunk (from the neck muscles downward through the intercostals), abdominal muscles, and finally the diaphragm. Recovery returns in the opposite manner. Protective reflex muscles of the pharynx and upper esophagus recover later than the diaphragm, larynx, hands, or face.
- Monitoring of the facial nerve for determination of onset and readiness for intubation may be preferable to monitoring of the ulnar nerve.
- Monitoring of the offset and recovery from neuromuscular blockade is probably better at the ulnar nerve.
- Tactile evaluation of train-of-four (TOF) and double-burst stimulation (DBS) fade reduces but does not eliminate the incidence of postoperative residual paralysis compared with the use of clinical criteria to assess readiness for tracheal extubation.
- Adequate spontaneous recovery should be established before pharmacologic antagonism of neuromuscular blocking drug (NMBD) block with anticholinesterases. This requirement does not apply to reversal with sugammadex.
- When there is only one response to TOF stimulation, successful reversal may take as long as 30 minutes.
- At a TOF count of two or three responses, recovery usually takes 4 to 15 minutes after intermediate-acting drugs and may take up to 30 minutes after administration of the long-acting relaxant pancuronium.
- When the fourth response to TOF stimulation appears, adequate recovery can be achieved within 5 minutes of reversal with neostigmine or 2 to 3 minutes after use of edrophonium.
- When the fourth twitch of the TOF returns, the train-of-four ratio (TOFR) may be determined. Compare the size of the fourth twitch (T_4) with the size of the first twitch (T_1), using T_4:T_1 as a ratio. The timing of tracheal extubation should be guided by quantitative monitoring tests such as TOF greater than 0.9 or DBS_3 greater than 0.9.

TABLE 12-4 Neuromuscular Blocking Agents: Dose, Onset, and Duration*

Agent	ED_{95} (mg/kg)	Intubating Dose (mg/kg)	Time to Onset	Duration of Action (min)
Succinylcholine (Anectine)	0.3	1-1.5	30-60 sec	Ultrashort, 5-15
Atracurium (Tracrium)	0.15	0.5	2-4 min	Intermediate, 30-60
Cisatracurium (Nimbex)	0.05	0.1	2-4 min	Intermediate, 30-60
Rocuronium (Zemuron)	0.3	0.6-1	1-1.5 min	Intermediate, 30-60
Vecuronium (Norcuron)	0.05	0.1	2-4 min	Intermediate, 30-60
Pancuronium (Pavulon)	0.05	0.08-1.8	2-4 min	Long, 60-90

*All data for adult patients without significant disease.
ED_{95}, Effective dose for 95% paralysis.

rooted in its unique ability to provide a quick onset and short duration of effect. A bolus of 0.5 to 1.5 mg/kg is the recommended dose for adequate adult paralysis and relaxation for intubation.[31] The dose of succinylcholine that provides the desired paralytic effect in 95% of the population (ED_{95}) is approximately 0.30 mg/kg.[32]

Pharmacokinetics

Onset. Succinylcholine has an extremely rapid onset and remains the gold standard against which other agents are compared. In general, muscle relaxants exhibit an inverse relationship between potency and onset speed. The lower the potency, the faster the speed. A lower potency drug requires larger doses so a muscle gradient will be achieved more quickly.[33] A typical intubating dose of 1 to 1.5 mg/kg results in a maximum suppression of muscle twitch and good to excellent intubating conditions within 1 to 1.5 minutes of administration.[34,35] Onset of action of succinylcholine at the larynx with administration of 1 mg/kg is 34 seconds.[36,37] The onset as measured at peripheral sites such as the adductor pollicis is slightly longer at 1 minute.[38] The rapid onset of succinylcholine is based on its action as an initial agonist at the nicotinic receptor, rather than as a competitive antagonist. Succinylcholine works by activating the muscle-type nicotinic cholinergic receptors, followed by desensitization.[30] This action results in the need for significantly less drug at the receptor site to produce neuromuscular block. In contrast, most NMBAs require 75% or more receptor occupancy for clinically useful paralysis to result. Variable onset must be considered in patients with altered physiology. Patients with atypical plasma cholinesterase may exhibit prolonged onset after succinylcholine administration.[39] A summary of the dose, onset, and duration of the neuromuscular blocking drugs is given in Table 12-4.

Duration. The plasma half-life of succinylcholine is 2 to 4 minutes.[40] The clinical duration of succinylcholine (i.e., the length of time during which its clinical effects can be recognized) is 5 to 10 minutes, with full recovery evident at 12 to 15 minutes. Twitch recovery of 25%, as measured by the laryngeal adductor pollicus responses, is 4.3 minutes, whereas 90% to 95% twitch recovery has been reported to occur in 8 minutes.[36] Other studies have yielded similar results, with researchers citing a range of duration of 7 to 12 minutes.[29,34]

Elimination. Succinylcholine is degraded via hydrolysis by plasma cholinesterases. These enzymes, although found in the plasma, are produced by the liver. Initially, hydrolysis results in the transformation of succinylcholine into succinylmonocholine and choline (Figure 12-8). Succinylmonocholine is further degraded by plasma cholinesterase into succinic acid and choline. Succinylcholine metabolism is so rapid that only 10% of the injected dose ever reaches the neuromuscular junction.[31] A summary of the elimination routes for the neuromuscular blocking drugs is given in Table 12-5.

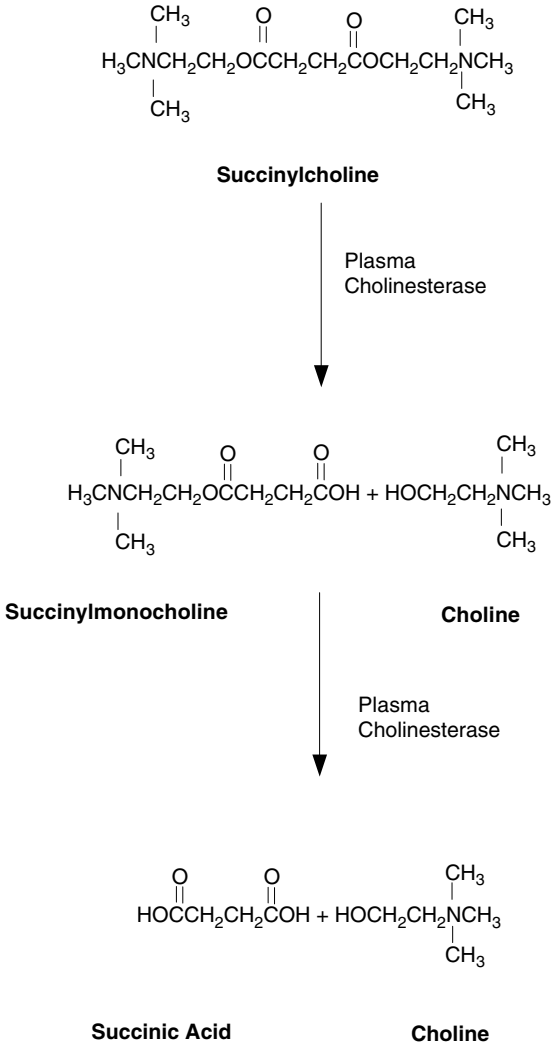


FIGURE 12-8 Metabolism of succinylcholine.

Central Nervous System

Like all muscle relaxants, succinylcholine contains a quaternary ammonium in its structure, rendering it water soluble in the body. It does not therefore pass the blood-brain barrier and has no direct central nervous system (CNS) effects. Succinylcholine indirectly increases intracranial pressure (ICP), and therefore concern has always existed as to the appropriateness of its use in certain neurosurgical procedures and in patients with brain pathology and increased intracranial pressure.[36] Research conducted in animals shows a small and transient rise of 10 to 15 mmHg for 5 to

TABLE 12-5 Neuromuscular Blockers: Elimination Mechanism

Agent	Elimination Mechanism	Comments
Atracurium	Hofmann elimination; nonspecific esterases	Non–organ-dependent elimination produces consistent duration in patients with significant hepatic and renal disease, as well as the elderly
Cisatracurium	Hofmann elimination; nonspecific esterases	Similar to atracurium but without the histamine release
Rocuronium	Renal; hepatic	May be prolonged with hepatic and renal disease
Vecuronium	Renal (20%-30%); hepatic (40%-80%)	May be prolonged with hepatic disease
Pancuronium	Renal primarily; some hepatic	May be prolonged with renal disease
Succinylcholine	Plasma cholinesterase	Prolonged in patients with cholinesterase deficiency

8 minutes after administration.[40] The rise is associated with an increased cerebral blood flow, muscle spindle afferent activity, and electroencephalogram arousal. Fasciculation of the neck muscles causing jugular vein stasis appears to be a factor.[41] The ICP effects are blocked by pretreatment with a small dose of nondepolarizing relaxant.[42] In clinical practice, the administration of succinylcholine is preceded by an anesthetic induction agent that lowers ICP, so that may help counteract this effect as well. Nevertheless, the routine use of succinylcholine in neurosurgery has declined. It remains widely used, with nondepolarizing relaxant and lidocaine pretreatment, for emergency procedures requiring rapid airway control via rapid sequence induction.[29]

Cardiovascular System

Succinylcholine usually results in slight tachycardia; however, sudden abrupt bradycardia may result from repeat dosing in adults and any dose in children. Many types of arrhythmias have been reported. The bradycardia results from autonomic ganglia and parasympathetic muscarinic receptor stimulation. Another possible mechanism for the bradycardia associated with succinylcholine administration is thought to be related to its metabolite, succinylmonocholine, which causes stimulation of cholinergic receptors in the sinoatrial node.[43]

An intubating dose of succinylcholine increases serum potassium levels by 0.5 to 1 mEq/L.[40] Although this may not be significant in the normokalemic patient, it may be life threatening in patients with preexisting hyperkalemia.[44] Gronert[45] presents a case that involved an 11-year-old girl who experienced cardiac arrest after receiving succinylcholine. Her cardiac arrest and eventual death were directly attributed to a high potassium release after the succinylcholine administration (10.2 mEq/L). The exaggerated potassium release after the succinylcholine administration in this case was determined to be related to a familial myopathy evidenced by extremely high patient levels of creatine kinase. Succinylcholine administration, hyperkalemia, and myopathy are discussed later. Some clinicians believe that a second dose of succinylcholine indicated by any event should be preceded by intravenous (IV) atropine or glycopyrrolate for its anticholinergic effects; however, others do not.[44,46]

Hepatic System

Cholinesterase enzyme subtypes are produced in the liver. Pseudocholinesterase (PChE) degrades succinylcholine; therefore certain types of liver damage may prolong the effects of the drug.[43] Ester compounds like succinylcholine are metabolized by adding water, the process referred to as *hydrolysis*. The basic reaction is ESTER + $H_2O \leftrightarrow$ ACID + ALCOHOL. Three esterase enzymes that can act as catalysts for these hydrolysis reactions exist in the plasma: cholinesterase, paraoxonase, and albumin esterase. Paraoxonase and albumin esterase are frequently referred to as *nonspecific esterases*. Additionally, red blood cells (RBCs) contain two esterase enzymes in their cytosol. One is referred to as *RBC esterase*, *esterase D*, or *S-formylglutathione*, and the other is AChE in small amounts.[47]

Cholinesterase is a generic term used for a family of related enzymes that hydrolyze choline esters at a faster rate than other esters under optimal conditions. The major function of cholinesterase is to terminate the action of ACh at cholinergic nerve endings in synapses or in effector organs.[48] Two subtypes of cholinesterase exist in the human body, with several variations and a confusing set of names. One type of cholinesterase is acetylcholinesterase, AChE, also known as *true*, *specific*, *genuine*, and *type I cholinesterase*. This enzyme is found in erythrocytes, nerve endings, the lungs, the spleen, and the gray matter of the brain. It is a membrane-bound glycoprotein and exists in several molecular forms. The other subgroup pseudocholinesterase, PChE, also known as *plasma*, *serum*, *benzoyl*, *false*, *butyryl*, *nonspecific*, and *type II cholinesterase*, exists in plasma and has more than 11 isoenzyme variants. PChE is also present in the liver, smooth muscle, intestines, pancreas, heart, and white matter of the brain.

Measurements of PChE activity can serve as a sensitive measure of the synthetic capacity of the liver. In the absence of known inhibitors, any decrease in activity reflects impaired synthesis of the enzyme. A moderate decrease (30% to 50%) is seen in acute hepatitis and long-standing chronic hepatitis, whereas a severe decrease (50% to 70%) is seen in advanced cirrhosis and in some carcinomas with metastases to the liver. Decreased levels of PChE are also found in pregnant women and newborns and in patients with acute infections, pulmonary embolism, muscular dystrophy, myocardial infarction, and after certain surgical procedures.[48] Essentially normal levels are noted in patients with mild cirrhosis or obstructive jaundice. Increased levels have been observed in cases of nephrotic syndrome, thyrotoxicosis, and hemochromatosis, in obese patients with diabetes, and in patients with anxiety and other psychiatric states. Patients generally develop neuromuscular symptoms at approximately 60% of normal activity, and serious neuromuscular effects are seen at approximately 20% of normal. Reference intervals are 2900 to 7100 units/L, although they vary with the analysis method.[49]

Table 12-6 lists some common anesthesia-related drugs that undergo hydrolysis, with the enzyme catalyst involved.

Genetic Variants of Pseudocholinesterase and the Dibucaine Inhibition Test

Some patients exhibit genetic variations in PChE that result in a prolonged response and apnea when the patient is exposed to succinylcholine. Although such individuals may lead a normal life in every other respect, their atypical variants of cholinesterase are unable to hydrolyze certain ester-containing drugs in the usual

TABLE 12-6 Common Esterase-Dependent, Anesthesia-Related Drugs

Drug	Enzyme
Succinylcholine	Pseudocholinesterase
Ester local anesthetics: Cocaine Procaine Chloroprocaine Tetracaine	Pseudocholinesterase
Neostigmine	Pseudocholinesterase
Edrophonium	Pseudocholinesterase
Atracurium	Nonspecific esterases (plasma)
Cisatracurium	Nonspecific esterases (plasma)
Remifentanil	Nonspecific esterases (plasma)
Esmolol	Nonspecific (RBC esterases) plasma
Clevidipine	Nonspecific estaerases (plasma)
MOC—Etomidate	Nonspecific esterases (plasma)

RBC, Red blood cell; *MOC*, methoxycarbonyl.

fashion. The most frequent variations in the PChE gene are the atypical (A) and Kalow (K) variants.[50] Over 60 mutations in the coding sequence have been reported; however, most are extremely rare.[49,51,52] The fluoride resistant (F), silent (S), and K variants are not tested for clinically because of assay difficulty and lack of clinical relevance. Phenotype-genotype concordance studies have recently been reported that allow detailed genetic mapping and clinical data to be evaluated.[49]

In the usual clinical scenario, a patient completes surgery and is unable to breathe. If succinylcholine was used to facilitate intubation, differential diagnosis leads the anesthesia provider to conclude that a potential atypical pseudocholinesterase may be present.[53-55] The patient is taken to the PACU, placed on a ventilator, sedated, and monitored until the succinylcholine wears off. The patient recovers and is subsequently discharged, but prior to discharge, a blood sample is taken to perform a dibucaine inhibition test to help determine (1) whether an atypical enzyme was present and (2) the cause of the prolonged apnea. The dibucaine number and enzyme activity are both determined. By treating the patient's serum with dibucaine and measuring the residual PChE activity compared with the PChE of an untreated sample, the metabolic sensitivity to succinylcholine can be measured. The patient is contacted post-discharge and counseled as appropriate, according to the findings. The administration of whole blood, fresh frozen plasma, or purified human cholinesterase has been suggested as a treatment for the prolonged apnea. Although they may be successful, there are additional transfusion risks and cost issues.[43] It is safer to let the effects of succinylcholine dissipate on their own with sedation and ventilation as noted earlier.

Dibucaine is an amide local anesthetic that inhibits typical or usual PChE but not atypical PChE. For example, the normal dibucaine number of 80 means that 80% of the PChE activity was inhibited by dibucaine. If a dibucaine number of 20 is obtained, the patient has atypical enzyme because dibucaine did not inhibit the patient's enzyme activity. If a patient experiences prolonged apnea after succinylcholine administration, it is imperative to differentiate between an atypical genetic variant of PChE or simply low levels of normal PChE enzyme. Possible interpretations of a dibucaine test are given in Box 12-3.

Patients with acute or chronic liver disease, organophosphate poisoning, or chronic renal disease, patients in the late stages of pregnancy, and those undergoing estrogen therapy may have markedly decreased PChE activities but normal enzyme. PChE phenotype interpretation is based on the total PChE activity and the percent of inhibition caused by dibucaine (Table 12-7).

BOX 12-3

Dibucaine Inhibition Test Outcomes

1. Low dibucaine number + slightly lower activity = atypical enzyme and prolonged apnea
2. Normal dibucaine number + low activity = normal enzyme with low levels present and prolonged apnea
3. Low dibucaine number + very low activity = possible rare variant-type enzyme with very low levels present and prolonged apnea
4. Normal dibucaine number + normal activity = normal enzyme and amount (Another reason for the prolonged apnea must be investigated.)

Gene sequencing combined with biochemical testing can provide patients and their families with a comprehensive assessment of the likelihood of this type of event.[49,50,52]

Renal System

Succinylcholine may be used in surgical patients with renal disease when preoperative potassium levels are normal. The use of succinylcholine in patients with elevated preoperative potassium levels is contraindicated.[56] Patients with renal failure and end-stage renal disease are frequently dialyzed prior to surgery, so as long as the serum potassium is within normal limits, succinylcholine may be used safely.[57] Patients with renal disease may have lower cholinesterase levels.[58]

Effects in Special Populations

Elderly Patients. The onset of succinylcholine may be slightly prolonged in the elderly due to a slower circulation time, but the clinical relevance is minimal.[59] Reduced plasma cholinesterase levels in elderly men may allow for a reduced dose of succinylcholine. A unique possible drug interaction has been noted in elderly patients taking tacrine (Cognex), donepezil (Aricept), rivastigmine (Exelon), or galantamine (Razadyne). These are anticholinesterase drugs used to treat Alzheimer's disease and select forms of dementia. They increase acetylcholine levels in the CNS and are referred to as *cognitive enhancers*. Theoretically, the inhibition of cholinesterase produced by these agents may prolong the action of succinylcholine. The amount of systemic cholinesterase inhibition, however, does not produce clinically significant prolongation of succinylcholine[60] (Box 12-4).

Obese Patients. No contraindication to the use of succinylcholine exists in obese patients. The utility of rapid-sequence induction in anesthetic management of the obese patient makes its use common.[61] The recommended dose of succinylcholine is 1.0 mg/kg, based on total body weight, to produce excellent intubating conditions.[62] In a 2003 study by Brodsky and Foster,[63] succinylcholine was given to 14 morbidly obese patients (body mass indices ranging from 35.8 to 58) who underwent laparoscopic gastric bypass surgery. The authors administered doses ranging from 120 to 140 mg and successfully intubated all of the patients. Only 2 of the 14 patients complained of postoperative myalgia. Dosing should be based on total body weight. Because succinylcholine is water soluble, it would seem that doses based on lean body weight would suffice. Morbidly obese patients have increased

TABLE 12-7 Select Inherited Variants of Plasma Cholinesterase

PChE Variant	Genetic Label	Frequency (%)	Population Incidence	Enzyme Activity	Duration of Succinylcholine
Usual	Homozygote U	96	Normal	Normal	Normal; dibucaine number 70-80
—	Heterozygote U/A	3	1 in 480	Decreased	Slightly prolonged; dibucaine number 50-69
Atypical	Homozygote A	0.3	1 in 3200	Decreased by 70% or more	Significantly prolonged; dibucaine number 16-30
Fluoride	Homozygote F	0.03	Extremely rare	Decreased by 60%	Moderately prolonged
Silent	Homozygote S	0.04	Extremely rare	No activity	Significantly prolonged

PChE, Plasma cholinesterase.

BOX 12-4

Drugs That May Inhibit Cholinesterase

Agents Used to Treat Alzheimer's Disease

- Donepezil (Aricept)
- Rivastigmine (Exelon)
- Galantamine (Razadyne)—herbal medicine also available over the counter
- Tacrine (Cognex)—rarely used due to high number of adverse effects

fluid compartments and pseudocholinesterase levels, however, and require higher doses to ensure adequate paralysis.[64,65]

Pediatrics. In children, succinylcholine is used only in emergency situations to secure an airway. Routine use in elective procedures was abandoned in the early 1990s, owing to several widely reported cases of severe hyperkalemia and rhabdomyolysis in what appeared to be healthy children. The cases involved routine procedures in children with undiagnosed Duchenne muscular dystrophy (DMD).[66-70] This is an X chromosome–linked disorder with onset of symptoms usually around 5 years of age. Patients exhibit a typical progression of weakness and atrophy that starts in the legs and pelvis, spreads to the shoulders and neck, and finally involves the upper extremities and respiratory muscles. Life expectancy is rarely more than 30 years; death is often a consequence of cardiac and respiratory diseases. Children with DMD frequently require orthopedic surgery for repair of scoliosis or contractures.[71,72]

The Food and Drug Administration, in conjunction with the anesthesia community, placed the following warning on the use of succinylcholine:

RISK OF CARDIAC ARREST FROM HYPERKALEMIC RHABDOMYOLYSIS.

There have been rare reports of acute rhabdomyolysis with hyperkalemia followed by ventricular dysrhythmias, cardiac arrest, and death after the administration of succinylcholine to apparently healthy children who were subsequently found to have undiagnosed skeletal muscle myopathy, most frequently Duchenne muscular dystrophy.

This syndrome often presents as peaked T-waves and sudden cardiac arrest within minutes after the administration of the drug in healthy appearing children (usually, but not exclusively, males, and most frequently 8 years of age or younger). There have also been reports in adolescents.

Therefore, when a healthy appearing infant or child develops cardiac arrest soon after administration of succinylcholine not felt to be due to inadequate ventilation, oxygenation, or anesthetic overdose, immediate treatment for hyperkalemia should be instituted. This should include administration of intravenous (IV) calcium, bicarbonate, and glucose with insulin, with hyperventilation. Due to the abrupt onset of this syndrome, routine resuscitative measures are likely to be unsuccessful. However, extraordinary and prolonged resuscitative efforts have resulted in successful resuscitation in some reported cases. In addition, in presence of signs of malignant hyperthermia, appropriate treatment should be instituted concurrently.

Since there may be no signs or symptoms to alert the practitioner to which patients are at risk, it is recommended that the use of succinylcholine in children should be reserved for emergency intubation or instances where immediate securing of the airway is necessary (e.g., laryngospasm, difficult airway, full stomach) or for intramuscular use when a suitable vein is inaccessible.[73]

Because neither succinylcholine nor halothane is routinely used in children, the incidence of masseter spasm and malignant hyperthermia has decreased. Older studies have been reported in which jaw-opening ability and the presence or absence of masseter spasm, often considered a precursor of malignant hyperpyrexia, were studied. Research was conducted on 63 children anesthetized with halothane, then relaxed with succinylcholine, pancuronium, or vecuronium. Although vecuronium and pancuronium did not cause problems with jaw opening, succinylcholine was associated with this problem, and some of the succinylcholine patients were difficult to intubate.[73] Masseter spasm was noted to be more frequent in children administered succinylcholine concomitantly with halothane, compared with children who received succinylcholine and thiopental.[33,74]

A random sample of 6500 anesthetic records (53% of 12,169 anesthetic procedures performed) was reviewed. Fifteen cases of masseter spasm were identified. In each case, the patient underwent halothane induction and was then given succinylcholine intravenously. Seven of the 15 cases of masseter spasm developed in children between ages 8 and 10 years.[75] Researchers noted an increased incidence of masseter spasm in children with strabismus who were anesthetized with halothane and received IV succinylcholine. Of 1468 halothane anesthetic procedures, 15 cases of masseter spasm were discovered, and of these 15 cases, 6 occurred in the 211 patients with strabismus.[76]

In current practice, masseter spasm, although rare, is seen in adults during anesthesia induction and often in emergency rooms or critical care units during emergency airway management.[77,78] Common side effects of succinylcholine and contraindications for its use are noted in Table 12-8 and Box 12-5, respectively.

TABLE 12-8 Side Effects of Succinylcholine

Side Effect	Probable Cause
Hyperkalemia	Normally, serum K^+ is increased by up to 0.5 mEq/L secondary to potassium leaking from the depolarized muscle; in up-regulated patients, levels may rise much higher
Dysrhythmias	Tachycardia (usually mild) is the most common effect; bradycardia secondary to hyperkalemia, especially with repeat doses, can occur (Wide electrocardiographic complexes leading to cardiac arrest have been seen in children with Duchenne muscular dystrophy and other muscle disorders)
Myalgia	Secondary to fasciculation, even though some patients complain of muscle pain without having shown visible evidence of fasciculation
Myoglobinemia	Rare complication after extensive fasciculation or in malignant hyperthermia
Elevated intragastric pressure	Secondary to transient contraction of abdominal muscles during fasciculation; however, elevations of intragastric pressure seen after succinylcholine are not clinically relevant; less significant than occur with CO_2 insufflation during laparoscopic procedures
Elevated intracranial pressure (ICP)	Postulated to be secondary to fasciculation, increased central venous pressure; associated with increased cerebral blood flow secondary to muscle-spindle afferent activity and actions on peripheral neuromuscular junctions (ICP effects can be blocked by pretreatment with a small dose of nondepolarizing relaxant and the usual initial administration of an induction agent; may safely be used in neurosurgical procedures)
Elevated intraocular pressure (IOP)	Increases IOP within 1 minute and peaks at an increase of 9 mmHg within 6 min after administration; increase is a vascular event, with choroidal vascular dilation or a decrease in drainage secondary to elevated central venous pressure, temporarily inhibiting the flow of aqueous humor through the canal of Schlemm; generally considered safe in ocular emergencies
Malignant hyperthermia	Associated with a genetic predisposition; mechanism by which succinylcholine triggers the syndrome is not understood
Masseter spasm	Seen in adults in anesthetic and emergency use; sometimes followed by malignant hyperthermia

Modified from Kirby RR, et al, eds. *Clinical Anesthesia Practice*. 2nd ed. Philadelphia: Saunders; 2002; Atlee JL. *Complications in Anesthesia*. 2nd ed. Philadelphia: Saunders; 2007.
CO_2, Carbon dioxide; K^+, potassium.

BOX 12-5

Contraindications to the Use of Succinylcholine

- Hyperkalemia
- Burn patients with injuries of over 35% total body surface area (TBSA), third-degree burn
- Severe muscle trauma
- Neurologic injury (e.g., paraplegia, quadriplegia)
- Hyperkalemia resulting from renal failure
- Severe sepsis (e.g., abdominal)
- Muscle wasting, prolonged immobilization, extensive muscle denervation
- Malignant hyperthermia
- Duchenne muscular dystrophy
- Selected muscle disorders (see Table 12-9)
- Should be used in children under 8 years old only in emergency situations; not for routine intubation
- Genetic variants of pseudocholinesterase
- Allergy

Other Factors

Intraocular Pressure. Intraocular pressure (IOP) is known to increase by 5 to 15 mmHg for as much as 10 minutes after succinylcholine administration.[40,79] The average is about 10 mmHg for approximately 6 minutes. The exact mechanism of this increase is unknown. Some feel that tonic contractions of the extraocular muscles via fasciculation may explain this IOP increase. It is now thought, however, that succinylcholine-induced IOP increase is a vascular event, with choroidal vascular dilation or a decrease in drainage secondary to elevated central venous pressure temporarily inhibiting the flow of aqueous humor through the canal of Schlemm.[79]

This rise in IOP with succinylcholine administration is significantly less than the IOP increase associated with coughing or bucking. Patients who receive succinylcholine and are intubated 1 minute after its administration had IOPs that were not significantly higher than baseline. There are no documented reports of the extrusion of globe contents following the use of succinylcholine in open-eye emergency procedures. A recent review has essentially refuted the issue of eye damage after succinylcholine administration in open-globe injuries. It appears as a theoretical but not a clinical concern. Securing the airway remains the primary issue.[33,40,79] A thorough discussion of the use of succinylcholine and eye injuries is found in Chapter 39.

Hyperkalemia. Succinylcholine administration results in a transient hyperkalemia. A 0.5- to 1-mEq/L increase in serum potassium levels within 3 minutes after administration is usual. The effects were reported as lasting fewer than 10 to 15 minutes.[56]

A muscle receives signals to perform various functions from action potentials. As the action potential traverses the neuron, an influx of sodium and release of potassium occur. This mechanism of potassium release during normal muscle signaling is the same mechanism by which serum potassium increases because of the depolarization associated with receiving succinylcholine.[56]

Hyperkalemia may be profound in certain patients. In a review, Martyn and Richtsfeld[80] noted that lethal hyperkalemic responses to succinylcholine continue to be reported, although the mechanisms have not been completely elucidated. In the normally innervated mature muscle, acetylcholine receptors (AChRs) are located only in the junctional area. But in certain pathologic states—including upper or lower motor denervation, infection, direct

BOX **12-6**

Pathologic Conditions with Potential for Hyperkalemia with Succinylcholine

- Upper or lower motor neuron defect
- Spinal cord trauma
- Prolonged chemical denervation (e.g., muscle relaxants, magnesium, clostridial toxins)
- Direct muscle trauma, tumor, or inflammation
- Select muscular dystrophies and myopathies
- Thermal trauma
- Disuse atrophy
- Stroke
- Tetanus
- Severe infection

muscle trauma, muscle tumor, muscle inflammation, burn injury, immobilization, and prolonged chemical denervation by muscle relaxants, drugs, or toxins—there is an up-regulation (increase) of AChRs spreading throughout the muscle membrane. There is also an additional expression of two new isoforms of AChRs. The depolarization of these AChRs by succinylcholine and its metabolites leads to potassium efflux from the muscle and severe hyperkalemia. The nicotinic (neuronal) α7 acetylcholine receptors, which are also in muscle, are depolarized not only by acetylcholine and succinylcholine but by choline. Persistent choline stimulation may play a critical role in the hyperkalemic response to succinylcholine in patients with up-regulated AChRs.[80] Pathologic conditions with the potential for producing hyperkalemia associated with succinylcholine use are listed in Box 12-6.

Succinylcholine has been implicated in hyperkalemia after its administration to burn patients, so it is contraindicated in these patients.[81] Receptor up-regulation resulting from thermal trauma has been associated with several documented cases of cardiac arrest involving succinylcholine administration.[45] Indeed, plasma potassium levels as high as 15 mEq/L have been reported after the administration of succinylcholine, with this effect occurring 4 to 10 days after the burn and lasting for years after the burn.[82] The burn injury–related increase of AChRs is probably related to inflammation and local denervation of muscle. Major third-degree burns involving extensive body surface area may up-regulate AChRs throughout the body because of the extent and direct inflammation and injury to muscle. Hyperkalemia after burn injury to a single limb (8% body surface area) has been observed, indicating that burn size alone is not the only contributing factor. It is generally reported that the administration of succinylcholine to a burn patient more than 24 hours after the burn is unsafe; however, others note that succinylcholine can be safely used with burn patients for several days after the burn, because receptor up-regulation does not begin until 24 to 48 hours after the burn.[83,84] Changes in responses to both succinylcholine and the nondepolarizing agents have been noted for years after a major burn injury. Immobilization due to contractures may play a role. Succinylcholine should never be used in these patients, regardless of the time post-burn.[79,85]

Treatment of succinylcholine-induced hyperkalemia involves the emergency administration of drugs that promote the cellular uptake of potassium; these include insulin with glucose, catecholamines, and sodium bicarbonate.

The use of various muscle relaxants in patients with muscle disorders is reviewed in Table 12-9.

Malignant Hyperthermia. Malignant hyperthermia (MH) is a pharmacogenetic skeletal muscle disorder triggered by volatile anesthetics, succinylcholine, and stress. Succinylcholine is absolutely contraindicated in patients with known or suspected MH or who have MH in their families.[86] The mechanism for the possible triggering action remains unclear.[87] Mutations in the skeletal muscle ryanodine receptor gene may result in altered calcium release from sarcoplasmic reticulum stores, giving rise to MH. Patients who develop MH show signs such as muscle rigidity, rhabdomyolysis, increased carbon dioxide production, convulsions, metabolic acidosis, tachycardia, and a rapid increase in temperature.[88-90] A complete discussion of the physiologic and treatment aspects of MH can be found in Chapter 32.

Myalgias and Fasciculations. Postoperative muscle pain, particularly in the subcostal region, trunk, neck, upper abdominal muscles, and shoulders, is a common occurrence after succinylcholine administration.[91] A meta-analysis that included 52 randomized clinical trials found several interesting results.[92] The incidence of succinylcholine-induced myalgia is high, and symptoms sometimes last for several days. Small doses of nondepolarizing muscle relaxants, approximately 10% to 30% of the ED_{95} (effective dose, 95% response), reduce the incidence of fasciculations and myalgia, although pretreatment side effects occur. Higher doses of succinylcholine decrease the risk of myalgia compared with lower doses, and opioids do not have any impact; however, there is less myalgia with thiopental compared with propofol. There is no clear relation between succinylcholine-related fasciculation and myalgia. Pretreatment with sodium channel blockers (i.e., lidocaine) or nonsteroidal antiinflammatory drugs (diclofenac and aspirin) may prevent myalgia.

Myalgias are generally attributed to the occurrence of fasciculations resulting from repetitive firing of the motor nerve terminals, which causes uncoordinated muscle contractions. Patients who experience muscle pain most often are women and those persons who rarely participate in muscular activity. Conversely, patients at extremes of age, as well as pregnant patients, are least affected. Postoperative myalgias associated with succinylcholine increase in severity with early ambulation, which may consequently delay postoperative healing.[91]

Prevention is the key to avoiding postoperative muscle pain. Although not always effective, the incidence of myalgia is greatly reduced with nondepolarizer pretreatment. Use of no more than 10% of the ED_{95} is safe and effective and will avoid most of the difficulties of the patient experiencing weakness prior to loss of consciousness. Effective and equivalent doses have been reported as 2 mg rocuronium, 1.5 mg atracurium, and 0.3 mg vecuronium.[93]

Phase II Block. Administration of large doses of succinylcholine results in an alteration in the characteristics of the block.[44] Succinylcholine produces specific unique responses to nerve stimulation when compared with the nondepolarizing agents. These include a sustained response to tetanic stimulation, no fade with TOF or double-burst stimulation (DBS), and no posttetanic potentiation. Figures 12-9 and 12-10 show the characteristic train-of-four responses during onset and recovery from succinylcholine-induced block, respectively. Box 12-7 compares the characteristics of depolarizing and nondepolarizing neuromuscular blockade. Large doses of succinylcholine cause changes that resemble more of a nondepolarizing block, as evidenced by fade in response to tetanic stimuli, TOF, and DBS, the appearance of posttetanic potentiation, and theoretically, antagonism with drugs such as neostigmine. This commonly is referred to as a *desensitization, dual*, or *phase II block*. Some experts do not use these terms interchangeably.[43]

TABLE 12-9 Response of Neuromuscular Blocking Agents in Select Muscle Disorders

Neuromuscular Disorder	Succinylcholine	Nondepolarizing Neuromuscular Blocking Agents
Multiple sclerosis	Contraindicated	Increased sensitivity; anesthetic stress may increase rate of relapse
Motor neuron disease (amyotrophic lateral sclerosis [ALS, Lou Gehrig disease])	Contraindicated	Increased sensitivity
Guillain-Barré syndrome	Contraindicated	Increased sensitivity; avoid agents with cardiac side effects
Charcot-Marie-Tooth disease	Contraindicated	Response to atracurium and mivacurium normal; all others, increased sensitivity
Muscular dystrophies	Contraindicated	Increased sensitivity
Myotonias	Contraindicated	Increased sensitivity; anticholinesterase agents may precipitate myotonia
Myasthenic syndromes	Resistant; prolonged duration of action may be present with plasmapheresis or anticholinesterase therapy	Extreme sensitivity
Mitochondrial myopathies	Contraindicated	Increased sensitivity
Hyperkalemic periodic paralysis	Contraindicated	Normal response
Hypokalemic periodic paralysis	Contraindicated	Normal response
Malignant hyperthermia	Contraindicated	Normal response
Myasthenia gravis	Resistant	Increased sensitivity
Huntington chorea	Increased sensitivity	Increased sensitivity
Up-regulation of acetylcholine receptors because of spinal cord trauma, stroke, or prolonged immobility	Contraindicated	Usually resistant, but depends on time since injury

Modified from Naguib M, et al. Advances in neurobiology of the neuromuscular junction: implications for the anesthesiologist. *Anesthesiology*. 2002;96(1):202-231; Malignant Hyperthermia Association of America, 11 East State Street, PO Box 1069, Sherburne, NY 13460, 2012; Brambrink AM, Kirsch JR. Perioperative care of patients with neuromuscular disease and dysfunction. *Anesthesiol Clin*. 2007;25(3):483-509.

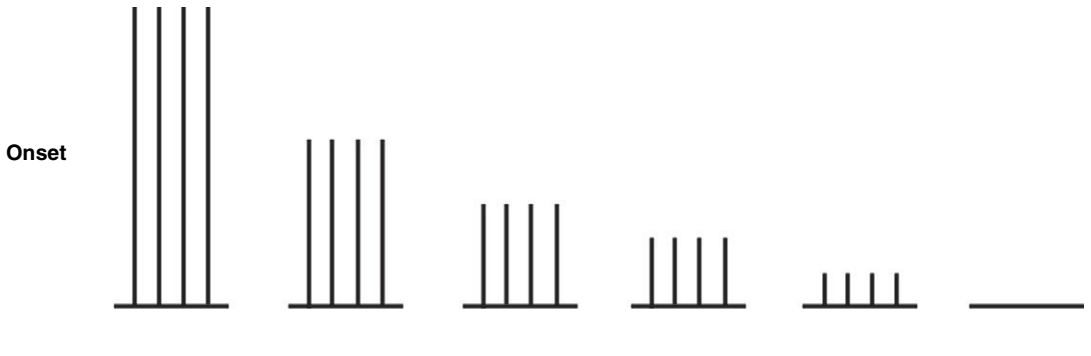


FIGURE 12-9 Characteristic train-of-four response during the onset of succinylcholine.

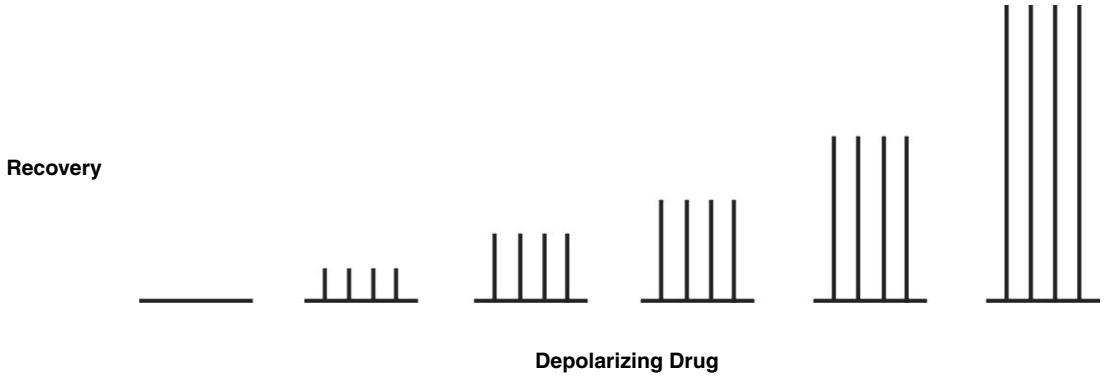


FIGURE 12-10 Characteristic train-of-four response during recovery from succinylcholine.

BOX **12-7**

Characteristics of Neuromuscular Blockade

Depolarizing (Phase I) Block

- Muscle fasciculation precedes onset of neuromuscular blockade
- Sustained response to tetanic stimulation
- Absence of posttetanic potentiation, stimulation, or facilitation
- Lack of fade to tetanus, train-of-four, or double-burst stimulation
- Block antagonized by prior administration of nondepolarizer as pretreatment (approximately 20% more succinylcholine required)
- Block potentiated by anticholinesterase drugs

Nondepolarizing (Phase II) Block

- Absence of muscle fasciculation
- Appearance of tetanic fade and posttetanic potentiation, stimulation, or facilitation
- Train-of-four and double-burst fade
- Reversal with anticholinesterase drugs
- In rare cases may be produced by an overdose and desensitization with succinylcholine at doses greater than 6 mg/kg

As explained earlier, tetanic fade is caused by an interaction with cholinergic presynaptic receptors mediating positive feedback–induced acetylcholine release from the motor nerve end.[30,80] The finding that high doses of succinylcholine inhibited presynaptic $\alpha_3\beta_2$ AChRs (i.e., the compound behaved like a nondepolarizing relaxant) may help explain how high or repeated doses of succinylcholine result in a nondepolarizing type of block (phase II block) characterized by fade and posttetanic potentiation.[94] The exact mechanism is unclear; however, an electrical imbalance caused by repeated opening of junctional channels has been proposed.[43] Development of a desensitization block is a historical discussion because doses exceeding 6 to 8 mg/kg are required, and high doses, as seen with succinylcholine infusions, are rarely used in current practice.

NONDEPOLARIZING AGENTS

The efficacy of the nondepolarizing relaxants is similar, so the choice of one drug over another is largely made on other factors. Specific patient characteristics, type of surgical procedure, pharmacokinetics, and side-effect profile guide the selection of an individual relaxant for a given situation. The intermediate duration nondepolarizing relaxants are almost exclusively used in current clinical practice.

Rocuronium Bromide

Rocuronium is the most widely used nondepolarizing relaxant in the United States.[13] The introduction of vecuronium and atracurium, both of which were marketed as intermediate-acting neuromuscular blocking agents (NMBAs) improved the flexibility of the clinician in matching the agent to the expected duration of surgery.[95] Slow onset, solution stability, and histamine release remained problems to be overcome.[96] Rocuronium (Zemuron) has been developed to partially fill this void. It combines a duration and cardiovascular profile comparable to those of vecuronium, with an onset that is only slightly longer than that of succinylcholine.[95-97]

A derivative of vecuronium, rocuronium bromide is chemically designated as 1-[17β-(acetyloxy)-3α-hydroxy-2β-(4-morpholinyl)-5α-androstan-16β-yl]-1-(2-propenyl) pyrrolidinium bromide, and

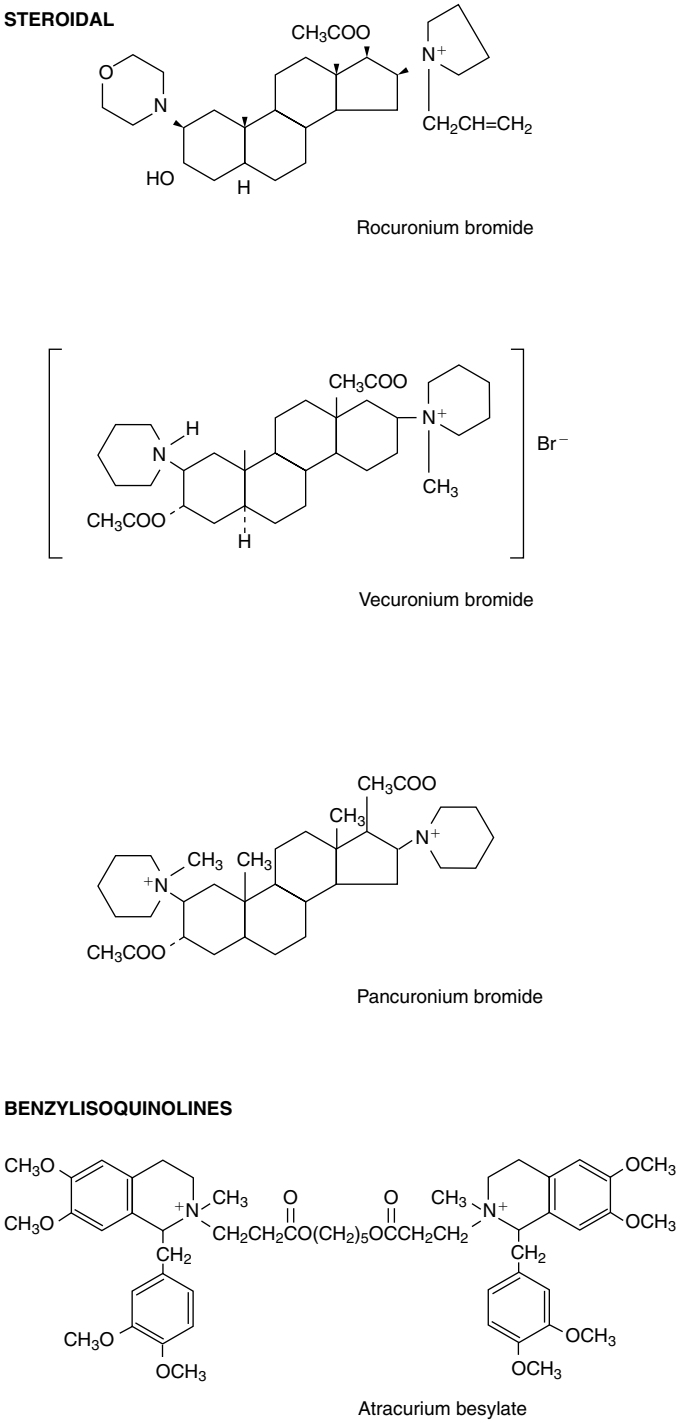


FIGURE **12-11** Chemical structures of nondepolarizing muscle relaxants.

it has one seventh to one eighth the potency of its derivative.[35,44,97] It is a monoquaternary structure that also shares its aminosteroid structure with pancuronium.[98] It has a molecular weight of 609.7 and a molecular formula of $C_{32}H_{53}BrN_2O_4$ (Figure 12-11). The pH of rocuronium is adjusted to 4.0, and the agent contains no preservative. It exists in a solution that is stable at room temperature for up to 30 days.[99] Each 1 mL of solution contains 10 mg of rocuronium bromide and 2 mg of sodium acetate.

Results of clinical studies of both healthy children and healthy adults suggest an ED_{95} of approximately 0.3 mg/kg.[34] Its steady-state volume of distribution in healthy adults is 207 (14) mL/kg

and is slightly smaller for children ages 4 to 8 years. Rocuronium is approximately 46% bound to human plasma proteins, somewhat less than other neuromuscular blockers. This decreased plasma protein binding may lead to a more rapid onset because more unbound drug is readily available at the neuronal binding sites.[100]

Pharmacokinetics

Onset. Rocuronium is the drug of choice and is widely used as the NMBA for rapid sequence induction (RSI) when succinylcholine is contraindicated. A disadvantage of using rocuronium during RSI is its long duration of action.[101,102]

Administration of rocuronium with doses ranging from 0.6 to 1.2 mg/kg provides good to excellent intubating conditions within 45 to 90 seconds.[36,103,104] A meta-analysis noted that there was no statistical difference in intubation conditions when succinylcholine was compared to 1.2 mg/kg rocuronium.[105-107] The onset of muscle relaxants is related to potency. The less potent an agent, the faster the onset. Rocuronium has an onset of action that is inversely proportional to its potency,[97] and it is less potent than other steroidal-based neuromuscular blockers.[108,109] This decreased potency together with the decrease in the amount of drug that is protein bound allow a larger mass of drug at the prejunctional and postjunctional cholinoreceptors.[36,108] This large drug mass at the receptor site yields a faster onset.[110,111]

One method used clinically to accelerate the onset of rocuronium when administering it to intubate during RSI is referred to as *priming*. Priming involves giving 10% of the calculated intubating dose prior to inducing anesthesia. After a period of 1 to 3 minutes, the patient is anesthetized, and the remaining rocuronium is given. Giving a small portion of the relaxant dose in this manner speeds the onset by valuable seconds.[112-114] Priming, however, produces respiratory distress in 10% of the patients in which it is used.[115]

Duration. Rocuronium is classified as an intermediate duration relaxant.[38] In usual ED_{95} doses, it lasts 30 to 60 minutes. The duration of action is similar to that of vecuronium, and its duration depends, like that of any other agent, on the dose administered.[35] An intubating dose of 0.6 to 1 mg/kg provides a clinical duration of 30 to 90 minutes.[35,36] The administration of 0.6 mg/kg resulted in 10% recovery of T_1 within 27.2 (5.5) minutes, whereas 25%, 75%, and 90% recovery of T_1 occurred in 31.1 (5.6) minutes, 39.3 (6.2) minutes, and 41.2 (6.1) minutes, respectively.[116] Recovery of the TOF ratio to 0.8 when rocuronium was administered with sevoflurane, isoflurane, and propofol occurred in 103 (30.7), 69 (20.4), and 62 (21.1) minutes, respectively.[117]

Elimination. Rocuronium undergoes both hepatic and renal elimination. The primary means of rocuronium elimination is biliary elimination of unchanged drug. It also undergoes deacetylation via the liver.[116-118] Renal excretion accounts for 33% of elimination.[44] Plasma levels of rocuronium follow a three-compartment open model. This results in extensive redistribution after IV injection. Therefore before elimination occurs, serum levels of the drug are low enough to result in recovery.[34] The elimination half-life of rocuronium is 60 to 120 minutes. The elimination half-lives of the agent in children, normal adults, and elderly persons are 38.3 minutes, 56 minutes, and 137 minutes, respectively.[108,119] Patients with significant liver or kidney disease will have a prolonged effect.[48,58]

Vecuronium Bromide

Vecuronium bromide (Norcuron) is a potent nondepolarizing neuromuscular blocker. Studies comparing vecuronium with pancuronium, its predecessor, found vecuronium to be 1.5 times more potent than its parent compound.[120] Both agents were developed by manipulation of the steroid nucleus. The molecule was successfully altered from bisquaternary pancuronium to a monoquaternary compound, creating an agent with a more rapid onset and a shorter duration. Vecuronium is more lipophilic than pancuronium, although it is still predominantly a hydrophilic compound. This change in its solubility is thought to be the cause of its differing pharmacokinetic profile.[121-123]

The chemical formula of vecuronium bromide is $C_{34}H_{57}BrN_2O_4$, and the drug has a molecular weight of 637.74 (see Figure 12-11). It is chemically designated as piperidinium 1-[(2β, 3α, 5α, 16β, 17β)-3, 17-bis(acetyloxy)-2-(1-piperidinyl) androstan-16-yl]-1-methyl bromide.[122]

Vecuronium is available as a 10- or 20-mg, sterile, nonpyrogenic powder for IV use only. Once reconstituted, the solution has a pH of 4.0 and is stable for 24 hours at 25° C.[122] Miller et al.[121] constructed dose-response curves to derive the ED_{95}, which they found to be 0.03 mg/kg. The agent has a steady-state volume of distribution of 0.21 to 0.27 L/kg.[123]

Pharmacokinetics

Onset. Vecuronium has an onset of action that is 1.5 times that of pancuronium, a proportion similar to that of its potency.[124,125] At a dose of twice the ED_{95}, 0.1 mg/kg, the maximum suppression of muscle twitch occurs within 3 minutes of administration. The onset varies with the concurrent anesthetic administered and is inversely proportional to the dose.[126] With balanced anesthesia, a 0.1-mg/kg dose of vecuronium resulted in an onset of 3.1 minutes, whereas in patients receiving isoflurane, N_2O-O_2 anesthesia, the onset time decreased to 1.8 minutes.[123,127-129]

Duration. Duration of action varies with the type of anesthetic being administered and the dose of the agent. This phenomenon has been noted with other nondepolarizing agents, as well as with vecuronium.[129] Haines[127] reported a duration of 36.2 ± 6.4 minutes after a dose of 0.1 mg of vecuronium per kilogram was given patients undergoing balanced anesthesia. The time from 25% twitch recovery to 75% twitch recovery at a dose of 0.1 mg/kg was 11 to 12 minutes and the duration 30 to 45 minutes.

Elimination. Vecuronium is eliminated via hepatic and renal mechanisms. Vecuronium undergoes elimination via an orthodox three-compartment model. Because it is more lipophilic than other agents in its class, vecuronium does not depend solely on the kidneys for elimination. Only 20% to 30% of the administered dose is recovered unchanged in the urine within 24 hours.[121] A major portion of the dose, 40% to 80%, is taken up by the liver and excreted in bile.[125] Small amounts of its metabolites (3-hydroxy, 17-hydroxy, and 3,17-hydroxy) can be detected by thin-layer chromatography. The 3-desacetyl metabolite is thought to have around 50% the potency of vecuronium.[9] It is avoided in critical care units for long-term administration because of accumulation. Reported elimination half-lives range from 51 to 90 minutes in healthy adults. Total clearances have been reported from 3 to 5.6 mL/kg/min.[120,130,131]

Pancuronium Bromide

Pancuronium bromide was first synthesized for Organon in England in 1966. Researchers, especially Lewis and colleagues, were searching for an agent that was nondepolarizing, had a rapid onset, had an intermediate duration of action, was easily reversed, and had no significant unwanted side effects.[6] After clinical use by Baird and Reid in 1967 in Europe, the agent was introduced in the United States in 1972.[132-135]

The chemical designation of pancuronium bromide is 2β, 16β-dipiperidine-5α-androstane-3α, 17-β-diol diacetate dimethobromide (see Figure 12-11). It has a volume of distribution of 0.18 to 0.26 L/kg; is an odorless, white, crystalline powder; and has a melting point of 215° C. Extensive testing revealed an effective dose of 0.02 to 0.05 mg/kg in mice, rats, rabbits, cats, and dogs.[6] Further research determined the ED_{95} of pancuronium to be 0.075 mg/kg in humans.[130,131]

Pharmacokinetics

Onset. The mean time to depression of twitch to 5% of control values after a dose of twice the ED_{95} (0.14 mg/kg) is 4.4 (0.5) minutes.[136] At a dose of 1.5 ED_{95}, which is estimated as 0.08 mg/kg, an onset time to 90% blockade was 2.3 ± 0.3 minute.[137,138]

Duration. Pancuronium is a long-acting nondepolarizer that does not release histamine.[133] At an ED_{90} dose of 0.062 mg/kg, the mean duration of blockade was 109 minutes.[139] The average duration is 60 to 90 minutes.

Elimination. Pancuronium is excreted mainly via the kidney. Thirty-five percent of the drug is also released in the bile.[88] Up to 24 hours after the injection of pancuronium, anywhere from 43% to 67% of unchanged drug may be found in the urine.[135] Its half-life is prolonged and clearance is reduced in patients with renal failure.[140] A summary of the selected properties of the neuromuscular blocking agents is given in Table 12-10.

Atracurium Besylate

Atracurium (Tracrium) was developed as a result of a joint venture between the Department of Pharmaceutical Chemistry at the University of Strathclyde and Wellcome Research Laboratories.[141] The objective of the investigators was to develop an agent with the following characteristics:

- Competitive bisquaternary neuromuscular blocker
- Highly selective in action
- Degradable without renal or hepatic intervention[141,142]

The resulting agent was a bisquaternary competitive neuromuscular blocker in the form of a besylate salt.[121,141] Atracurium besylate is designated as 2,2′-[1,5-pentanediylbis[oxy(3-oxo-3,1-propanediyl)] bis[1-[(3,4-dimethoxyphenyl) methyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinolinium] dibenzenesulfonate. It has a molecular weight of 1243.49 and a molecular formula of $C_{65}H_{82}N_2O_{18}S_2$ (see Figure 12-11). The pH of atracurium is adjusted to 3.25 to 3.65, and the agent contains the preservative benzyl alcohol. Atracurium loses potency at the rate of 6% per year when it is refrigerated at 5° C. At room temperature, the agent degrades approximately 5% per month, and its recommended unrefrigerated shelf life is 14 days. It was developed with an intermediate duration in mind, and it spontaneously degrades to inactive products. It is well absorbed intravenously, with an ED_{95} of 0.10 to 0.25 mg/kg.[121,143]

Atracurium is rapidly distributed throughout the extracellular space after IV injection and has a volume of distribution of 153 (13) mL/kg. It is approximately 82% protein bound and does not distribute into the fat, because it is ionized.[144] Obese patients who received atracurium according to ideal body weight demonstrated no difference in recovery indices or recovery times when compared with control patients of normal weight because of the agent's lack of organ dependency for elimination.[145-147] The chemical structure of atracurium besylate is shown in Figure 12-11.

Pharmacokinetics

Onset. As expected, atracurium has an onset time that is inversely proportional to dosage, in the range of 1.2 to 2.8 minutes. When various doses of atracurium were given to 70 patients anesthetized with fentanyl, thiopental, and nitrous oxide–oxygen (N_2O-O_2) anesthesia, clinical effects were seen at doses of 0.3 to 0.6 mg/kg. Other investigators, however, have found the onset to be longer, in the range of 2.31 to 3.55 minutes.[126,127,148]

Duration. The duration of atracurium increases as its dose increases. Duration of maximum effect and duration to 95% recovery of peak contraction are reported in the range of 5.6 to 69.5 minutes.[127,149,150] On average, as an intermediate relaxant, the duration of action is 30 to 60 minutes.

Elimination. The development of atracurium arose from the discovery of the plant *Leontice leontopetalum* and one of its components, designated *petaline*. This component was similar to tubocurarine and was observed to undergo an unexpectedly facile degradation in mild alkali by the well-known Hofmann elimination pathway, with loss of water and formation of a tertiary base.[143] Stenlake's pursuit of this research led to the development of atracurium, which does not rely on any organ system for its breakdown and elimination. Study of the clinical pharmacology of atracurium reveals that its molecules decompose by Hofmann elimination, as well as by nonspecific ester hydrolysis.[141,143,145,151]

Hofmann elimination is a temperature- and pH-dependent breakdown of the drug molecule. In the vial, atracurium is at room temperature in an acidic medium. When injected, the pH rises to blood pH of 7.4, and the temperature increases to body temperature. These increases in pH and temperature allow the Hofmann elimination to ensue. Atracurium degrades via Hofmann elimination (10% to 40%). In mild alkaline states, fission occurs at the quaternary nitrogen position, and laudanosine is subsequently released.[151,152] The agent then degrades further. Ester hydrolysis also occurs, and it is catalyzed by nonspecific esterases into a quaternary alcohol and a quaternary acid.[141,151] These metabolites are excreted primarily in bile and urine.

Cisatracurium Besylate

The most notable of the 10 stereoisomers of atracurium, cisatracurium besylate (Nimbex) has gained popularity in the clinical arena since the mid-1990s. It is a nondepolarizing muscle relaxant, three times more potent than atracurium with a slower onset of action. The agent is available as a sterile, nonpyrogenic aqueous solution in 5-, 10-, and 20-mL vials. The pH is 3.25 to 3.65, and the concentration is 2 mg/mL (except in the 20-mL vial, in which the concentration is 10 mg/mL for convenience in the intensive care unit setting).[153] Advantages of cisatracurium include maintenance of cardiovascular stability, non-organ–dependent elimination, and a lack of histamine release after injection.[154,155]

Pharmacokinetics

Onset. Cisatracurium is regarded as intermediate in its onset and duration of action. In adults the ED_{95} is 0.05 mg/kg during N_2O-O_2 opioid anesthesia.[156] It has been noted to be five times more potent than rocuronium, with a slower onset of action, longer duration, and slower spontaneous recovery.[157,158] An IV bolus of 0.1 mg/kg (twice the ED_{95}) produces desired levels of relaxation within 3.1 minutes.[159] Doses of three to four times the ED_{95} (0.15 to 0.2 mg/kg) decrease the mean time of onset to 3.4 and 2.8 minutes, respectively.[160]

Duration. After doses of three to four times the ED_{95}, the average time for the first twitch in a TOF to recover to 25% of control is 65 minutes.[161] Further studies report that the duration of cisatracurium with an intubating dose of 0.25 mg/kg is 55 to 75 minutes. Full recovery at the aforementioned dose occurs in 75 to

TABLE **12-10** Summary of Select Properties of Neuromuscular Blocking Agents

Classification	ED_{95} (mg/kg)	Intubating Dose Usually 2-3 × ED_{95} (mg/kg)	Onset	Duration	Metabolism	ELIMINATION		AUTOMATIC GANGLIA EFFECT	CARDIAC MUSCARINIC EFFECT	Histamine Release	Resulting Cardiac Action
						Kidney (%)	Liver (%)	(SNS & PNS)	(Vagal Block)		
Ultrashort											
Succinylcholine (Anectine, Quelicin)	0.3	1-1.5	30-60 sec	5-10 min	Plasma cholinesterase	<2	0	Stimulates	Stimulates and/or blocks	0 ?	Usually tachycardia, bradycardia with repeat doses
Intermediate											
Atracurium (Tracrium)	0.15	0.5	2-4 min	30-60 min	Hofmann elimination, nonspecific esterase hydrolysis	10-40 metabolites	0	0	0	yes	Hypotension, tachycardia, flushing
Cisatracurium (Nimbex)	0.05	0.1	2-4 min	30-60 min	Hofmann elimination, nonspecific esterase hydrolysis	Up to 77 metabolites	0	0	0	0	0
Rocuronium (Zemuron)	0.3	1	1-3 min	30-60 min	Hepatic and renal	10-30	70-90	0	0	0	0
Vecuronium (Norcuron)	0.05	0.1	2-4 min	30-60 min	Hepatic and renal	40-50	50-60	0	0	0	0

100 minutes. Additional sources report the duration as 55 to 61 minutes.[162]

Elimination. Cisatracurium, like atracurium, undergoes Hofmann elimination (which is pH and temperature dependent) in the plasma and tissues. Hofmann elimination accounts for 77% of total body clearance, and nonspecific esterases are responsible for 23% of total body clearance. Of the organ-dependent clearance, 16% occurs through renal pathways.[163] Studies have demonstrated a half-life of approximately 26 to 36 minutes, with an increase in the rate of degradation as pH increases.[164] As with atracurium, one of the metabolites of cisatracurium is laudanosine along with acrylates. However, cisatracurium liberates one fifth as much laudanosine as atracurium.[165]

Nondepolarizing Agents' Effect on Various Organ Systems

Central Nervous System

All muscle relaxants are quaternary ammonium compounds and therefore water soluble at physiologic pH. As such, they are unable to cross physiologic barriers such as the blood-brain, placental, and gastric, and therefore have no CNS effects.

Cardiovascular System

The NMBAs have no direct effect on cardiac muscle. Any cardiovascular changes that occur with the administration of a muscle relaxant are caused by indirect actions such as histamine release or effects on the autonomic nervous system. Of the current nondepolarizing relaxants, only atracurium and pancuronium exhibit any cardiac effects. Atracurium has been associated with increases in heart rate and decreases in blood pressure at doses of 0.5 mg/kg and greater because of histamine release.[166,167] Systolic and diastolic pressures significantly decrease, and cardiac output was significantly increased at 2, 5, and 10 minutes after a bolus dose. The increase in cardiac output is the result of a markedly decreased systemic vascular resistance. Nearly all of the hemodynamic changes associated with the administration of atracurium have been linked to the release of histamine.[132,166,167] Administration of cisatracurium does not result in histamine release. The effects of stimulation of histamine receptors and the resulting effects are listed in Box 12-8.

Pancuronium produces tachycardia. Significant increases in heart rate 3 minutes after the administration of the agent were noted in patients with coronary artery disease who were scheduled for coronary artery bypass graft and who received a dose of 0.1 mg/kg, despite administration of narcotics.[166,168,169] Increases in heart rate are often accompanied by mild increases in mean arterial pressure. The tachycardia results from a vagolytic and an indirect sympathomimetic action. The other steroidal relaxants vecuronium and rocuronium have no significant cardiac effects at clinical doses. The cardiovascular effects of the neuromuscular blocking agents are summarized in Box 12-9.

Hepatic System

The steroidal relaxants rocuronium, vecuronium, and pancuronium are affected by changes in hepatic status. They are primarily eliminated by a combination of liver metabolism and biliary and renal excretion, and therefore their duration of action is prolonged in patients with hepatic disease. Vecuronium, which is metabolized in the liver, has been administered to patients with hepatic disease.[170-174] Lebrault et al.,[170] for example, compared patients with cirrhosis who received 0.2 mg of vecuronium per kilogram with healthy control patients and found that elimination half-life was prolonged approximately 60%. This effect resulted in a time to return of 50% twitch height of 130 minutes in the cirrhotic group, compared with 62 minutes in healthy patients. Differences in clearance among alcoholic patients with liver disease are dose dependent and usually not significant.[174] Rocuronium and pancuronium have an increased volume of distribution and elimination times, resulting in significantly longer durations.[170-173] The duration of action of rocuronium, as well as the onset, is typically prolonged in patients with hepatic disease such as cirrhosis. Patients with hepatic dysfunction demonstrate an elimination half-life that is increased to 173 minutes, compared with the normal 60 to 120 minutes. This supports the finding that the route of plasma clearance of rocuronium is predominantly hepatic with much of the drug excreted being unchanged in bile.[175] Cautious dosing is warranted, along with vigilant monitoring of neuromuscular function in these patients.

An active desacetyl metabolite results from the breakdown of each of the steroidal relaxants. These metabolites exhibit relaxant activity and accumulate with prolonged use. Although this does not pose a problem perioperatively, prolonged paralysis and myopathies in patients with multiorgan failure in critical care units has been a problem with multiday use. Practice guidelines for sustained neuromuscular blockade in critically ill adults and children have been published.[176,177] Nondepolarizing relaxants are used in intensive care to immobilize patients for procedural interventions, decrease oxygen consumption, facilitate mechanical ventilation, reduce intracranial pressure, prevent shivering, and manage

BOX 12-8

Effects of Stimulation of Histamine Receptors by Neuromuscular Blockers

H_1 Receptors	H_2 Receptors
Increased capillary permeability	Increased gastric acid production
Bronchoconstriction	Systemic and cerebral vasodilation
Intestinal contraction	Positive inotropic effects
Negative dromotropic effects	Positive chronotropic effects

Atracurium releases modest amounts of histamine. Slight histamine release may occur with succinylcholine. The amount of histamine release is dependent on dose and speed of injection.

With endogenous histamine release, all receptor responses are elicited.

Prophylaxis against histamine release requires administration of both H_1- and H_2-receptor blockers.

H, Histamine.

BOX 12-9

Cardiac Effects of Neuromuscular Blocking Drugs

- Atracurium causes histamine release and may produce hypotension and tachycardia.
- Pancuronium is vagolytic and causes slight catecholamine release (indirect sympathomimetic), producing tachycardia.
- Succinylcholine usually results in slight tachycardia. Repeat dosing in adults and any dose in children may produce sudden, abrupt bradycardia. Many types of arrhythmias have been reported.

tetanus and acute respiratory distress syndrome (ARDS). Emerging data may support the use of cisatracurium in select patients with ARDS.[178,179] Cisatracurium may be kinetically preferred for patients with organ dysfunction. Close monitoring with peripheral nerve stimulation is recommended with sustained use of nondepolarizing relaxants to avoid drug accumulation and minimize the risk for adverse drug events. Reversal of paralysis is best achieved by discontinuing therapy.[178]

Atracurium and cisatracurium are not affected by changes in liver function and are the agents of choice for use in patients with liver disease because of their unique method of metabolism, specifically their breakdown pathway via Hofmann elimination and nonesterase-dependent hydrolysis.[121] Cisatracurium is preferred for its lack of histamine release. The pharmacokinetics of atracurium in patients with hepatic and renal disease was compared with those in nonimpaired control subjects. No differences in plasma elimination half-lives were noted.[134,180] The effect of atracurium infusions in patients with fulminant hepatic failure who were awaiting liver transplantation, as well as during liver transplantation, has been studied. Plasma clearances and half-lives were similar to those reported in healthy individuals, and no cumulative effects were noted.[181,182]

Renal System

The steroidal relaxants rocuronium, vecuronium, and pancuronium are affected by changes in renal status. Because all three drugs depend to varying degrees on renal and hepatic elimination, their duration of action is prolonged in patients with decreases in renal function. Pancuronium is largely (80% to 85%) dependent on renal elimination, which is markedly decreased in patients with chronic renal failure and therefore leads to the prolongation of neuromuscular blockade.[183] A small portion of rocuronium is excreted unchanged in the urine, resulting in a prolonged elimination half-life in patients with renal disease.[175] The onset time of rocuronium is not affected by renal failure.

Atracurium and cisatracurium are considered the agents of choice in patients with renal disease. Onset and duration are not affected by changes in renal function. Doses of three times the ED_{95} (0.15 mg/kg) of cisatracurium were given to 39 patients with decreased renal function, all of whom were induced with fentanyl and thiopental. Onset time, mean arterial blood pressure, heart rate, and time to recovery of 25% T_1 were assessed, and there was no significant variation in the drug effects compared with patients with normal renal function.[184]

Effects in Special Populations

Elderly Patients. The onset times of the NMBAs are generally delayed in the elderly due to slower circulation times and other kinetic changes associated with aging.[185] This is true for all relaxants. The dosing interval and duration of action of the steroidal relaxants rocuronium, vecuronium, and pancuronium are prolonged in the elderly due to decreased hepatic and renal clearance and an increased volume of distribution.[185-188] The duration of atracurium and cisatracurium is not affected by aging, making these the most predictable NMBAs in the elderly.

Obese Patients. The use of the NMBAs in obese patients raises some special clinical considerations. Obese patients require a rapid-sequence induction more frequently than nonobese patients, owing to their higher risk for gastroesophageal reflux disease and pulmonary aspiration. A difficult airway is more often encountered. It is especially important to ensure full reversal of the relaxant actions in this patient group because of the higher occurrence of breathing abnormalities and lung compromise. Sleep apnea syndrome and the associated anesthetic management must be considered.[189-192] The duration of action of the steroidal relaxants rocuronium, vecuronium, and pancuronium are all prolonged. This is likely due to a decrease in elimination.

The kinetics of atracurium and cisatracurium are not significantly changed in obese patients, making these the most reliable agents. Cisatracurium is preferred for its lack of histamine release. Several authors recommend that to avoid overdosing, NMBAs should be dosed at ideal body weight, except for succinylcholine, which is given according to total body weight.[64,65,191,193-196]

Pediatrics. When compared with adults, several differences exist among neonates, infants, and children in relation to their response to NMBAs. A more complete discussion of neonatal and pediatric pharmacology is given in Chapters 47 and 48. A few general observations can be made here. The neuromuscular junction is incomplete at delivery and continues to mature throughout infancy.[197] The sensitivity to any relaxant may change from birth through childhood. Neonates and infants have a higher volume of distribution and differences in redistribution, elimination, and metabolic rates, which vary with age. Infants appear to be more sensitive to nondepolarizing drugs than adults. The onset of action of the relaxants tends to be faster in children than adults. The duration of action of the intermediate NMBAs is longer in infants younger than 10 months of age than in children 1 to 5 years of age.[198] Recovery is faster in children than adults.[199]

Other Factors

Hypothermia. The importance of keeping the patient's core body temperature normothermic cannot be overstated. Hypothermic patients exhibit a prolonged duration of action to all muscle relaxants. This is due to decreased metabolism and delayed hepatic and renal clearance.[43] Severe (but not mild) hypothermia makes it more difficult to antagonize a neuromuscular block.[200-202]

Allergy. The role of muscle relaxants in perioperative anaphylaxis is well established. An ongoing report from France reported on 1861 cases of IgE-mediated anaphylaxis. The most common causes were NMBAs (n = 1067, 58.08%), latex (n = 361, 19.65%), and antibiotics (n = 236, 12.85). Succinylcholine (n = 356, 33.40%) and rocuronium (n = 313, 29.30%) were the most frequently involved, and pancuronium and cisatracurium are the least. Cross-sensitization among the different agents is common and is more frequent with aminosteroid than with the benzylisoquinoline drugs.[203,204] Quaternary and tertiary ammonium ions in the relaxant molecules are the main component of the allergenic sites on the reactive drugs. The flexibility of the chain between the ammonium ions as well as the distance between the substituted ammonium ions might be of importance during the elicitation phase of IgE-mediated reactions. Flexible molecules, such as succinylcholine, were considered more potent in stimulating sensitized cells than rigid molecules, such as pancuronium.[204] Skin testing and follow-up guidelines have been published.[205] A complete discussion of anaphylaxis management and anesthesia is given in Chapter 41.[206,207]

REVERSAL OF NEUROMUSCULAR BLOCKADE

Complete and effective reversal of the action of the muscle relaxants is one of the most important aspects of clinical practice. Incomplete relaxant reversal and the resulting difficulties continue to be a challenge. The use of nerve stimulators and our knowledge of relaxant pharmacology continue to evolve; however, a significant incidence of postoperative residual paralysis stubbornly remains. Three anticholinesterase agents for reversal of the relaxants are available, although neostigmine is used overwhelmingly.

BOX **12-10**

Adverse Effects of Residual Neuromuscular Block

Volunteer Studies

- Impairment of pharyngeal coordination and force of contraction
- Swallowing dysfunction/delayed initiation of the swallowing reflex
- Reductions in upper esophageal sphincter tone
- Increased risk of aspiration
- Reductions in upper airway volumes
- Impairment of upper airway dilator muscle function
- Decreased inspiratory airflow
- Upper airway obstruction
- Impaired hypoxic ventilatory drive
- Profound symptoms of muscle weakness (visual disturbances, severe facial weakness, difficulty speaking and drinking), generalized weakness

Clinical Studies in Surgical Patients

- Increased risk of postoperative hypoxemia
- Increased incidence of upper airway obstruction during transport to the postanesthesia care unit (PACU)
- Higher risk of critical respiratory events in the PACU
- Symptoms and signs of profound muscle weakness
- Delays in meeting PACU discharge criteria and achieving actual discharge
- Prolonged postoperative ventilatory weaning and increased intubation times (cardiac surgical patients)
- Increased risk of postoperative pulmonary complications (atelectasis or pneumonia)

From Murphy GS, Brull SJ. Residual neuromuscular block: Lessons unlearned. Part I: definitions, incidence, and adverse physiologic effects of residual neuromuscular block. *Anesth Analg* 2010;111(1):120-128; Brull SJ, Murphy GS. Residual neuromuscular block: Lessons unlearned. Part II: Methods to reduce the risk of residual weakness. *Anesth Analg*. 2010;111(1):129-140.

BOX **12-11**

Reversal Considerations in Clinical Practice

Considerations When Return of Muscle Function Is Incomplete

- As with any reversal agent, the ability to counteract a nondepolarizing blocking agent depends on the amount of spontaneous recovery before the administration of a reversal drug.
- Has enough time been allowed for the anticholinesterase to antagonize the block (at least 15 to 30 minutes)?
- Is the neuromuscular blockade too intense to be antagonized?
- Even if recovery appears clinically adequate, a small dose of neostigmine may be prudent if the time since relaxant administration is less than 4 hours.
- Has an adequate dose of antagonist been given?
- Are the other anesthetics and adjunctive agents contributing to patient weakness?
- Has metabolism or excretion of the relaxant been reduced by a possibly unrecognized process?
- Have acid-base and electrolyte status, temperature, age, drug interactions, and other factors that may prolong relaxant action been contemplated?
- The safest approach when any question as to successful reversal remains is to provide proper sedation and controlled ventilation until adequate recovery is ensured.

Edrophonium may be used when a faster onset is desired, but its efficacy is less than that of neostigmine. This lower effectiveness limits its use to situations in which significant recovery has already occurred. Pyridostigmine is largely historical and rarely used. Fortunately, a new paradigm is unfolding with the introduction of the selective relaxant binding agent (SRBA) sugammadex.[208]

A thorough evaluation of the current data on the clinical use of relaxants and their reversal has been reported and discussed in several publications.[9,12,13,18,20] The criteria for determination that successful recovery has taken place have been clarified and factors that can affect recovery have been noted. The decision faced by the clinician at the end of a procedure involves determining when the relaxant effects have dissipated and the patient can safely control his or her own airway. A convenient and reliable bedside clinical test for evaluating reversal is needed but not yet available. A number of factors combining objective monitoring with clinical signs must be obtained to assure safe recovery. Several studies have indicated that the incidence of residual paralysis may be as high as 45%.[13] Debaene et al.[209] noted that 45% of patients arrived in the recovery room with residual muscular block after intermediate-duration relaxant administration. Residual paralysis is evident even up to 4 hours after use of an intermediate relaxant.[210] This phenomenon is frequently referred to as *recurarization*, implying that adequate reversal was obtained but the drug effect was reestablished. This term is a misnomer because the noted effect is most likely unrecognized residual paralysis. Reversal should not be attempted unless spontaneous recovery of 1 to 2 twitches of the TOF has occurred because the block may be too deep to obtain adequate reversal.[9-12] A TOFR of 0.7 along with additional clinical signs such as strong hand grip and 5-second head lift were used as criteria for adequate reversal for many years. It since has been shown that a TOFR of 0.9 should be attained because even small degrees of residual block increase the incidence of adverse respiratory events and may increase longer-term morbidity as well.[211,212] This is due to previously unrecognized decreases in airway patency and swallowing unless a TOFR of 0.9 is present. An increased incidence of adverse effects such as hypoxia, hypercarbia, atelectasis, and airway obstruction may occur in the PACU.[11] A study by Murphy et al.[213] suggests the incidence of significant respiratory adverse events in the PACU is 0.8%. Qualitative assessments of the signs of recovery are frequently misinterpreted by even the most experienced clinicians. It can be difficult to detect subtle differences in fade of TOF and tetanus with subjective qualitative tests.[9]

Some adverse effects of residual neuromuscular block are noted in Box 12-10.

General principles for avoiding residual paralysis are given in Box 12-11. Factors influencing the incidence of postoperative residual neuromuscular blockade are shown Box 12-12.

CHOLINESTERASE INHIBITORS

The mechanism of action of the cholinesterase inhibitors is primarily the result of its structural relationship and interaction with AChE, a protein with a molecular weight of approximately 320,000 and the capacity to hydrolyze an estimated 300,000 molecules of ACh per minute.[214,215]

BOX **12-12**

Factors Influencing the Incidence of Postoperative Residual Neuromuscular Blockade

Definition of Residual Neuromuscular Blockade
- Objective train-of-four (TOF) measurements (TOF ratio less than 0.9)
- Clinical signs or symptoms of muscle weakness

Type and Dose of Neuromuscular Blocking Drug (NMBD) Administered Intraoperatively
- Intermediate-acting NMBD
- Long-acting NMBD

Use of Neuromuscular Monitoring Intraoperatively
- Qualitative monitoring (TOF and double-burst stimulation studied)
- Quantitative monitoring (acceleromyography studied)
- No neuromuscular monitoring (clinical signs)

Degree of Neuromuscular Blockade Maintained Intraoperatively
- TOF count of 1 to 2
- TOF count of 2 to 3

Type of Anesthesia Used Intraoperatively
- Inhalation drugs
- Intravenous anesthesia (total intravenous anesthesia [TIVA])

Type and Dose of Anticholinesterase Reversal Drug
- Neostigmine
- Edrophonium

Duration of Anesthesia
Time Interval Between Anticholinesterase Administration and Objective
- TOF measurements

Patient Factors
- Metabolic derangements in the postanesthesia care unit (PACU) (acidosis, hypercarbia, hypoxia, and hypothermia)

Drug Therapy in PACU
- Opioids
- Antibiotics

From Murphy GS, Brull SJ. Residual neuromuscular block: Lessons unlearned. Part I: Definitions, incidence, and adverse physiologic effects of residual neuromuscular block. *Anesth Analg.* 2010;111(1):120-128.

Edrophonium, pyridostigmine, and neostigmine all contain an ionized center that actively combines either at the active center or at the site specifically removed from the active center of AChE. Edrophonium is a simple alcohol that contains a quaternary ammonium group.[215] It is considered a reversible inhibitor of cholinesterase because it electrostatically attaches to the anionic site of AChE and is stabilized by hydrogen binding at the esteratic site of the enzyme. Because a true chemical bond is not formed, ACh competes with edrophonium for the binding site of AChE, and therefore it has a shorter duration of action than those of compounds that form a bond.[216]

Neostigmine and pyridostigmine are carbamic acid esters of alcohols and contain a quaternary or tertiary ammonium group.[215] These agents form a carbamyl-ester complex at the esteratic site of cholinesterase. This drug-enzyme complex then degrades in the same manner as the ACh-cholinesterase complex. The carbamate group is transferred to AChE, leaving it unable to hydrolyze ACh.[214]

The indirect-acting cholinesterase inhibitors exert their effect by inhibiting AChE, thereby increasing the concentration of endogenous ACh around the cholinoreceptors.[215] They act as alternative substrates for the enzyme. This provides a twofold mechanism in the reversal of neuromuscular blockade. First, increasing the concentration of ACh in the junctional cleft changes the agonist-antagonist ratio, thereby increasing the likelihood that the ACh will reoccupy the receptor site once occupied by the neuromuscular blocker, as well as occupying sites not previously engaged. Second, the life of the ACh within the cleft is increased. The increased concentration of ACh prolongs the time it remains in the cleft, allowing time for the antagonist dissociation and the reactivation of the receptor site. Evidence also suggests that these agents have direct influences on neuromuscular transmission independent of enzyme inhibition. These include at least three distinct although possibly interacting mechanisms, including a weak agonist action, the formation of desensitized receptor complex intermediates, and the alteration of the conductance properties of active channels.[217]

Although the result of inhibition of AChE is the same when edrophonium, neostigmine, or pyridostigmine is administered, the means by which these agents accomplish the task varies. Edrophonium binds reversibly with the negatively charged enzyme site by electrostatic attraction of its positively charged nitrogen. This effect prevents catalytic binding with ACh for the short time that edrophonium occupies the binding site. Although the duration of receptor site occupation is short for edrophonium, the duration of its effects is prolonged by the fact that once it leaves the receptor site, it finds another to occupy and continues with this process until eliminated.[218]

Enzymatic inactivation is accomplished by neostigmine and pyridostigmine. Electrostatic interaction between the ionized centers of drug and enzyme takes place initially as with edrophonium. This phenomenon then leads to a hydrolytic chemical reaction in which a shift in covalent bonds occurs, resulting in the formation of a carbamylated enzyme. This methyl-carbamyl AChE is much more stable and resistant to hydrolysis than the acetyl enzyme, resulting in an enzyme that is incapable of inactivating ACh.

These differences in chemical deactivation of AChE result in differing pharmacokinetic profiles. Edrophonium, neostigmine, and pyridostigmine are all quaternary ammonium compounds that are poorly lipid soluble. At moderate doses, penetration through lipid barriers (e.g., gastrointestinal tract, placenta, and blood-brain barrier) is minimal if present at all.

Edrophonium is the most rapid acting of these agents, with an onset time of 30 to 60 seconds after IV administration and a duration of 5 to 10 minutes. Intramuscular administration results in an onset of 2 to 10 minutes.[219] Renal excretion accounts for approximately 75% of the edrophonium eliminated, although in the absence of renal function, hepatic metabolism accounts for the inactivation of 30% of the injected dose; this amount undergoes conjugation to inactive edrophonium glucuronide. The elimination half-life of edrophonium is 110 minutes in the healthy patient and 304 minutes in the anephric patient. The volume of distribution is 1.1 and 0.7 L/kg in normal and anephric patients, respectively.

TABLE 12-11 Commonly Used Anticholinesterase, Anticholinergic, and Select Relaxant Binding Agents

Agent	Dose Range	Onset (min)	Duration	Comments
Neostigmine	25-75 mcg/kg	5-15	45-90 min	Most commonly used reversal agent; may increase incidence of postoperative nausea and vomiting
Pyridostigmine	100-300 mcg/kg	10-20	60-120 min	Slow onset, long duration, and slow reversal Rarely used
Edrophonium	500-1000 mcg/kg	5-10	30-60 min	Not recommended for deep block; rapid onset, short duration
Atropine	15 mcg/kg	1-2	1-2 hr	Should be combined with edrophonium because of more rapid onset
Glycopyrrolate	10-20 mcg/kg	2	2-4 hr	Less initial tachycardia than atropine; no central nervous system effects; most frequently used
Sugammadex	2-16 mg/kg	1-2	2-16 hr	Selective relaxant binding agent; up to 16 mg/kg has been safely used

Although similar in structure and mechanism of AChE deactivation, neostigmine is more potent than pyridostigmine and has a more rapid onset of action. After IV administration of neostigmine, onset occurs within 4 to 8 minutes. Duration of action is 0.5 to 2 hours, although other sources suggest durations from 60 minutes to 4 hours. Renal excretion accounts for roughly 50% of the neostigmine eliminated, primarily by glomerular filtration. The remaining 50% of the neostigmine dose is hydrolyzed by plasma esterases and hepatic metabolism to 3-hydroxyphenyltrimethyl ammonium (3-OH PPM) and conjugated 3-OH PPM. These metabolites have approximately one tenth the activity of the parent compounds and are renally eliminated. The elimination half-life of neostigmine is 70 to 80 minutes, increasing to 181 to 183 minutes in anephric patients. The volume of distribution of 0.7 L/kg in healthy patients increases to 0.8 L/kg in those with renal failure.[215,218] Successful reversal is usually attained in 10 minutes.

Pyridostigmine is the cholinesterase inhibitor with the longest onset and duration. The slow onset limits its clinical popularity. Onset of action after IV administration is from 2 to 5 minutes. Duration of action has been reported to be from 90 minutes to 3 to 6 hours.[215] Pyridostigmine is 75% eliminated by the kidneys.[25,193] The remaining 25% is metabolized by the hepatic microsomal enzyme system to 3-hydroxy–methyl pyridinium, its major metabolite, and six other minor metabolites. All of these metabolites are excreted in the urine. The elimination half-life and volume of distribution are 113 minutes and 1.1 L/kg, respectively. In patients with renal failure, the elimination half-life dramatically rises to 379 minutes, whereas the volume of distribution decreases slightly to 1 L/kg. As discussed previously, the efficacy of the reversal drugs is dependent on (1) the depth of blockade at the time of reversal; (2) the dose and specific drug used; (3) the duration of action of the relaxant being reversed; and (4) the anesthetic drugs being used.[218]

The pharmacology of the reversal agents is summarized in Table 12-11. The common clinical signs of muscle recovery after administration of a muscle relaxant are listed in Box 12-13. Some considerations that apply when reversal is incomplete are noted in Box 12-10. Factors that may prolong paralysis are listed in Box 12-14.

BOX 12-13

Common Clinical Signs of Recovery from Neuromuscular Blockers

- Adequate tidal volume and rate
- Respirations smooth and unlabored
- Opens eyes widely on command; no diplopia
- Sustained protrusion and purposeful movement of tongue
- Effective swallowing and sustained bite
- Able to sustain head or leg lift for at least 5 seconds (In small children, a strong knee-to-chest movement is equivalent.)
- Arm lift and touch the opposite shoulder
- Strong, constant hand grip
- Effective cough
- Adequate vital capacity of at least 15 mL/kg
- Adequate inspiratory force of at least 25 to 30 cm H_2O negative pressure
- Sustained tetanic response to 50 Hz for 5 seconds
- Train-of-four ratio greater than 0.9 with no fade
- No fade to double-burst stimulation

ANTICHOLINERGICS

Atropine or glycopyrrolate are used in combination with neostigmine or edrophonium to prevent the parasympathomimetic side effects of the anticholinesterase drugs. If given alone, neostigmine and the other anticholinesterase drugs would cause severe vagal effects due to the systemic buildup of acetylcholine. These would include bradycardia and arrhythmias, hypotension, bronchoconstriction, hypersalivation, diarrhea, and an increase in postoperative nausea and vomiting. Glycopyrrolate is used more often because it produces less initial tachycardia and has no CNS effects. The antimuscarinic can be given first or the glycopyrrolate and neostigmine may be mixed in the same syringe.

Anticholinergic, *antimuscarinic*, and *parasympatholytic* are three common terms used to describe compounds that originate from alkaloids of the belladonna plant. Each group name divides these compounds into subgroups that have a more similar mechanism of action. For the purposes of this section, all of the compounds are referred to as *antimuscarinics*. Atropine (*dl*-hyoscyamine) is the prototype of this group, and many of the currently available products are structural derivatives obtained both naturally and synthetically.[220] Atropine is found in the plant *Atropa belladonna*, or deadly nightshade, and in *Datura stramonium*, also known as *jimson weed*.[144] Preparations of these plants have been used by clinicians for centuries; belladonna was used as a poison during the time of the Roman Empire and in the Middle Ages. In 1867, Bezold and Bloebaun began to study the cardiac effects of bella donna's vagal inhibition, and in 1931 Mein isolated atropine in the pure form.[22]

BOX 12-14

Factors That May Prolong Paralysis

Pathophysiologic Causes
- Acid maltase deficiency
- Adrenocortical dysfunction
- Acute intermittent porphyria
- Amyotrophic lateral sclerosis
- Anoxia and ischemia
- Carcinomatous polyneuropathy
- Cholinesterase deficiency or genetic variance
- Compressive neuropathy
- Critical illness polyneuropathy
- Diphtheria
- Eaton-Lambert syndrome
- Guillain-Barré syndrome
- Hypokalemia and hypocalcemia
- Hypomagnesemia
- Hypophosphatemia
- Hypothermia
- Motor neuron disease
- Multiple sclerosis
- Muscular dystrophy
- Myasthenia gravis
- Myotonic syndromes
- Neurofibromatosis
- Nonspecific nutritional deficiency
- Poliomyelitis
- Pyridoxine abuse
- Polymyositis
- Renal failure (variable prolongation)
- Respiratory acidosis
- Sepsis
- Thiamine deficiency
- Tick bite paralysis
- Trauma
- Vitamin E deficiency
- Wound botulism

Pharmacologic Causes
- Aminoglycoside toxicity
- Penicillin toxicity
- Steroid myopathy

Antihypertensives
- Calcium channel blockers
- β-blockers
- Furosemide

Antidysrhythmics
- Quinidine
- Procainamide
- Local anesthetics in large doses

Antibiotics
- Aminoglycoside antibiotics
- Polymyxin B
- Clindamycin
- Tetracycline

Miscellaneous Drugs
- Cyclosporine
- Steroids
- Volatile anesthetics
- Dantrolene
- Magnesium
- Lithium
- Azathioprine
- Organophosphate (poisoning)

Modified from Kirby RR, et al, eds. *Clinical Anesthesia Practice*. 2nd ed. Philadelphia: Saunders; 2002.

Atropine and scopolamine are naturally occurring tertiary amines. Semisynthetic congeners of the belladonna alkaloids represented by glycopyrrolate are usually quaternary ammonium derivatives. These quaternary ammonium derivatives often have potent peripheral effects without CNS activity.

All the antimuscarinics are absorbed orally to some extent, although this route is often unpredictable. Intramuscular or IV administration is usually the route used. Scopolamine has the additional advantage of transdermal absorption. Atropine is well absorbed from the gastrointestinal tract by inhalation via endotracheal administration and by IV and intramuscular routes. Given orally, 90% of the dose is absorbed and reaches peak plasma levels within 1 hour. Intramuscular and IV administration results in peak plasma levels within 30 minutes and 2 to 4 minutes, respectively. Atropine is well distributed throughout the body. It crosses both the blood-brain barrier and the placental barrier. Both the kidneys and liver aid in the elimination of atropine. Although elimination is biphasic, the terminal half-life is 2 to 3 hours. Metabolism by the liver results in several metabolites: tropic acid, tropine, and glucuronide conjugates. Approximately 30% to 50% of a dose is excreted unchanged in the urine. Small amounts of atropine may also be eliminated in expired air as carbon dioxide and in feces.[220]

Glycopyrrolate is a quaternary ammonium compound whose ionization limits gastrointestinal absorption, blood-brain barrier, and placental penetration. After IV administration, glycopyrrolate has an onset of 1 minute. Intramuscular and subcutaneous administration results in an onset of 15 to 30 minutes. Vagal blockade can persist for 2 to 3 hours. Serum levels of glycopyrrolate decline quickly, and less than 10% of the drug remains in the serum after 5 minutes. Glycopyrrolate is excreted in feces and urine, primarily as unchanged drug. Small amounts are metabolized to inactive metabolites. Eighty-five percent of an IV dose is excreted in the urine within 48 hours.[144]

Atropine and glycopyrrolate are commonly administered to prevent the muscarinic effects of anticholinesterase inhibitors. Atropine induces its vagolytic effect more rapidly than glycopyrrolate. Atropine appears to be somewhat better suited for use with edrophonium, whereas the onset times of glycopyrrolate and neostigmine are more closely matched. When administered with edrophonium, the usual recommended dose of atropine is 7 mcg/kg.[144,221] With 0.5 to 2.5 mg of neostigmine, the recommended dose of atropine is 0.6 to 1.2 mg, and that of glycopyrrolate is 0.2 to 0.6 mg.[220] (See Chapter 13, Table 13-7 for a comparison of the anticholinergics.)

Selective Relaxant Binding Agents—Sugammadex

Sugammadex (Bridion) is the first selective relaxant binding agent (SRBA) to be introduced as a reversal for clinical neuromuscular blockade. The name sugammadex is a contraction of *sugar* and *gamma*-cyclo*dex*trin. It is a modified gamma-cyclodextrin that works by encapsulating and forming very tight water-soluble complexes at a 1:1 ratio with steroidal neuromuscular blocking drugs. Once encapsulation occurs, it does not dissociate and the sugammadex-relaxant complex is excreted in the urine. Reversal occurs independent of the depth of block; therefore, even deep blockade can be reversed with the appropriate dose. The concentration of free muscle relaxant falls rapidly, and muscle strength is reestablished. It is most effective reversing rocuronium, vecuronium, and pancuronium in that order. It does not affect the bezylisoquinolones atracurium and cisatracurium.[222,223] Used in appropriate doses, sugammadex can reverse any depth of rocuronium or vecuronium block within 3 minutes.

Pharmacokinetics

Sugammadex is biologically inactive. The pharmacokinetics of sugammadex show a linear dose relationship in doses up to 8.0 mg/kg. Clearance is approximately 120 L per minute and the volume of distribution is 18 liters. The elimination half-life is 2.3 hours. Up to 80% of an administered dose of sugammadex is eliminated in the urine within 24 hours. Sugammadex does not bind to plasma proteins or erythrocytes. Due to the dependence on renal elimination, the drug should be avoided in patients with significant renal disease.[218,223]

Clinical Use

The dosage range of sugammadex varies from 2 to 16 mg/kg according to the depth of blockade at the time of reversal. The dose for reversal of shallow or moderate block (2 responses to TOF present) is approximately 2 mg/kg. Deeper blocks (PTC 1-2) in which there is little recovery require a dose of 4 mg/kg. A larger dose of sugammadex (16 mg/kg) is used when reversing high doses of rocuronium in the range of 1 to 1.2 mg/kg, such as the doses used for intubation.

The 16 mg/kg dose is also used in an immediate rescue situation such as a "can't intubate, can't ventilate" scenario.[224,225]

Sugammadex appears to be safe and well tolerated. The most commonly reported adverse drug reactions included dry mouth, dysgeusia, nausea, vomiting, allergy, chills, and postural hypertension.[223] Allergy is rare but possible, and the clinical significance remains to be clarified. In the rare event that neuromuscular block needs to be reestablished, a bezylisoquinolone such as atracurium or cisatracurium should be given. Succinylcholine is also not affected.[225] Recurarization is rare but has been reported.[226] As the clinical use of sugammadex evolves, it is expected to produce significant benefits in current practice.[227] The cost of sugammadex is a concern and economic assessments are uncertain.[228]

SUMMARY

Like every other agent used in the practice of anesthesia, neuromuscular blocking agents are useful tools in the hands of skilled clinicians. It should go without saying that these agents ought never to be administered without first appropriately sedating the patient. The exception is if the patient's condition is so marginal that even the most careful use of sedation could increase the chance for morbidity or death. The decision to use neuromuscular blockers in the absence of sedation should be made only after the most careful and thorough consideration. Prevention of movement should provide the surgeon with the optimum field on which life-saving skills can be practiced.

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13 CHAPTER Autonomic and Cardiac Pharmacology

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Cardiovascular medicine continues to be one of the most rapidly changing specialties in modern clinical practice. Management guidelines are continuously being refined as data from large-scale clinical trials are reported. The number of patients requiring noncardiac surgery who have had coronary interventions is increasing. Many patients are being managed with complex management plans that require consultation with their cardiologists. Providing high-quality anesthetic care involves continuous monitoring of all the body's systems, with a special emphasis on the cardiovascular status of the patient. Complex anesthetic plans and invasive surgical intervention can produce profound stress on patients' cardiovascular balance and require careful manipulation of vital signs. The array of diagnostic tests, monitors, and drugs available makes a thorough understanding of autonomic and cardiac pharmacology essential. A well-devised treatment plan will make the anesthetic course flow smoothly. Intraoperative planning for the immediate and late postoperative periods is critical to avoiding untoward outcomes. The number and variety of medications in a patient's profile require a delicate balance between the anesthetic requirements and maintaining a successful continuum of therapy for the long-term needs of the patient. This chapter presents a broad overview of the many autonomic and cardiovascular medicines that may be encountered during the perioperative period and their important anesthetic considerations.

AUTONOMIC DRUGS—SYMPATHOMIMETIC AMINES

The sympathomimetic amines include the three naturally occurring catecholamines epinephrine, norepinephrine, and dopamine and a number of synthetic agents such as phenylephrine and dobutamine. These drugs are used in a variety of situations, including the treatment of anesthesia-induced hypotension, bradycardia, anaphylaxis, shock, heart failure, and cardiac resuscitation.

The basic structure of the sympathomimetic amines is β-(3,4-dihydroxyphenyl)-ethylamine. This structure consists of a substituted benzene ring and an ethylamine side chain.[1] The effects elicited by this pharmacologic class are the result of the stimulation of β-adrenergic, α-adrenergic, and dopamine adrenergic receptors. The innervation of the effector organs by the autonomic system is outlined in Table 13-1.

The efficacy of a particular sympathomimetic amine depends on its concentration at the receptor site, its affinity for specific receptors, and the population of receptors available for binding. The effects of the common autonomic drugs are summarized in Table 13-2.

Epinephrine

Epinephrine, one of the naturally occurring catecholamines, is the final product in the chain of catecholamine synthesis. (See Chapter 33 for a complete description of catecholamine synthesis.) Although both epinephrine and norepinephrine have agonistic activity at both α- and β-receptors, norepinephrine has minimal β_1 activity in low doses, whereas epinephrine strongly stimulates both β_1- and β_2-receptors.

Epinephrine is useful not only in the treatment of anaphylaxis and cardiopulmonary resuscitation, but also its combination of α and β effects makes it an appropriate choice for the treatment of some shock states in which poor tissue oxygen delivery and hypotension are combined. In small doses, epinephrine may well be useful as a sympathomimetic agent in patients unresponsive to indirect-acting agents and in those in whom simultaneous β_1 (cardiac stimulation) and β_2-receptor stimulation (vasodilation) may be helpful. With epinephrine, the dominance of α or β effects is dose related.

Epinephrine's β_1 effect produces marked positive inotropic (force of contraction), chronotropic (heart rate), and dromotropic (conduction velocity) actions. It should be noted that as heart rate, left ventricular stroke work, stroke volume, and cardiac output increase, so does myocardial oxygen consumption. In addition, the corresponding increased automaticity of all foci, including those that are ectopic, may lead to arrhythmia. Marked vigilance must be maintained in an effort to ensure that an imbalance of myocardial oxygen supply and demand does not occur. It should be recalled that the effects resulting from epinephrine administration are capable of both increasing myocardial demand and decreasing supply.

Beneficial effects of β_2 stimulation include bronchodilation, vasodilation, and stabilization of mast cells, with a resultant diminution of histamine release. Concurrently, α stimulation promotes a decrease in bronchial secretion. The net effect is a decrease in airway resistance with an improvement in oxygenation.

With low doses of epinephrine (10 mcg/min) the peripheral vasculature promotes the redistribution of blood flow to skeletal muscle, thereby producing a decrease in systemic vascular resistance. As the dose of epinephrine is increased, the α effect predominates, with resultant vasoconstriction and an increase in systemic pressures. The systolic pressure is increased, whereas the diastolic pressure remains relatively unchanged, with a resultant increase in pulse pressure. It should be noted that if the coronary arteries are not obstructed, autoregulation increases oxygen delivery to meet the increased demand.[2] However, in the presence of a coronary artery lesion, oxygen delivery may be insufficient to meet demand, and myocardial ischemia results.[3]

The increased α effect that occurs with greater doses of epinephrine also results in renal and splanchnic vasoconstriction. Renal vascular resistance and ultimately renal blood flow are decreased. Beta stimulation leads to activation of the renin-angiotensin system and also to an increase in lipolysis, glycogenolysis, gluconeogenesis, ketone production, and lactate release by skeletal muscle. Insulin secretion is inhibited by an overriding β_2 stimulation. Epinephrine-induced β_2 stimulation also can cause a transient hyperkalemia as potassium follows glucose out of hepatic cells. This is followed by a longer hypokalemia as β_2 stimulation then forces this extracellular potassium into red blood cells.[4]

TABLE 13-1 Typical Autonomic Influences on Peripheral Effector Organs

Organ System	Sympathetic Effect	Adrenergic Receptor Type	Parasympathetic Effect	Cholinergic Receptor Type
Eye				
Radial muscle, iris	Contraction (mydriasis)	α_1		
Sphincter muscle, iris			Contraction (miosis)	M_3, M_2
Ciliary muscle	Relaxation for far vision	β_2	Contraction for near vision (accommodation)	M_3, M_2
Heart				
Sinoatrial node	Increase in heart rate	β_1	Decrease in heart rate	M_2
Atria	Increase in contractility and conduction velocity	β_1	Decrease in contractility	M_2
Atrioventricular node	Increase in automaticity and conduction velocity	β_1	Decrease in conduction velocity; AV block	M_2
His-Purkinje system	Increase in automaticity and conduction velocity	β_1	Little effect	M_2
Ventricle	Increase in contractility, conduction velocity, automaticity	β_1	Slight decrease in contractility	M_2
Blood Vessels				
Arteries				
Coronary	Constriction; dilation	α; β_2	None	—
Skin and mucosa	Constriction	α_1; β_2	None	—
Skeletal muscle	Constriction; dilation	α_1; β_2	None	—
Cerebral	Constriction (slight)	α_1	None	—
Pulmonary	Constriction; dilation	α_1; β_2	None	—
Abdominal viscera	Constriction; dilation	α_1; β_2	None	—
Salivary glands	Constriction and reduced secretions	α_1; α_2	Dilation and increased secretions	M_3
Renal	Constriction +++; dilation	α_1, α_2; β_1, β_2	None	—
Veins	Constriction; dilation	α_1, α_2; β_2	None	—
Lung				
Tracheal and bronchial smooth muscle	Relaxation	β_2	Contraction	M_2, M_3
GI Tract				
Motility and tone	Decrease	α_1, α_2; β_1, β_2	Increase	M_2, M_3
Sphincters	Contraction	α_1	Relaxation	M_3, M_2
Secretion	Inhibition	α_2	Stimulation	M_3, M_2
Gallbladder and ducts	Relaxation	β_2	Contraction	M
Kidney				
Renin secretion	Increase	β_1	None	—
Urinary Bladder				
Detrusor	Relaxation	β_2	Contraction	M_3, M_2
Trigone and sphincter	Contraction	α_1	Relaxation	M_3, M_2
Uterus	Contraction (pregnant)	α_1	None	—
	Relaxation (pregnant and non-pregnant)	β_2		
Liver	Glycogenolysis and gluconeogenesis; increased blood sugar	α_1; β_2		
Pancreas				
Islets (β cells)	Decreased insulin secretion	α_2	None	—
	Increased insulin secretion	β_2	None	—
Adipocytes	Lipolysis	α_1; β_1, β_2, β_3	None	—

α, Alpha receptor; β, beta receptor; GI, gastrointestinal; M, muscarinic receptor.

TABLE 13-2 Effects of Autonomic Drugs

Organ Systems	Alpha Agonists	Alpha Blocker	Beta Agonists	Beta Blocker	Cholinergic Agonists	Anticholinergic
Eye	Mydriasis	Miosis (slight)	NCRE	↓ Intraocular pressure	Miosis, ↓ intraocular pressure	Mydriasis, cycloplegia, ↑ intraocular pressure
Heart						
Rate	Bradycardia (reflex)	Tachycardia (reflex)	Tachycardia	Bradycardia	Bradycardia	Tachycardia
Contractility	NCRE	Slight increase (reflex)	↑	↓	↓ (slight)	↑ (slight)
Conduction velocity	NCRE	NCRE	↑	↓	↓	↑
Blood (vessels)	Vasoconstriction	Vasodilation	Vasodilation	Vasoconstriction	NCRE	NCRE
Lungs	NCRE	NCRE	Bronchodilation	Bronchoconstriction	Bronchoconstriction	Bronchodilation (slight)
GI Tract	↓ Motility and secretion	NCRE	↓ Motility and secretion	NCRE	↑ Motility and secretion	↓ Motility and secretion
Uterus	Contraction	NCRE	Relaxation	NCRE	NCRE	NCRE
Liver	↑ Blood sugar	NCRE	↑ Blood sugar	Hypoglycemia	NCRE	NCRE

↑, Increase; ↓ decrease; *GI*, gastrointestinal; *NCRE*, no clinically relevant effect.

Norepinephrine

Norepinephrine is a potent vasopressor. Although it is not as potent as epinephrine in stimulating α-receptors in equal doses, it has little β_2 activity at low doses, and the end result is, for the most part, unopposed α stimulation. The chronotropic effect seen with β_1 stimulation is generally absent with norepinephrine in low doses because of the increase in systemic vascular resistance, which induces reflex vagal activity.

The aforementioned combination of adrenergic stimulation results in a decrease in vital organ flow; however, coronary artery perfusion may be increased because of the increase in diastolic pressure. Renal vascular resistance is increased, and urine output may fall. An increase in preload may be seen because norepinephrine is a venoconstrictor.[5,6]

Both norepinephrine and dopamine are used as first-line therapy for shock. There is an ongoing debate as to whether one is superior. A recent large multicenter clinical trial suggests that they are equally effective, although dopamine produces more adverse events such as arrhythmias.[7] Norepinephrine is generally used in patients with adequate cardiac output but low systemic vascular resistance. In this group of patients, however, the underlying problem of peripheral tissue perfusion-oxygenation may be exacerbated by the intense norepinephrine-induced peripheral vasoconstriction, even if adequate blood pressure has been achieved.

Norepinephrine does have some generalized metabolic effects, such as a decrease in insulin production, but these metabolic effects are present to a lesser degree than those seen with epinephrine. Adverse effects are usually a result of the intense vasoconstriction associated with norepinephrine.

Dopamine

Dopamine is an endogenous central and peripheral neurotransmitter that is derived from dopa in the chain of catecholamine synthesis. Pharmacologically, dopamine stimulates dopamine receptors, β-receptors, and α-receptors in a dose-dependent manner because of differing receptor affinities. Dopaminergic receptors are stimulated with low doses of less than 2 mcg/kg/min. At moderate doses of 2 to 5 mcg/kg/min, β effects are elicited, and α effects are seen with high infusion rates of greater than 10 mcg/kg/min. Dopamine also has an indirect sympathomimetic effect, eliciting the release of norepinephrine via β_1 stimulation.[8]

Dopamine is often the first inotropic agent chosen for a patient in shock. Some clinicians have found dopamine to have a poor response in cases of gram-negative sepsis because of a down-regulation in which the sensitivity of β-receptors is diminished.[9,10]

During surgery and anesthesia, dopamine is administered for its dopaminergic effect. The stimulation of dopamine receptors in the renal artery promotes an increase in renal blood flow and a resultant increase in glomerular filtration rate and urine output. Benefits, however, of so-called "renal" dopamine are in doubt, and many clinicians have abandoned the practice.[11-14] The urine output is increased but long-term morbidity and mortality are not improved. Dopamine also inhibits aldosterone, resulting in an increase in sodium excretion and urine output.

Dopamine has been implicated in several cases of severe limb ischemia. If dopamine is administered through a peripheral line, increased vigilance in pediatric patients and in patients with any type of vascular disease such as diabetes, atherosclerosis, or Raynaud's phenomenon is advised. The presence of an arterial line in the affected limb also increases the incidence of limb ischemia with concurrent dopamine infusion. Other metabolic and central nervous system (CNS) effects, similar to those seen with epinephrine but less extensive, have been attributed to dopamine administration.[4]

The monoamine oxidase enzymes metabolize dopamine; therefore, the effects of dopamine can be prolonged in patients receiving a monoamine oxidase inhibitor. Tricyclic antidepressants may also augment the activity of sympathomimetic drugs.

Isoproterenol

Isoproterenol is a synthetic catecholamine with the same underlying chemical structure as the endogenous catecholamines. It is a potent nonselective agonist of β_1- and β_2-receptors but has no agonistic activity at α-receptors or dopamine receptors. The current use of isoproterenol is limited since the emergence of dobutamine and milrinone. In current practice, it is occasionally used in the treatment of bradycardia with heart block and torsades de pointes ventricular tachycardia.[15] Isoproterenol is also used after

heart transplant for chronotropic support. The mechanism is in part due to β_2-receptor stimulation.[16]

The profound β_1 stimulation of isoproterenol results in both positive inotropic and chronotropic effects. In combination with the peripheral β_2-induced vasodilation and resultant drop in systemic vascular resistance, an increase in cardiac output is seen. However, the positive inotropic and chronotropic effects dramatically increase myocardial oxygen consumption, which may already be compromised by the β_2-induced peripheral vasodilation, causing a decrease in diastolic blood pressure and ultimately a decrease in coronary artery perfusion. These effects are especially detrimental in patients with coronary artery disease. Isoproterenol is also a potent bronchial dilator and pulmonary vasodilator.

The detrimental effects of isoproterenol on the heart, such as excessive tachycardia, induction of myocardial ischemia, and arrhythmia production are the major factors limiting its use to the treatment of significant heart block unresponsive to atropine. Other side effects are similar to those seen with epinephrine but occur to a lesser extent.

Dobutamine

Dobutamine is a synthetic sympathomimetic amine. It is a modification of isoproterenol, but its use is much more widespread. Dobutamine is primarily a β_1-agonist with some β_2 effects.[17] Dobutamine displays a strong inotropic response with minimal chronotropy. It also produces a slight drop in systemic vascular resistance, owing to peripheral vasodilation. The resultant increase in cardiac output compensates for the decrease in systemic vascular resistance, and the blood pressure is increased or, at low doses, relatively unchanged. Pulmonary artery pressure decreases, and an increase in left ventricular stroke work index is observed.[18]

The positive inotropic effects, coupled with the lack of chronotropy and maintenance of normal blood pressure, have made this agent an option in cardiogenic and septic shock and in select patients with mild heart failure.[19] It is also frequently used for heart stimulation for cardiac stress testing.[15] Recent evidence indicates significant adverse effects when dobutamine is used in cardiac surgery, and clinicians have stopped using it for inotropic support in this situation.[20]

DIRECT-ACTING α-AGONISTS

α_1-Agonists

Phenylephrine

Phenylephrine (Neo-Synephrine) is the most commonly employed pure α-agonist. Phenylephrine has strong α-stimulating effects, with virtually no β stimulation. A sharp rise in blood pressure is produced as a result of a significant increase in peripheral resistance secondary to the α_1 stimulation. A reflex bradycardia can be elicited secondary to baroreceptor stimulation. Careful titration of intravenous (IV) boluses of phenylephrine is necessary to avoid large changes in blood pressure and decreases in heart rate. The onset of action of IV phenylephrine is immediate, with the duration of action ranging from 5 to 20 minutes. Because of its vasoconstricting effects, phenylephrine is frequently used topically for the prevention of nosebleeds during nasal intubation or for a reduction in bleeding in ear, nose, and throat surgery. Severe hypertension may occur with excessive doses. It is recommended that the topical dose should not exceed 0.5 mg (4 drops of 0.25% in adults) and 20 mcg/kg in children.[21]

Other Inotropes

Vasopressin

Arginine vasopressin is an endogenous hormone that is produced in the hypothalamus, stored in the posterior pituitary, and released from the magnocellular neurons of the hypothalamus. It functions to control osmoregulation. Its release is stimulated by an increased osmolality and hypovolemia. It is also referred to as antidiuretic hormone. Vasopressin deficiency and down-regulation of vasopressin receptors are common in septic shock.[22] Vasopressin is a potent vasoconstrictor; however, it selectively dilates renal afferent, pulmonary, and cerebral arterioles. Low-dose vasopressin infusion (0.03 to 0.04 units/min) increases blood pressure, urine output, and creatinine clearance and decreases the dosage of norepinephrine required to maintain blood pressure in patients with septic shock. It is mostly used as an add-on therapy with catecholamine vasopressors. Increases in blood pressure occur in the first hour of administration, and the catecholamine vasopressor can then be titrated down. In a randomized trial, low-dose vasopressin added to norepinephrine was not significantly better than as-needed norepinephrine alone although added vasopressin may be useful in patients with less severe shock. Complications of vasopressin include gastrointestinal ischemia, decreased cardiac output, skin or digital necrosis, and cardiac arrest (especially at doses greater than 0.04 units/min).[23-25] Vasopressin agonists such as terlipressin and desmopressin have a variety of uses including bleeding reduction, antidiuresis in diabetes insipidus, and treatment of enuresis.[26]

Phosphodiesterase Inhibitors

Milrinone. The phosphodiesterase 3 (PDE 3) inhibitors, also known as *nonglycoside noncatecholamines*, include milrinone (Primacor). They differ structurally and functionally from the catecholamines and are generally used as alternatives or adjuncts to the standard inotropes in cardiac surgery and heart failure.[27-30]

Phosphodiesterases (PDEs) are a group of enzymes that play a role in a variety of physiologic actions. Eleven subfamilies have been identified.[31] They break down the second messengers, cyclic adenosine monophosphate (cAMP) or cyclic guanosine monophosphate (cGMP), in various cells. The PDE 3 inhibitors such as milrinone prevent the breakdown of cAMP and thus enhance its action. Milrinone produces a positive inotropic action and vasodilation without producing tachycardia. It is occasionally referred to as an *inodilator*.[32] Milrinone substantially improves left ventricular function in association with an acceleration of calcium uptake by the sarcoplasmic reticulum. This acceleration appears to result from an inhibition of membrane-bound PDE 3 in the sarcoplasm, which induces a local elevation of cAMP. This allows for the buildup of cAMP and a subsequent increase in the uptake of intracellular calcium. Adrenergic receptors are not used to achieve the inotropic effect. It follows that these drugs retain their inotropic effect even in the presence of β-blocking agents or the phenomenon of β-receptor down-regulation, situations frequently encountered in patients with heart failure. Therefore PDE 3 inhibitors may be used, by virtue of their alternative pathway, to augment the effect of direct-acting β-agonists such as dobutamine or dopamine. Milrinone improves weaning of high-risk patients from cardiopulmonary bypass.[29,30]

These agents act as vasodilators because of the differential mechanism of cAMP in the smooth muscle versus its actions in the myocardium. In the smooth muscle, cAMP causes an efflux of calcium, with a resultant relaxation of the muscle and vasodilation. The clinical result is a decrease in both preload and afterload. This effect, along with the absence of an associated increase in heart rate, probably contributes to the absence of an increase in myocardial oxygen consumption. Sildenafil (Viagra, Revatio) is a PDE 5 inhibitor that produces vasodilation and is being used to treat pulmonary arterial hypertension. Pulmonary vasodilation reduces the workload of the right ventricle and improves symptoms of right-sided heart failure.

TABLE 13-3 Vasopressor Agents

		PERIPHERAL VASCULATURE		CARDIAC EFFECTS			
Agent	**Dose Range**	**Vasoconstriction**	**Vasodilation**	**Heart Rate**	**Contractility**	**Dysrhythmias**	**Typical Use**
Dopamine	1-4 mcg/kg/min	0	1+	1+	1+	1+	"Renal dose" does not improve renal function; may be used with bradycardia and hypotension
	5-10 mcg/kg/min	1-2+	1+	2+	2+	2+	
	11-20 mcg/kg/min	2-3+	1+	2+	2+	3+	Vasopressor range
Vasopressin	0.04-0.1 units/min	3-4+	0	0	0	1+	Septic shock, as an add-on to conventional inotropes such as norepinephrine
Phenylephrine	20-200 mcg/min	4+	0	0	0	1+	Vasodilatory shock
Norepinephrine	1-20 mcg/min	4+	0	2+	2+	2+	First-line vasopressor for septic shock, vasodilatory shock
Epinephrine	1-20 mcg/min	4+	0	4+	4+	4+	Refractory shock, shock with bradycardia, anaphylactic shock
Dobutamine	1-20 mcg/kg/min	1+	2+	1-2+	3+	3+	Cardiogenic shock, septic shock
Milrinone	37.5-75 mcg/kg bolus followed by 0.375-0.75 mcg/min	0	2+	1+	3+	2+	Cardiogenic shock, right heart failure, dilates pulmonary artery; caution in renal failure

From Rivers EP. Approach to patient with shock. In: Goldman L, Schafer AI. *Goldman's Cecil Medicine*. 24th ed. Philadelphia: Saunders; 2012:645-653.

Milrinone acts to enhance diastolic function, increases cardiac output, and decreases pulmonary wedge pressure. Side effects can include arrhythmias. Elimination is via the kidney; therefore, milrinone should be used with caution in patients in renal failure because of the potential for life-threatening arrhythmias. The current manufacturer's recommendation for the administration of milrinone is an IV loading dose of 50 mcg/kg, administered slowly over 10 minutes, followed by an infusion of 0.5 mcg/kg as needed. Table 13-3 outlines the current vasopressors and some of their uses.

MIXED FUNCTION AGONISTS

Ephedrine

Ephedrine is a synthetic noncatecholamine sympathomimetic commonly used in anesthesia practice. It stimulates both α- and β-receptors directly, and it indirectly causes release of endogenous catecholamines, leading to multiple mechanisms of action. It has both central and peripheral actions. Ephedrine's effects are similar to those seen with epinephrine; however, they are lesser and not accompanied by a dramatic increase in serum glucose concentrations. The duration of action of ephedrine is also longer than that of epinephrine, owing to its lack of a basic catechol structure; this characteristic makes it resistant to metabolism by monoamine oxidase.[15]

Ephedrine produces dose-related increases in blood pressure, cardiac output, heart rate, and systemic vascular resistance. Ephedrine often is the first sympathomimetic chosen for alleviation of hypotension because of the cardiac-depressant effects of anesthetic agents or vasodilation resulting from spinal anesthesia. Intravenously administered ephedrine, in doses ranging from 5 to 25 mg, has an immediate onset and a duration of action of 15 minutes to 1.5 hours depending on dose. This drug should be used cautiously in patients with questionable coronary perfusion, because myocardial oxygen consumption may be more dramatically increased than is anticipated as a result of ephedrine's positive inotropic effect. In obstetrics, ephedrine has long been considered the drug of choice to address maternal hypotension after regional anesthesia because it was felt that it maintains uterine blood flow better than phenylephrine. Newer data are questioning this long-standing practice, with phenylephrine being recommended over ephedrine.[33-35] Ephedrine produces increases in fetal metabolic rate leading to fetal acidosis due to beta stimulation and phenylephrine does not.[36] As with any indirect-acting agent, tachyphylaxis may develop with subsequent dosing, because catecholamine stores become depleted.[37] Ephedrine also may be administered by oral, intramuscular, or subcutaneous routes.

SELECTIVE β_2-AGONISTS

The β_2-agonists include albuterol (Proventil, Ventolin, others), levalbuterol (Xopenex), pirbuterol (Maxair), and salmeterol (Serevent). These "selective" β_2-agonists are effective in treating obstructive airway diseases such as asthma, chronic obstructive pulmonary disease, and acute bronchospasm. Long-acting formulations include formoterol (Foradil) and salmeterol (Serevent).[38,39]

The selectivity of these agents for β_2-receptors results in the desired response of bronchodilation and a lower incidence of the undesired β_1 responses of tachycardia and arrhythmia. None of these agents are, however, completely selective. These agents are available in aerosol form, and it is widely accepted that aerosol delivery is as effective as subcutaneous or other means of administration. Drugs of this class also have an increased duration of action because of their noncatecholamine structure; this renders them resistant to methylation by catechol-O-methyltransferase. Two puffs of nebulized or metered-dose inhaler–administered albuterol,

TABLE 13-4 Doses of Select Vasoactive Drugs

Drug	Bolus Dose	Infusion Dose Rate	Comments
Calcium chloride ($CaCl_2$) or gluconate	500-1000 mg (chloride)		Onset: <1 min Peak effect: <1 min Duration: 10-20 min
Dobutamine (Dobutrex)	500-2000 mg (gluconate)	2-20 mcg/kg/min	Onset: 1-2 min Peak effect: 1-10 min Duration: 10 min
Dopamine		1-2 mcg/kg/min (renal doses) 2-10 mcg/kg/min (cardiac doses) 10-20 mcg/kg/min (vasopressor doses)	Onset: 2-4 min Peak effect: 2-10 min Duration: <10 min
Ephedrine	5- to 10-mg incremental doses		Dilute to 5 or 10 mg/mL Onset: <1 min Peak effect: 2-5 min Duration: 10-60 min
Epinephrine	10-100 mcg	0.01-0.03 mcg/kg/min (β doses) 0.03-0.15 mcg/kg/min (α and β doses) 0.15-0.3 mcg/kg/min (α doses)	Onset: <1 min Peak effect: 1-2 min Duration: 5-10 min
Fenoldopam		0.1-1.6 mg/kg/min	Onset: 4-5 min Peak effect: 7 min Duration: 15 min
Glucagon	1-5 mg over 2-5 min		
Isoproterenol (Isuprel)	1 mL over 1 min *after diluting* in 10 mL (= 0.02 mg/mL)	0.015-0.15 mcg/kg/min	Onset: <1 min Peak effect: 1 min Duration: 1-5 min
Milrinone (Primacor)	50 mcg/kg	0.375-0.75 mcg/kg/min	
Nesiritide (Natrecor)		0.01 mcg/kg/min	Onset: 15 min Peak effect: 1 hr Duration: 60 min
Norepinephrine (Levophed)		0.01-0.2 mcg/kg/min	Onset: <1 min Peak effect: 1-2 min Duration: 2-10 min
Phentolamine	5 mg (50-100 mcg/kg) Repeat as required	1-10 mcg/kg/min	Onset: 1-2 min Peak effect: 2 min Duration: 10-15 min
Phenylephrine (Neo-Synephrine)	40-100 mcg	0.15-0.75 mcg/kg/min	Onset: <1 min Peak effect: 1 min Duration: 15-20 min
Sodium nitroprusside (Nitropres)		0.1-10 mcg/kg/min	Onset: <1 min Peak effect: 1-2 min Duration: 1-10 min
Vasopressin (Pitressin)	10-20 units	0.1-1.0 units/min	Onset: 1-5 min Peak effect: 5 min Duration 10-30 min

or salmeterol, 10 to 15 minutes before exercise have been shown to have similar efficacy in preventing exercise-induced asthma. Long-acting β_2-agonists should be used in combination with an inhaled corticosteroid.[40]

Chronic use of these agents can result in tachyphylaxis secondary to down-regulation (i.e., diminished quantity) of β-receptors. Increased hyperresponsiveness of the airway also has been suspected with chronic use of these agents. A black box warning about a higher risk of asthma-related death was added to the package inserts of all preparations containing a long-acting β_2-agonist.[41,42]

The β_2-agonists have been given to delay premature labor although there use has declined dramatically because of a high frequency of adverse events and lack of efficacy. This is referred to as a *tocolytic effect*. Uterine relaxation is achieved through increases in the levels of cAMP; this decreases intracellular calcium levels and ultimately diminishes the level of actin-myosin coupling. Terbutaline is the agonist used.

The effectiveness of tocolytic therapy was recently reviewed, with the following practice points: (1) β_2-agonists are effective in delaying delivery for 48 hours but have no effect on perinatal mortality. (2) There is no evidence to support the use of magnesium sulfate or the nitric oxide donors such as nitroglycerin. (3) Indomethacin is an effective tocolytic, but there are concerns about possible fetal and neonatal effects. (4) Nifedipine is an effective tocolytic with a low maternal side effect profile and positive effects on neonatal outcomes. (5) The oxytocin receptor antagonist atosiban is no better than other tocolytics in delaying or preventing preterm birth and has significant side effects.[43,44] Women with failed tocolysis often need emergency surgery. In such cases, regional anesthesia may be preferable. Epidural blockade produces less hypotension than spinal anesthesia and is preferred. If vasopressors are necessary, phenylephrine is the drug of choice because it does not increase the heart rate.[45] Doses of selected vasoactive drugs are listed in Table 13-4. A complete discussion of tocolysis is in Chapter 46.

α_2-Agonists

Clonidine

Clonidine (Catapres) is a presynaptic α_2-agonist. Clonidine decreases blood pressure by acting as an agonist at peripheral presynaptic α_2-receptors and central α_2-receptors. Stimulation of the peripheral presynaptic α_2-receptors causes inhibition of catecholamine release, with subsequent vasodilation. Stimulation of the central α_2-receptors, which is considered the main antihypertensive mechanism of action, results in diminished sympathetic outflow and a resultant decrease in circulating catecholamines and renin activity. It is usually reserved for short-term oral treatment of severe hypertension as an add-on drug.[46] Rebound hypertension, seen after abrupt discontinuation of clonidine use, is a major concern. The resultant increase in catecholamine levels manifests as tachycardia and hypertension. Continuing the medication throughout the perioperative period is essential. Tapering the dose and discontinuation may occasionally be indicated. Patches may also be used during surgery to prevent withdrawal.

Clonidine is available in oral, transdermal, and epidural forms. The transdermal form is frequently encountered and administered at a fixed rate for a period of 1 week. Additional uses of clonidine include premedicant sedative, an analgesic combined with opiates for epidural treatment of severe pain (Duraclon), and suppression of alcohol withdrawal symptoms.[47] Clonidine is used as a catecholamine suppression test in the diagnosis of pheochromocytoma.

Dexmedetomidine

Dexmedetomidine is an α_2-agonist that is marketed for short-term sedation in critical care. It is being used as an adjunct to anesthesia in a variety of situations.[48] Dexmedetomidine provides dose-dependent sedation, analgesia, sympatholysis, and anxiolysis without significant respiratory depression. The side effects are predictable from the pharmacologic profile of α_2-adrenoceptor agonists and include hypotension, bradycardia, oversedation, and delayed recovery. Dexmedetomidine is discussed in detail in Chapter 9. The mechanism of presynaptic α_2-agonism is shown in Figure 13-1.

α-RECEPTOR ANTAGONISTS

The α-receptor antagonists are used for treatment of hypertension, benign prostatic hyperplasia, pheochromocytoma, Raynaud's phenomenon, and ergot alkaloid toxicity.[49] Common side effects include orthostatic hypotension and baroreceptor-mediated reflex tachycardia, which may make their use in the treatment of hypertension somewhat difficult in the ambulatory patient. In addition, because of the significantly longer duration of action of the α-receptor antagonists, other agents are considered more predictable in the treatment of emergent episodes of hypertension.

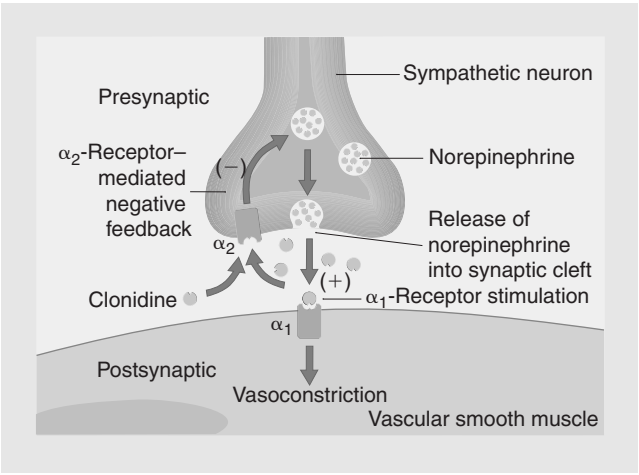

FIGURE **13-1** Presynaptic α_2-agonism. (From Page C, et al. *Integrated Pharmacology.* 3rd ed. Edinburgh: Mosby; 2006:420.)

Phenoxybenzamine

Phenoxybenzamine (Dibenzyline) is a halo alkylamine with both α_1- and α_2-blocking activity. The α-receptors are noncompetitively, irreversibly bound by phenoxybenzamine, and its action is terminated only by metabolism of the drug and generation of new α-receptors. Clinically this drug is used preoperatively in patients with pheochromocytoma for diminishing the response to endogenous catecholamines. The preoperative course is started 1 to 3 weeks before surgery, with the oral dosage titrated up to 40 to 120 mg in two or three divided daily doses. It may be combined with the tyrosine hydroxylase inhibitor metyrosine (Demser). Phenoxybenzamine also prevents the sympathomimetic response expected from phenylephrine. The response to norepinephrine is limited to its β_1-agonist activity, and epinephrine may show "epi-reversal," which is an enhanced β_2 response with a worsening of hypotension and tachycardia. The primary side effect is orthostatic hypertension. Nasal stuffiness has been frequently associated with phenoxybenzamine use.[15,50]

Phentolamine

Phentolamine, an imidazole, is a competitive antagonist of α_1- and α_2-receptors. It has a rapid onset after IV administration and a much shorter duration of action when compared with phenoxybenzamine. It can be used for the short-term control of hypertension in patients with pheochromocytoma. The recommended dose is 1 to 5 mg by slow IV push. Phentolamine has also been used in the treatment of local infiltrations of vasoconstricting agents. Phentolamine (5-10 mg) can be mixed with 10 mL of normal saline and injected directly into the site of the infiltration.[50]

Prazosin and Other α-Receptor Antagonists

Prazosin (Minipress), doxazosin (Cardura), and terazosin (Hytrin) are selective α_1-antagonists used in the chronic treatment of hypertension. Their lack of α_2-blocking activity indicates that they have no effect on norepinephrine levels. Therefore, selectivity for α_1-receptors leaves the inhibitory action of α_2-receptors on norepinephrine release intact, and less norepinephrine-induced tachycardia results than when a nonselective α-antagonist is used. Prazosin induces vasodilation in both arterioles and veins. Peripheral vascular resistance and cardiac preload and afterload are diminished. The drugs are administered orally, and orthostatic hypotension can be a major side effect.

Tamsulosin (Flomax), alfuzosin (Uroxatral), and silodosin (Rapaflo) are alpha 1_α-selective antagonists that produce relaxation of bladder neck and prostate, helping relax smooth muscle tone and relieve obstructive urinary symptoms. They are commonly used with 5α-reductase inhibitors such as finasteride (Proscar) and dutasteride (Avodart) for the treatment of benign prostatic hyperplasia (BPH). Because they do not antagonize alpha 1_β-receptors, they have less risk of hypotension.[51] Tamsulosin and possibly other α-antagonists have been noted to produce floppy iris syndrome, which may complicate cataract surgery. Discontinuing them prior to surgery is not required as long as the ophthalmologist is aware of their administration.[52,53]

Droperidol

Droperidol (Inapsine), a butyrophenone, is used as an antiemetic in anesthesia practice. It produces both dopamine and α-adrenergic blockade and thus small reductions in blood pressure may occur, especially in volume-depleted patients. The use of droperidol has

decreased markedly as a result of the "black box" warning required by the U.S. Food and Drug Administration (FDA) as part of the package insert for this drug. Use of droperidol has been associated with prolongation of the corrected Q-T interval in certain patients, increasing the probability of the development of torsades de pointes, which has led to serious morbidity and death. There has been considerable debate regarding the relationship between the anesthetic administration of droperidol in very low doses as an antiemetic and the complications described.[54] Little doubt remains, however, that the potential for administrative and legal difficulties added to issues of patient safety have led to significant changes in the pattern of use of this drug.[55,56] A 12-lead electrocardiogram is required by the FDA prior to the use of droperidol. Off-labeled use of very low doses as an antiemetic may still be useful. Evidence suggests that the serotonin type 3 receptor antagonists have a similar frequency of Q-T interval prolongation.[54,57]

β-ADRENERGIC BLOCKING AGENTS

The β-blockers are one of the most widely prescribed classes of drugs. Common applications of these agents include the treatment of angina pectoris, hypertension, postmyocardial infarctions, supraventricular tachycardias (including Wolff-Parkinson-White syndrome), and atrial fibrillation; the suppression of increased sympathetic activity (e.g., as occurs with intubation); the management of hypertrophic obstructive cardiomyopathies and congestive heart failure (CHF); the treatment of migraine headaches; and the preoperative preparation of hyperthyroid patients. They are also effective in the treatment of digitalis-induced arrhythmias and in the management of select atrial and ventricular arrhythmias.[58] The perioperative use of β-blockers in vascular and select general surgery patients to reduce morbidity and mortality has been an area of tremendous discussion, and many large-scale clinical trials have been reported. They also prevent detrimental cardiac remodeling, which occurs in many cardiac diseases.[59] The use of perioperative β-blockade in high-risk patients is discussed as follows and in Chapter 25.

The β-blockers are structurally related to isoproterenol. They bind β-receptors in a competitive manner and prevent the actions of catecholamines and other β-agonists. Because these agents are competitive antagonists if an agonist is present in sufficient concentration at the receptor, the blocking actions of the β-antagonists can be overcome.

The β-blockers are subdivided on the basis of their selectivity for cardiac β_1-receptors and other notable clinical differences such as their ability to vasodilate by additional mechanisms or whether they have partial agonist activity. Table 13-5 lists the beta blockers according to classification subtype.[60]

TABLE 13-5 Antihypertensive Drugs

Drug	Daily Adult Maintenance Dosage	Frequent or Severe Adverse Effects
Angiotensin-Converting Enzyme (ACE) Inhibitors		
Benazepril (Lotensin)	10-80 mg in one or two doses	Cough; hypotension, particularly with a diuretic or volume depletion; rash; acute renal failure with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney; angioedema; hyperkalemia if also taking potassium supplements or potassium-sparing diuretics; loss of taste, usually not severe; blood dyscrasias and renal damage rare, except in patients with renal dysfunction; increased fetal mortality with second- and third-trimester exposure; may decrease excretion of lithium
Captopril (Capoten)	12.5-150 mg in two or three doses	
Enalapril (Vasotec)	2.5-40 mg in one or two doses	
Fosinopril (Monopril)	10-80 mg in one or two doses	
Lisinopril (Prinivil or Zestril)	5-40 mg in one dose	
Moexipril (Univasc)	7.5-30 mg in one or two doses	
Perindopril (Aceon)	4-8 mg in one or two doses	
Quinapril (Accupril)	5-80 mg in one or two doses	
Ramipril (Altace)	1.25-20 mg in one or two doses	
Trandolapril (Mavik)	1-8 mg in one or two doses	
Angiotensin-Receptor Antagonists		
Azilsartan (Edarbi)	80 mg once a day	Similar to ACE inhibitors but do not cause cough
Candesartan (Atacand)	8-32 mg in one dose	
Eprosartan (Teveten)	400-800 mg in one or two doses	
Irbesartan (Avapro)	150-300 mg in one dose	
Losartan (Cozaar)	25-100 mg in one or two doses	
Olmesartan medoxomil (Benicar)	20-40 mg in one dose	
Telmisartan (Micardis)	40-80 mg in one dose	
Valsartan (Diovan)	80-320 mg in one dose	
β-Adrenergic Blocking Drugs		
Atenolol (Tenormin)	25-100 mg in one or two doses	Fatigue; depression; bradycardia; decreased exercise tolerance; congestive heart failure; aggravate peripheral arterial insufficiency; aggravate allergic reactions; bronchospasm; mask symptoms of and delay in recovery from hypoglycemia; Raynaud's phenomenon; insomnia; vivid dreams or hallucinations; acute mental disorder; impotence; increased serum triglycerides

Continued

TABLE 13-5 Antihypertensive Drugs —cont'd

Drug	Daily Adult Maintenance Dosage	Frequent or Severe Adverse Effects
Betaxolol generic	5-40 mg in one dose	
Bisoprolol (Zebeta)	5-20 mg in one dose	
Metoprolol (Lopressor, Toprol-XL)	50-200 mg in one or two doses; extended release 25-400 once	
Nadolol (Corgard)	20-320 mg in one dose	
Propranolol (Inderal)	40-240 mg in two doses	
Timolol generic	10-60 mg in two doses	
β-Adrenergic Blocking Drugs with Intrinsic Sympathomimetic Activity		
Acebutolol (Sectral)	200-1200 mg in one or two doses	Similar to other β-adrenergic blocking drugs but with less resting bradycardia and lipid changes; acebutolol has been associated with positive antinuclear antibody test and occasional drug-induced lupus
Penbutolol (Levatol)	10-80 mg in one dose	
Pindolol generic	10-60 mg in two doses	
α- and β-Blockers		
Carvedilol (Coreg)	12.5-50 mg in two doses	Similar to other β-adrenergic blocking drugs, but more orthostatic hypotension; no affect on serum lipids
Labetalol generic	200-1200 mg in two doses	
β-Blocker with Vasodilating Nitric Oxide–Mediated Activity		
Nebivolol (Bystolic)	5-40 mg once	Vasodilator due to nitric oxide-mediated action
Thiazide-Type Diuretics (Usually Once Daily)		
Chlorothiazide (Diuril)	125-500 mg once	Hyperuricemia; hypokalemia; hypomagnesemia; hyperglycemia; hyponatremia; hypercholesterolemia; hypertriglyceridemia; pancreatitis; rashes and other allergic reactions; sexual dysfunction; photosensitivity reactions; may decrease excretion of lithium
Hydrochlorothiazide (Microzide)	12.5-50 mg once	
Chlorthalidone (Thalitone)	12.5-50 mg once	
Indapamide generic	1.25-5 mg once	
Metolazone (Zaroxolyn)	1.25-5 mg once	
Loop Diuretics		
Bumetanide generic	0.5-2 mg in two doses	Dehydration; circulatory collapse; hypokalemia; hyponatremia; hypomagnesemia; hyperglycemia; metabolic alkalosis; hyperuricemia; blood dyscrasias; rashes; lipid changes as with thiazide-type diuretics
Ethacrynic acid (Edecrin)	25-100 mg in two or three doses	
Furosemide (Lasix)	20-320 mg in two doses	
Torsemide (Demadex)	5-20 mg in one or two doses	
Potassium-Sparing Diuretics		
Amiloride (Midamor)	5-10 mg in one or two doses	Hyperkalemia; GI disturbances; rash; headache
Eplerenone (Inspra)	25-100 mg in one or two doses	Hyperkalemia; hypernatremia
Spironolactone (Aldactone)	12.5-100 mg in one or two doses	Hyperkalemia; hyponatremia; mastodynia; gynecomastia; menstrual abnormalities; GI disturbances; rash
Triamterene (Dyrenium)	50-150 mg in one or two doses	Hyperkalemia; GI disturbances; nephrolithiasis
Calcium Channel Blockers		
Diltiazem (Cardizem CD)	120-360 mg in one dose	Dizziness; headache; edema; constipation (especially verapamil); AV block; bradycardia; heart failure; lupus-like rash with diltiazem
(Tiazac)	120-540 mg in one dose	
Verapamil (Calan)	120-480 mg in one or two doses	
(Calan SR)	120-480 mg in one or two doses	
(Isoptin SR)	120-480 mg in one or two doses	
(Verelan PM)	120-480 mg in one dose	
(Covera-HS)	180-540 mg in one dose	
Dihydropyridines		
Amlodipine (Norvasc)	2.5-10 mg in one dose	Dizziness; headache; peripheral edema (more than with verapamil and diltiazem; more common in women); flushing; tachycardia; rash; gingival hyperplasia
Felodipine (Plendil)	2.5-10 mg in one dose	

TABLE 13-5 Antihypertensive Drugs —cont'd

Drug	Daily Adult Maintenance Dosage	Frequent or Severe Adverse Effects
Isradipine (DynaCirc, DynaCirc CR)	5-10 mg in two doses	
Nicardipine generic Nicardipine extended release (Cardene SR)	60-120 mg in two or three doses	
Nifedipine (Adalat CC, Procardia XL)	30-90 mg once	
Nisoldipine (Sular)	17-34 mg once	
α-Adrenergic Blockers		
Prazosin (Minipress)	1-20 mg in two or three doses; first dose is 1 mg at bedtime	Syncope with first dose; dizziness and vertigo; headache; palpitations; fluid retention; drowsiness; weakness; anticholinergic effects; priapism
Terazosin (Hytrin)	Maintenance: 1-20 mg once; first dose is 1 mg at bedtime	Both similar to prazosin, but with less hypotension after first dose
Doxazosin (Cardura)	1-2 mg in one dose; first day: 1 mg at bedtime	
Central α-Adrenergic Agonists		
Clonidine (Catapres)	0.1-0.6 mg in two or three doses	CNS reactions similar to methyldopa, but more sedation and dry mouth; bradycardia; heart block; rebound hypertension (less likely with patches); contact dermatitis from patches
(Catapres TTS)	One patch weekly (0.1-0.3 mg/day)	Similar to clonidine
Guanfacine generic	1-3 mg in one dose	Drowsiness; sedation, fatigue; depression; dry mouth; heart block; autoimmune disorders, including colitis, hepatitis, hepatic necrosis; Coombs-positive hemolytic anemia; lupus-like syndrome; thrombocytopenia; red cell aplasia; impotence
Methyldopa generic	250 mg-2 g in two doses	
Direct Vasodilators		
Hydralazine generic	40-200 mg in two to four doses	Tachycardia; aggravation of angina; headache; dizziness; fluid retention; nasal congestion; lupus-like syndrome; hepatitis
Minoxidil generic	2.5-40 mg in one or two doses	Tachycardia; aggravation of angina; marked fluid retention; pericardial effusion; hair growth on face and body
Renin Inhibitor		
Aliskiren (Tekturna)	150-300 mg once daily	First direct renin inhibitor for treatment of hypertension; avid binding of renin and long half-life could lead to hypotension unresponsive to discontinuing drug

From Medical Letter Treatment Guidelines. Drugs for hypertension. *Med Lett.* 2012;10(113):1-10; Azilsartan medoximil (Edarbi)-the eighth ARB. *Med Lett* 2011;53(1364):39-40; Nebivolol (Bystolic) for hypertension. *Med Lett.* 2008;50(1281):17-19.
AV, Atrioventricular; *CNS*, central nervous system; *GI*, gastrointestinal; *HDL*, high-density lipoprotein.

The degree of receptor selectivity is important because antagonism of β_1-receptors results in lowered heart rate, decreased myocardial contractility, and diminished atrioventricular conduction velocity; it also has beneficial effects with regard to decreasing myocardial oxygen consumption and the treatment of arrhythmias. However, antagonism of β_2-receptors can result in adverse effects such as bronchoconstriction, hypoglycemia, and peripheral vasoconstriction. It is important to note that as the dose of the selective β-blockers is increased, the degree of selectivity is diminished.

Some of the β-blockers act as partial agonists and as such possess intrinsic sympathomimetic activity. A partial agonist does not stimulate β-receptors to the extent that a full agonist does, and in the presence of a full agonist, the partial agonist acts as a competitive antagonist. It follows that β-blockers with intrinsic sympathomimetic activity (ISA) competitively antagonize the effects of a full agonist (e.g., endogenous catecholamines released during times of maximal sympathetic tone) down to the activity level of its partial agonist component. Intrinsic sympathomimetic activity minimizes the risk of bronchoconstriction in patients with reactive airway disease who require β-blockade. Pindolol, acebutolol, penbutolol, and carteolol are β-adrenergic blocking agents that possess intrinsic sympathomimetic activity.

Membrane-stabilizing activity is another property of some β-blockers. These agents diminish arrhythmogenicity by exerting a quinidine-like effect in the heart. However, membrane-stabilizing activity is seen only with high drug concentrations.[61] Propranolol and pindolol are two β-blockers with membrane-stabilizing activity. Labetalol and carvedilol are mixed β- and α-receptor antagonists. The added α-receptor blockade makes them vasodilators. Nebivolol (Bystolic) is a new cardioselective β-blocker approved for the treatment of hypertension. It is unique in that it has nitric oxide–mediated vasodilating properties.[62]

Some potential problems with β-adrenergic blocking agents have already been mentioned. β-blockade can result in both bronchospasm and the development of overt cardiac failure in some patients with high doses or IV administration. Other potential problems arise with β_2-receptor blockade in patients with peripheral vascular disease and Raynaud's disease because of the possible potentiation of peripheral vasoconstriction. In diabetic patients, signs of hypoglycemia may be masked, and the patient's ability to

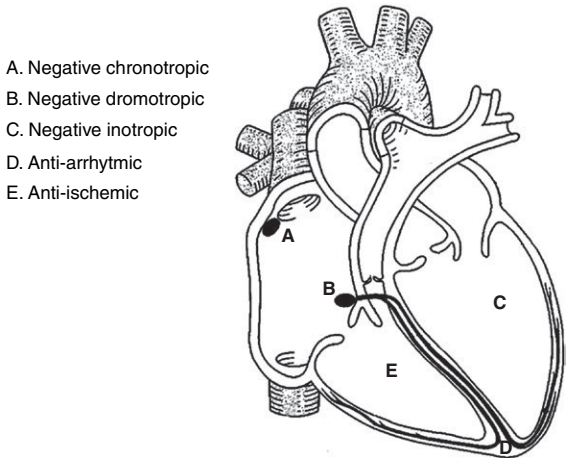

FIGURE **13-2** Cardiac effects of beta adrenergic blocking drugs. **A,** Negative chronotropic. **B,** Negative dromotropic. **C,** Negative inotropic. **D,** Antiarrhythmic. **E,** Antiischemic.

increase serum glucose levels may be impaired. Serum potassium levels may also become elevated with β_2-blockade, because uptake into skeletal muscle is inhibited. In patients whose heart rate is controlled to maintain cardiac output, β-blockade may have a significant impact on blood pressure.

The β-receptors are considered to be "labile" receptors—that is, they are subject to significant up- and down-regulation. Chronic therapy with β-blockers can lead to up-regulation of β-receptors or an increase in the absolute number and activity of receptors. This phenomenon is suspected to be the underlying cause of the withdrawal syndrome seen with abrupt discontinuation of β-adrenergic antagonist use. Raynaud's phenomenon is characterized by increased sympathetic activity for up to 2 days. Obviously this means the patient receiving β-blockers should continue to receive them without interruption throughout the perioperative period. The effects of the β-blocking agents on the ischemic heart are summarized in Figure 13-2.

Anesthetic Uses

Metoprolol, Esmolol, and Labetalol

Three β-adrenergic blocking agents, which are available IV, are especially useful in the perioperative period. They are metoprolol, esmolol, and labetalol. Esmolol has replaced propranolol in most instances of β-blocker application in anesthesia because of its rapid onset and short duration of action. Esmolol has an onset time of 2 minutes and an elimination half-life of approximately 9 minutes. Its rapid onset and short half-life, as well as its duration of action of 10 to 15 minutes, make it easily and reliably titratable in acute-care situations. The recommended IV loading dose of esmolol is 500 mcg/kg; this is followed by an infusion of 100 to 300 mcg/kg/min as needed. Small boluses of 10 to 15 mg may be given with repeat administration according to patient response. Esmolol is metabolized by nonspecific plasma esterases found in the cytosol of red blood cells. Metoprolol is frequently used after myocardial infarction or in some types of angina and hypertension, once the patient is stable, to normalize vital signs. Administration of 5-mg doses intravenously at 5-minute intervals to a maximum dose of 15 mg is recommended.[60]

Labetalol (Normodyne, Trandate) is classified as a nonselective β-blocker but is unique in that it also possesses an α-blocking component. It provides β-blockade along with α-blockade in a ratio of 7:1. Unlike the standard β-blocker, labetalol produces vasodilation secondary to its α-blocking properties. This action can be extremely beneficial in situations in which an acute rise in blood pressure could be devastating to the clinical outcome. The usual IV dose of labetalol is 0.25 mg/kg; this dose can be repeated every few minutes as indicated and followed by an infusion, if indicated, at a rate of 2 mg/min. In clinical practice, a bolus dose of labetalol (5-10 mg) is titrated and repeated on the basis of patient response. Labetalol can have a duration of action ranging from 2 to 6 hours, depending on dose. Because labetalol provides both β- and α-blockade, an adequate heart rate must be present before labetalol can be used in the acute management of hypertension. It is recommended for hypertensive episodes in obstetric patients. Uterine blood flow is not affected in obstetric patients, even in the event of a dramatic decrease in systemic blood pressure.[62] Labetalol undergoes hepatic metabolism and renal elimination.[63]

Prophylactic β-blockers showed a positive benefit in reducing major postoperative cardiac events in select high-risk patients. A large-scale clinical trial (POISE) of extended-release metoprolol indicated that there was a lower incidence of perioperative myocardial infarction (MI), clinically significant atrial fibrillation, and the need for coronary revascularization, but an increase in strokes and overall mortality secondary to more hypotension and bradycardia.[64] There are concerns that anemia might complicate perioperative β-blockade by further limiting oxygen delivery. β-blockade is associated with worse outcomes when hemoglobin levels are decreased by greater than 35%. In elderly patients, this is a potential mechanism for the increased stroke rate found in the POISE trial. Gender differences exist as well. Men benefited from β-blockade with reduced MI, but women suffered from clinically significant increases in CHF. Evidence for pharmacogenetic variation in metabolism suggests that metoprolol might not be the best choice of β-blocker in the perioperative period.[65] Many other studies have noted conflicting results, and the proper use of β-blockers has been a much discussed and researched area.[66,67] The American College of Cardiology Foundation and the American Heart Association (ACCF/AHA) have issued revised guidelines on the use of perioperative β-blockers.[68]

In general, β-blockers should be continued in surgical patients who are already taking them. β-blockers may benefit vascular surgery patients at high risk for MI but not for stroke. They are more likely to be beneficial when started at a lower dose well in advance of surgery and titrated to a heart rate of 55 to 70 beats per minute (bpm). Avoid starting β-blockers immediately before surgery, in emergency surgery, or in patients with prior cerebrovascular disease or sepsis. A protocol for perioperative β-blocker therapy is listed in Box 13-1. The detailed recommendations for the use of β-blockers in noncardiac surgery can be found in the ACCF/AHA guidelines.[68] In situations where β-blockers are contraindicated, such as patients with asthma, bradyarrhythmias, acute heart failure, or advanced heart block, an α_2-adrenergic agonist such as clonidine may have some benefit.[69]

Statins reduce endovascular inflammation and plaque. Current data suggest they should be continued perioperatively and started prophylactically in select patients.[70,71]

CHOLINERGICS

Cholinergic agents mimic the actions of the neurotransmitter acetylcholine but have been developed to differ in terms of comparative nicotinic and muscarinic activity and duration of action. Acetylcholine (Miochol) has no clinical application, owing to its generalized enhancement of cholinergic effects throughout the body and its extremely short duration of action (approximately 1 msec), which is a result of its rapid metabolism by acetylcholinesterase.

BOX 13-1

Protocols for Prophylactic Perioperative β-Blockers

General Principles

- Start β-blocker at least 1 week before surgery (if possible).
- Titrate the dose to an ideal target heart rate of 55 to 70 bpm.
- Use half the dose if the heart rate is less than 65 bpm, if systolic blood pressure is less than 120 mmHg, or the patient is small and elderly or frail.
- Hold the dose if the heart rate is less than 55 bpm or systolic blood pressure is less than 100 mmHg.
- Continue β-blocker postoperatively for at least 1 to 4 wk (or indefinitely if independent criteria such as known coronary artery disease, peripheral arterial disease, or hypertension are present). Taper the dose if discontinuing.
- Before increasing the dose for postoperative tachycardia, evaluate the patient for other potential causes, including pain, bleeding, and sepsis (where β-blockers may be detrimental).

Specific Drugs: Atenolol, Bisoprolol, or Metoprolol

- Preoperatively (recommended starting dose, then titrate to the target heart rate):
  - Atenolol: Start at 25 mg orally daily
  - Bisoprolol: Start at 5 mg orally daily at least 7 days before surgery
  - Metoprolol: Start at 25 to 50 mg orally twice daily up to 30 days preoperatively
- Day of surgery—continue the usual dose or increase the oral dose to control the heart rate or give additional intravenous (IV) doses (atenolol or metoprolol, 5-10 mg) as needed if unable to take orally. Esmolol can also be used (500 mcg/kg IV loading dose over a 1-min period; then infuse at 50-200 mcg/kg/min and titrate to the target heart rate).
- Postoperatively—continue the usual preoperative dose:
  - *Atenolol:* 25 to 100 mg orally daily for at least 7 days
  - *Bisoprolol:* 2.5 to 5 mg orally daily for at least 30 days
  - *Metoprolol:* 25 to 100 mg orally twice daily for at least 14 days
  - Substitute IV atenolol or metoprolol (5-mg doses) as needed if unable to take medication orally

From Cohn SL. Preoperative evaluation. In Goldman L, Schafer AI. *Goldman's Cecil Medicine*. 24th ed. Philadelphia: Saunders; 2012:2482; Wiest DB, Haney JS. Clinical pharmacokinetics efficacy of esmolol. *Clin Pharmacokinet*. 2012;51(6):347-356.

Methacholine (Provocholine), carbachol (carbamylcholine chloride), and bethanechol (carbamylmethylcholine) are choline esters that have limited clinical applications. Methacholine can be used as an aerosol in the diagnosis of reactive airway disease, whereas carbachol, because of its significant muscarinic and nicotinic activity, is used only as a topical ophthalmic solution in the treatment of narrow-angle glaucoma and for inducing miosis during diagnostic testing and surgery. Bethanechol is theoretically useful in instances of ileus and urinary retention, such as in postvagotomy and postpartum patients, respectively. Bethanechol's relative lack of nicotinic activity makes it the most attractive of these three agents, and it is the agent most frequently encountered in clinical practice. Potential side effects of these agents include any cholinergic-induced response such as bradycardia, varying degrees of heart block, hypotension, bronchoconstriction, and an increase in gastric secretions.[72]

ANTICHOLINERGICS

The anticholinergics are familiar agents in anesthesia practice. Atropine, scopolamine, and glycopyrrolate are the three anticholinergics used in anesthesia practice. These agents are competitive antagonists of acetylcholine at muscarinic receptors. A comparison of the basic properties of the anticholinergic agents is given in Table 13-6. Subtypes of muscarinic and nicotinic receptors are summarized in Table 13-7 and Table 13-8.

TABLE 13-6 Comparative Effects of Anticholinergic Drugs

Effect	Atropine	Scopolamine	Glycopyrrolate
Sedation	+	+++	0
Antisialagogue	+	+++	++
Increase heart rate	+++	+	++
Relax smooth muscle	++	+	++
Mydriasis, cycloplegia	+	+++	0
Prevent motion-induced nausea	+	+++	0
Decrease gastric hydrogen ion secretion	+	+	+

Atropine

Atropine, a belladonna alkaloid, is the prototype anticholinergic. The anesthetist can use atropine for its antisialagogue effects, for the prevention or treatment of bradycardia, and concurrently with anticholinesterase agents in the reversal of muscle relaxants for preventing the resultant bradycardia from anticholinesterase-induced acetylcholine buildup. The usual adult IV dose for increasing heart rate during anesthesia is 0.4 to 0.6 mg, with the time to onset being 1 to 2 minutes. Atropine is a tertiary amine; this allows it to cross the blood-brain barrier freely and may result in transient bradycardia during onset when low doses are given. However, at usual clinical doses, significant CNS effects are rarely evident. Hepatic metabolism accounts for approximately half of a dose of atropine, with the remainder being eliminated unchanged in the urine. The elimination half-life of atropine is approximately 4 hours. Atropine should be avoided in patients with narrow-angle glaucoma because it increases intraocular pressure. Atropine poisoning or belladonna alkaloid toxicity manifests with extreme antimuscarinic effects, with potential progression to CNS depression and coma. The decades-old mnemonic "red as a beet, blind as a bat, dry as a bone, mad as a hatter, and hot as a hare" was devised to be an easy way to remember the signs and symptoms of belladonna overdose. These include flushing ("red as a beet"); extreme mydriasis ("blind as a bat"); lack of secretions and dry mouth ("dry as a bone"); confusion ("mad as a hatter"); and hyperthermia ("hot as a hare").[72]

Scopolamine

Scopolamine (Isopto Hyoscine) is another belladonna alkaloid with anticholinergic effects. Scopolamine is a tertiary amine. Compared with atropine, scopolamine has CNS effects that are much more pronounced at lower doses. Compared with atropine, it does not substantially increase heart rate. It can be used as a preoperative medication, with sedation and amnesia being a desirable effect. Scopolamine also is used to diminish the incidence of postoperative nausea and vomiting. A scopolamine patch (Transderm Scōp) containing a total dose of 1.5 mg is usually applied behind the ear. The patches have an onset of 4 hours and a duration of 3 days.[73]

TABLE 13-7 Properties of Muscarinic (M_1-M_5) Receptors

	M_1	M_2	M_3	M_4	M_5
Location	CNS Stomach	Heart CNS	Glands GI, CNS	CNS Heart	CNS
Important clinical effects	Increased cognition and memory; gastric acid production	Bradycardia, smooth muscle contraction	Salivary secretions, bladder contraction	Promotes dopamine release	Promotes dopamine release, dilation of cerebral arteries

CNS, Central nervous system; *GI*, gastrointestinal.

TABLE 13-8 Characteristics of Subtypes of Nicotinic Acetylcholine Receptors (nAChRs)

Receptor Subtype	Main Synaptic Location	Membrane Response
Skeletal muscle (N_M)	Skeletal neuromuscular junction (postjunctional)	Excitatory; endplate depolarization; skeletal muscle contraction
Peripheral neuronal (N_N)	Autonomic ganglia; adrenal medulla	Excitatory; depolarization; firing of postganglion neuron and secretion of catecholamines
Central nervous system (CNS)	CNS; pre- and postjunctional	Pre- and postsynaptic excitation Prejunctional control of transmitter release

Tiotropium

Tiotropium (Spiriva) is a long-acting inhaled muscarinic antagonist that is used as a bronchodilator for patients with chronic obstructive pulmonary disease (COPD). Tiotropium improves lung function, quality of life, and decreases exacerbations of COPD but does not significantly reduce the rate of decline in the forced expiratory volume (FEV1).[74]

Glycopyrrolate

Glycopyrrolate (Robinul), a synthetic quaternary ammonium compound, has become the most frequently used anticholinergic in anesthesia practice. It has an excellent antisialagogue action,[75] with a longer duration of action than belladonna alkaloids. It prevents bradycardia without inducing significant levels of tachycardia. The quaternary ammonium structure of glycopyrrolate prevents it from crossing the blood-brain barrier to any significant degree; therefore, CNS effects are not seen. This is an important advantage of glycopyrrolate because atropine and scopolamine cross the blood-brain barrier and have CNS effects that can contribute to postoperative delirium.[76] This property also makes it the agent of choice in obstetrics because it does not pass the placental barrier. Adult IV doses are generally 0.1 to 0.2 mg for antisialagogue activity and for the treatment of bradycardia. Onset of action is rapid, and the duration of action is up to 4 hours. It is used in combination with neostigmine for reversal of nondepolarizing neuromuscular blockers. It produces less tachycardia than atropine in the period in which you are awaiting the onset of neostigmine.[72]

DIRECT VASODILATORS

Within the category of direct vasodilators, sodium nitroprusside, nitroglycerin, and hydralazine are the three drugs most commonly employed (Table 13-9). All three produce direct vasodilation. Sodium nitroprusside produces arterial and venous relaxation; nitroglycerin has a greater effect on venous than arterial relaxation; and hydralazine produces primarily arterial relaxation. The mechanism of action of all three agents is believed to be primarily an induced increase in the concentration of vascular nitric oxide, although that has not been confirmed with hydralazine.[77] The mechanism of action is depicted in Figure 13-3. The vasodilators nitroprusside and nitroglycerin are frequently used for controlled hypotension under anesthesia. Combined with the inhalation and intravenous anesthetics, they facilitate a reduction in blood loss and need for transfusions during a variety of surgical procedures.[78]

Nitrovasodilators

Sodium Nitroprusside

Sodium nitroprusside is frequently used for the emergent control of hypertension, for inducing hypotension to decrease blood loss during surgical procedures, and for the treatment of acute cardiac disorders. Its rapid onset (within seconds) and its short duration of action (1-3 min) make it unique among agents for the rapid control of blood pressure. Sodium nitroprusside reduces both afterload and preload, which results in a decrease in cardiac filling pressures and an increase in stroke volume and cardiac output. Left ventricular volumes are decreased, and diminished myocardial wall tension should contribute to a decrease in myocardial oxygen consumption.

Usually, sodium nitroprusside is started as an infusion at 0.3 mcg/kg/min and is titrated until a response occurs. An infusion rate of 3 mcg/kg/min is rarely exceeded, but young, normotensive patients may require up to 5 mcg/kg/min to achieve the desired response.[79] The maximum recommended infusion rate is 10 mcg/kg/min. Sodium nitroprusside is mixed with 5% dextrose in water, and the bottle and tubing are covered in a protective wrap; light causes the sodium nitroprusside to decompose. An infusion pump should always be used with sodium nitroprusside because of its potency and the associated risk of cyanide toxicity.

Cyanide Toxicity. Sodium nitroprusside contains five cyanide ions within its chemical structure, and its metabolism by plasma hemoglobin causes the release of these cyanide ions. One cyanide ion binds methemoglobin to form cyanmethemoglobin, whereas the other four cyanide ions undergo rhodanese-catalyzed conversion to thiocyanate in the liver, with the thiocyanate undergoing renal elimination. This conversion to thiocyanate requires the cofactor thiosulfate B_{12}. Cyanide toxicity results when these metabolic pathways are quantitatively overwhelmed. Preventing cyanide toxicity from sodium nitroprusside begins with awareness of maximum doses and lengths of administration. In general, when more than 500 mcg/kg of sodium nitroprusside is administered faster than 2 mcg/kg/min, cyanide is generated faster than the patient can eliminate it. Chronic administration should not exceed 0.5 mcg/kg/min.

TABLE 13-9 Parenteral Drugs for Treatment of Severe Hypertension

Drug	Class	Route and Dose	Onset	Duration	Comments
Fenoldopam (Corlopam)	Dopamine-1 receptor agonist	IV infusion pump: 0.1-1.6 mcg/kg/min	4-5 min	<10 min	May cause reflex tachycardia; may increase intraocular pressure
Labetalol (Trandate Normodyne)	α- and β-adrenergic blocker	IV: 20 mg initially, then 40-80 mg every 10 min (300 mg max)	5 min or less	3-6 hr	Not for patients with bronchospasm, congestive heart failure, first-degree heart block, cardiogenic shock, or severe bradycardia
Nicardipine (Cardene IV)	Calcium channel blocker	IV: 5 mg/hr, increased by 2.5 mg/hr every 15 min up to 15 mg/hr	1-5 min	3-6 hr	May cause reflex tachycardia
Clevidipine (Cleviprex)	Calcium channel blocker	IV infusion: 1-2 mg/hr initially; double the dose at 90-sec intervals until desired results are achieved (16 mg/hr/max)	2-4 min	5-15 min	Rapidly degraded by tissue and blood esterases; contraindicated with allergy to soy or eggs; may cause reflex tachycardia
Nitroglycerin	Venous arteriolar vasodilator	IV infusion pump: 5-100 mcg/min	2-5 min	5-10 min	Headache, tachycardia can occur; tolerance may develop with prolonged use
Sodium nitroprusside	Arteriolar and venous vasodilator	IV infusion pump: 0.3-10 mcg/kg/min	Seconds	3-5 min	Thiocyanate or cyanide toxicity with prolonged or too rapid infusion
Esmolol	β-blocker	IV: 500 mcg/kg/min for 1 min titration to effect, usually 50 mcg/kg/min	1-2 min	5-10 min	Cardioselective; however, use with caution in patients with asthma
Labetalol	Combined α- and β-blocker	5-80 mg bolus titrated to effect; 2 mg/min infusion	1-2	3-6	Generally used in 5-10 mg incremental doses titrated to effect in the perioperative period

From Medical Letter Treatment Guidelines. Cardiovascular drugs in the ICU. *Med Lett.* 2002;4:19-24; Aggarwal M, Kahn IA. Hypertensive crises: hypertensive emergencies and urgencies. *Cardiol Clin.* 2006;24:135-146; Clevidipine (Cleviprex) for IV treatment of severe hypertension. *Med Lett. 2011*;50(1295):73-75.

Clinically the development of metabolic acidosis, increased mixed venous oxygen content, tachycardia, and tachyphylaxis during sodium nitroprusside use are signs of cyanide toxicity.

Treatment of cyanide toxicity consists of discontinuing the sodium nitroprusside infusion, administering oxygen, and treating metabolic acidosis. Sodium nitrite 3%, 4 to 6 mg/kg, can be administered over 3 to 5 minutes to promote the production of methemoglobin so that excess cyanide ions can be bound. Sodium thiosulfate, 150 to 200 mg/kg over 15 minutes, can be administered every 2 hours as needed; vitamin B_{12} also can be administered. If available, hydroxycobalamin can be used. Methylene blue 1 to 2 mg/kg may also be useful. A new prodrug, sulfanegen sodium, is also being tested.[80]

Nitroglycerin

Nitroglycerin is used in the treatment of angina pectoris and ischemia under anesthesia and also can be used for lowering blood pressure. It has a rapid onset and short duration so it is easily titratable. Nitroglycerin causes venodilation, with an increase in venous capacitance and a resultant decrease in preload. This results in a lowering of cardiac filling pressures, a lessening of myocardial wall tension, and ultimately a decrease in myocardial oxygen requirements. Nitroglycerin's primary mechanism of action in the relief of angina is a decrease in preload and cardiac work. Some of the larger coronary vessels may become dilated, with a resultant redirection and increase in blood flow to ischemic myocardium. It also relieves coronary spasm. At higher concentrations of nitroglycerin, arterial vasodilation also can occur.[81]

Use of sublingual nitroglycerin (0.3-mg tablets), up to a total of three tablets, is the most efficient treatment for acute angina. Relief is generally achieved in 1 to 2 minutes and lasts up to 30 minutes. Intravenous nitroglycerin also has an onset time of 1 to 2 minutes and duration of action of up to 10 minutes. Nitroglycerin is extensively metabolized in the liver and has a half-life of only 3 minutes.[80] Intravenous nitroglycerin is used for "unloading" of the heart in CHF and myocardial infarction.[82] Guidelines suggest that intravenous infusions should be instituted following three sublingual doses of 0.4 mg every 5 minutes in patients having a ST-segment elevation myocardial infarction (STEMI). Nitroglycerin infusions are usually started at 10 to 20 mcg/min and are titrated up until effective. Intravenous nitroglycerin can also be used for controlled hypotension but is not as effective as an infusion of sodium nitroprusside. Because nitroglycerin exerts its main effect on venous capacitance, any decrease in blood pressure is more volume dependent when compared with sodium nitroprusside–induced hypotension. Nitrates should be avoided in patients with a blood pressure less than 90 mmHg, a heart rate less than 50 bpm or above 100 bpm, and in patients with right ventricular infarction. Of note to the anesthesia provider is the ability of nitroglycerin to relax the smooth muscle of the biliary tract and provide relief from narcotic-induced biliary spasm. Generally, 50 mg of nitroglycerin

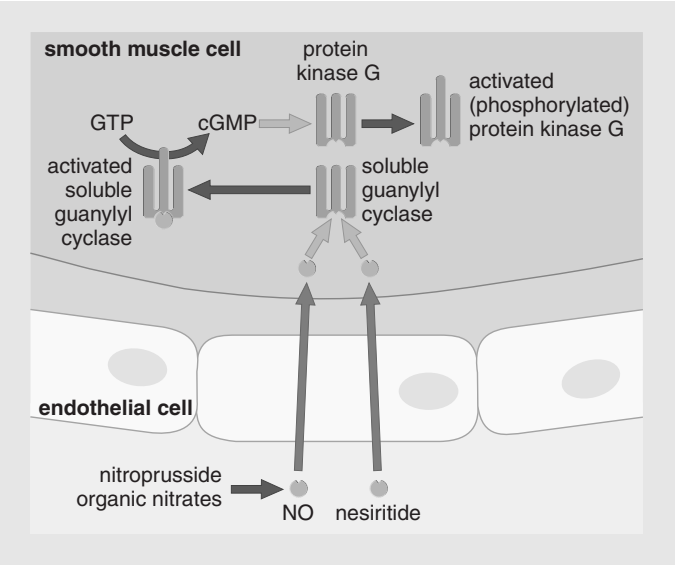

FIGURE **13-3** Molecular and cellular mechanisms of action of nitrate and nitrite vasodilators, nitric oxide (NO) and nesiritide. The primary molecular target, soluble guanylyl cyclase, is accessed by drug or NO diffusion between cells. The product, phosphorylated protein kinase, causes vascular smooth muscle relaxation by phosphorylating (and inactivating) myosin light chain kinase. (From Page C, et al. Integrated Pharmacology. 3rd ed. Elsevier: Edinburgh; 2006: 391.)

is mixed with 250 mL of dextrose 5% in water.[83] For extended coverage, nitroglycerin patches and ointments are also available. A summary of antihypertensive agents dosing information is found in Table 13-5.

Hydralazine

Hydralazine causes direct relaxation of arterial smooth muscle. It can be administered intravenously for the control of hypertension in doses ranging from 2.5 to 20 mg. Tachycardia frequently accompanies the decrease in blood pressure secondary to the preferential reduction in afterload. It is important to remember that the onset of action can occur from 2 to 20 minutes after administration; therefore, adequate time should be allowed before the initiation of repeat dosing so that profound decreases in blood pressure can be prevented. The elimination half-life in plasma is approximately 1 hour, but the duration of vasodilating action can be as long as 12 hours.[84-86] Hydralazine undergoes hepatic metabolism with renal excretion. Acetylation is partly responsible for the metabolism of hydralazine. Slow acetylators may be more prone to a drug-induced lupus syndrome that can result from high serum concentrations of hydralazine during chronic treatment. Currently, hydralazine is usually reserved for hypertensive episodes during pregnancy.

CALCIUM CHANNEL BLOCKERS

The calcium channel antagonists, also referred to as calcium channel blockers (CCBs) have proved to be useful pharmacologic agents in the treatment of angina, hypertension, arrhythmias, peripheral vascular disease, esophageal spasm, cerebral vasospasm, and controlled hypotension.[87] There are three chemical classes of calcium channel blockers: 1,4-dihydropyridine derivatives, such as Nifedipine (Adalat, Procardia); diltiazem (Cardizem) is a benzothiazepine derivative; and verapamil (Calan, Isoptin) is a phenylalkylamine derivative.

All CCBs have negative inotropic and chronotropic actions. They are class 4 antiarrhythmics that block calcium channels; therefore they depress electrical impulses in the sinoatrial (SA) and atrioventricular (AV) nodes. They produce coronary and systemic vasodilation. Different drugs in the three classes vary as to their individual ability to produce each of these effects.[61]

A discussion of the generalized mechanism of action of the calcium antagonists is necessary for a better understanding of their role. Depolarization of the sinoatrial and atrioventricular nodes is dependent on the inward flux of calcium during the depolarization phases of the cardiac action potential. Calcium channel antagonists "block" these channels, diminishing the inward flux of calcium and prolonging phase 2, and in this way exert a negative chronotropic effect on the heart. Ventricular pacemaker foci are dependent on the inward flux of sodium, which is minimally if at all affected by the calcium antagonists. It then follows that the calcium antagonists are effective in patients with atrial tachyarrhythmias. Verapamil and diltiazem are the most commonly used CCBs as antiarrhythmics. They are effective in treating atrial tachyarrhythmias (including Wolff-Parkinson-White syndrome) and in controlling the ventricular response to atrial fibrillation and flutter. Verapamil is not indicated for the treatment of atrial fibrillation associated with Wolff-Parkinson-White syndrome, nor is it indicated for the treatment of "simple" atrial tachycardia, for which β-blockers may be a better choice.

Calcium channel blockers also exert a negative inotropic effect on the heart, which can be beneficial in patients with angina. Cardiac contractility is dependent on the influx of calcium into cardiac cells and this is slowed by the CCBs. This negative inotropic effect then leads to a decrease in myocardial oxygen consumption. Calcium channel antagonists produce relaxation of vascular smooth muscle resulting in vasodilation. Systemic vasodilation of both arteries and veins result in a decreased preload and afterload, which contributes to an increase in cardiac output and a decrease in myocardial work and oxygen consumption. The negative inotropic action and vasodilation account for the antihypertensive effect.[88] Coronary arteries also are affected, with an increase in coronary blood flow. The CCBs are especially beneficial in the prevention of angina resulting from spasm of the coronary arteries, such as Prinzmetal's angina.

Nimodipine has been a long-standing treatment for treatment of cerebral vasospasm associated with neurologic emergencies such as ruptured aneurisms and neurosurgery.[89-91]

Verapamil, 2.5 to 10 mg intravenously (dose can be repeated every 30 minutes), can be given for the treatment of atrial tachyarrhythmias. The onset time is up to 10 minutes, and the duration of action ranges from 2 to 4 hours. Verapamil is metabolized hepatically, has an elimination half-life of 4 to 7 hours, and is renally eliminated. Verapamil has been largely replaced by adenosine as the first-line drug of choice in the treatment of supraventricular tachycardias. Nicardipine is also useful as an IV preparation for the treatment of perioperative hypertension.[92,93] The effects of calcium channel blockers on the ischemic heart are summarized in Figure 13-4.

Varying degrees of atrioventricular block, myocardial depression, and hypotension are associated with the use of the calcium antagonists. An additive effect should be anticipated if the calcium channel antagonists are used with other cardiodepressant agents such as anesthetics.[94]

Clevidipine (Cleviprex) is a dihydropyridine L-type calcium channel blocker indicated as an IV antihypertensive. It is highly selective for vascular muscle and does not affect myocardial contractility or conduction. Its antihypertensive effect

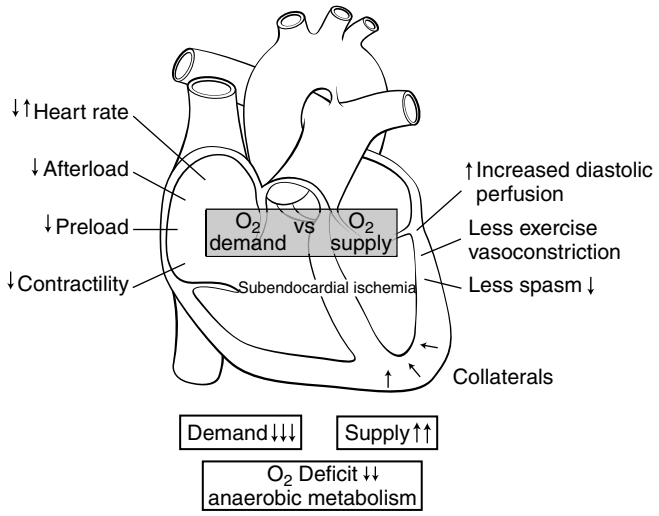

FIGURE **13-4** Effects of calcium channel blockers on the ischemic heart.

is largely due to vasodilation. Clevidipine is rapidly metabolized by nonspecific esterases in the blood. The terminal half-life is approximately 15 minutes. It is formulated as a lipid emulsion so careful handling is essential. Starting dose is 1 to 2 mg/hr titrated up to 16 mg/hr or less according to patient response. Onset is 2 to 4 minutes and duration is 5 to 15 minutes[95,96] (see Table 13-9).

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

Angiotensin-converting enzyme (ACE) inhibitors are widely prescribed for the treatment of hypertension, angina, diabetic neuropathy, CHF, and in the management of the postmyocardial infarction patient.[97,98] These drugs exert their action by inhibiting the ACE. A brief description of the renin-angiotensin system is necessary for a full understanding of the actions of the ACE inhibitors (Figure 13-5).

Renin, a proteolytic protein, is released from the juxtaglomerular apparatus in the kidney in response to diminished blood pressure. Renin is responsible for the conversion of precursor angiotensinogen, which is released from the liver to the decapeptide angiotensin I. Angiotensin I is then converted to the octapeptide angiotensin II by the ACE. Angiotensin-converting enzyme is primarily located in the endothelial tissue of the lung. Angiotensin II is a potent vasopressor that also stimulates the release of endogenous norepinephrine and aldosterone. The end result is an increase in peripheral vasoconstriction, with an increase in blood pressure and a resultant decrease in cardiac output. The higher aldosterone level results in increased sodium and water reabsorption, with concomitant secretion of potassium.[97] The ACE inhibitors block this action and produce vasodilation. Common ACE inhibitors are listed in Table 13-5. Enalapril is a prodrug, and it undergoes hepatic metabolism to its active form of enalaprilat. Enalaprilat is available for IV administration for use in perioperative hypertension but it is rarely used. All of these agents are renally eliminated, and their elimination half-lives can be expected to be prolonged in renally compromised patients.

Adverse effects with the ACE inhibitors include cough, angioedema, renal failure, hyperkalemia, neutropenia, and proteinuria. The dry cough resulting from the ACE inhibitors occurs in up to 25% of patients and is the most common reason for discontinuation

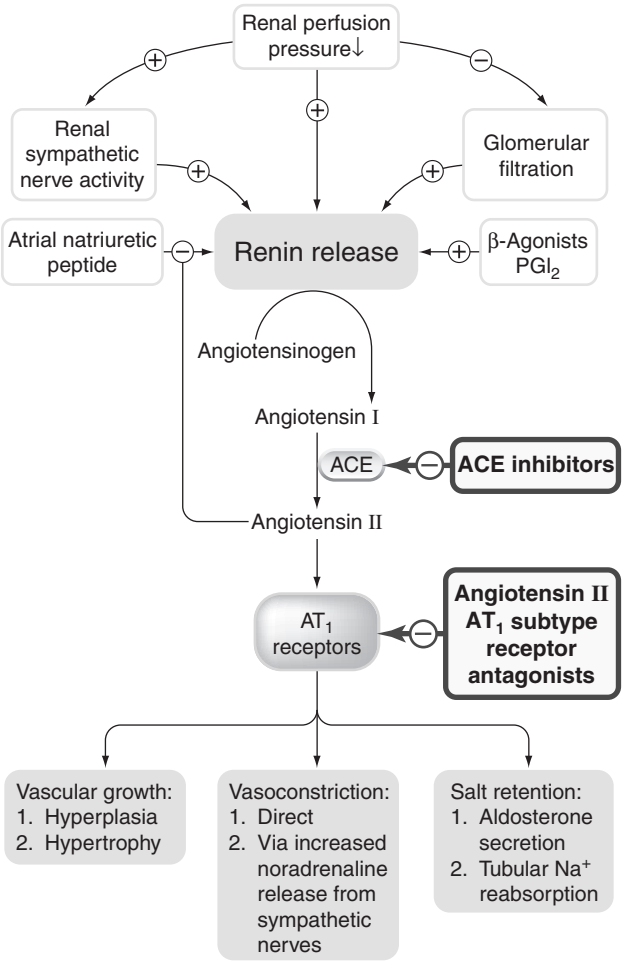

FIGURE **13-5** Control of renin release and formation, and action of angiotensin II. Sites of action of drugs that inhibit the cascade are shown. *ACE*, Angiotensin-converting enzyme; *AT_1*, angiotensin II receptor subtype 1. (From Rang HP, et al. *Rang and Dale's pharmacology.* 7th ed. Edinburgh: Churchill Livingstone; 2012:270.)

of the drug. If an ACE inhibitor cannot be tolerated, an angiotensin receptor blocker is substituted. The reason for the cough has been determined. Angiotensin-converting enzyme is also responsible for the metabolism of bradykinin, which is blocked by these drugs. The resulting buildup of bradykinin is felt to contribute to the cough.[99-101]

There has been a controversy for many years about whether the ACE inhibitors should be withheld the morning of surgery. Most, if not all, cardiac medications are continued preoperatively up to and including the day of surgery.[102] The ACE inhibitors were reported to result in an increase in refractory hypotension during induction of anesthesia if not discontinued prior to surgery. This phenomenon is referred to as vasoplegic syndrome. Vasoplegic syndrome (VS) is defined as unexpected refractory hypotension under general anesthesia with a mean arterial pressure <50 mmHg, a cardiac index >2.5 L/min/m^2, and a low systemic vascular resistance despite adrenergic vasopressor administration. It is most commonly seen with cardiac surgery, but can occur during any anesthetic. The incidence of VS in cardiac surgical patients is 8% to 10%, but may increase to upwards of 50% of patients taking renin-angiotensin system (RAS) antagonists. In cardiac surgical patients with persistent hypotension into the postoperative period, the associated mortality approaches 25%. Some clinicians

suggest, however, that there is a lack of evidence for withholding RAS antagonists preoperatively in order to prevent VS. Clear guidelines have not been established. The proposed mechanism involves selective depression of the three blood pressure support systems: the sympathetic nervous system, renin angiotensin, and vasopressin systems. Sympathetic nervous system depression under anesthesia leaves maintenance of blood pressure dependent on the renin-angiotensin and the vasopressinergic systems. Angiotensin converting enzyme inhibitors and angiotensin receptor blockers inhibit the RAS, leaving only vasopressin to maintain blood pressure. Other proposed mechanisms for developing VS include: cytokine and nitric oxide–mediated smooth muscle relaxation, catecholamine receptor down-regulation, cell hyperpolarization, and endothelial injury. Treatment of VS can be difficult. When conventional therapies such as decreasing the anesthetic agent, volume expansion, phenylephrine, ephedrine, norepinephrine, and epinephrine are not effective, the administration of vasopressin may increase blood pressure. A 0.5-1.0 unit bolus of vasopressin may be given followed by an infusion dose of 0.03 units/min for vasopressin or 1-2 mcg/kg/hr for terlipressin as needed. Methylene blue is suggested as a second-line therapy. A bolus dose of 1-2mg/kg over 10-20 minutes followed by an infusion of 0.25mg/kg/hr for 48-72 hours is recommended with a maximum dose of 7 mg/kg. Methylene blue is believed to interfere with the nitric oxide (NO)-cyclic guanylate monophosphate (cGMP) pathway, inhibiting the vasodilating effect on smooth muscle. Withholding the RAS antagonists the morning of surgery appears to reduce the incidence in noncardiac surgical patients.[103,104] It has recently been suggested that withholding these drugs prior to non-cardiac surgery is not necessary. If hypotension occurs, it is treatable and it simplifies patient instructions if they are told to continue all of their cardiac medications as normal.[105,106] The issue of how to manage patients on the RAS antagonists remains to be clarified.

ANGIOTENSIN II RECEPTOR ANTAGONISTS

Angiotensin receptor blockers (ARBs) are a class of drugs useful for the treatment of hypertension and congestive heart failure. Their pharmacologic actions are similar to the ACE inhibitors, but their mechanism of action is competitive blockade of type 1 angiotensin II (AT_1) receptors[107] (see Table 13-5 and Figure 13-5). They are effective for lowering blood pressure without the cough and angioedema associated with ACE inhibitors. Unlike the ACE inhibitors, they do not prevent the breakdown of bradykinin, and therefore do not produce cough. There are no intravenous preparations currently marketed. Due to cost, the ARBs are usually reserved for patients who cannot tolerate an ACE inhibitor.[108]

CATECHOLAMINE-DEPLETING AGENTS

Catecholamine-depleting agents are rarely encountered in modern anesthesia practice, but the anesthetist should be familiar with their mechanism of action. The classic member of this group is reserpine. Reserpine blocks the uptake of catecholamines into storage vesicles within the presynaptic adrenergic neuron by inhibiting the vesicular monoamine transporter (VMAT). This exposes the catecholamines to metabolism by monoamine oxidase in the axoplasm. This "catecholamine depletion" is responsible for the antihypertensive action of reserpine.[109]

TYROSINE HYDROXYLASE INHIBITORS

Metyrosine (Demser) is a tyrosine hydroxylase inhibitor. Tyrosine hydroxylase is responsible for catalyzing the conversion of tyrosine to dopa and is considered the rate-limiting step in the synthesis of catecholamines. Inhibition of tyrosine hydroxylase results in a decrease in circulating catecholamine levels. It is used as an add-on drug to the α- and β-receptor blockers for the control of the blood pressure in patients with pheochromocytoma.[110]

CATECHOL-*O*-METHYLTRANSFERASE INHIBITORS

Tolcapone (Tasmar) and entacapone (Comtan) are used for the treatment of Parkinson's disease as an adjunct to levodopa or carbidopa therapy. A third drug nebicapone is in clinical trials. They are selective and reversible inhibitors of catechol-*O*-methyltransferase (COMT). They enhance the action of levodopa and produce less fluctuation in drug response. There are concerns that COMT inhibitors may interact with various cardiac drugs by reducing their metabolism. Caution should be taken when administering such drugs as isoproterenol, dobutamine, dopamine, norepinephrine, and epinephrine. Reduced doses should be started initially until the response can be assessed.[111,112]

CARDIAC GLYCOSIDES

Characterized by the digitalis preparations, the cardiac glycosides have been used to treat CHF for two centuries. The most common preparation used is digoxin. The primary inotropic effect of digitalis is achieved by the binding to the α-subunit of the sodium-potassium adenosine triphosphatase (Na/K ATPase) in cardiac cells. The Na/K ATPase is somewhat erroneously referred to as the *sodium/potassium pump*.[32] This results in an increase in the concentration of intracellular calcium during systole, which augments myocardial contractility. Normally the Na/K ATPase exchanges intracellular sodium for extracellular potassium against their concentration gradients. Inhibition of this exchange results in an increase in intracellular sodium that results in a decreased calcium exchange and a higher intracellular calcium. The mechanism of action of digitalis is shown in Figure 13-6. The additional calcium enhances contraction. Digitalis produces an increase in both diastolic filling and ejection fraction.

Electrophysiologically, enhancement of vagal tone, another prominent effect of digitalis, results in slowing of the heart rate and prolongation of AV conduction. Because of its vagal effects, digitalis also is used to control the ventricular response to atrial fibrillation and other atrial tachyarrhythmias. The digitalis-induced enhancement of vagal tone leads to slowing of impulse conduction through the atrioventricular node and prolongation of the effective refractory period of the atrioventricular node. Its use as both an antiarrhythmic and inotrope has decreased significantly in recent years with the introduction of more efficacious and safer drugs.

Digitalis preparations have a narrow therapeutic index, great variability in action among patients, and several serious side effects. Hypokalemia greatly enhances the effects of digoxin, whereas hyperkalemia has the opposite effect.[113] A patient with hypokalemia whose digitalis level is within a therapeutic range may show toxic effects. Digoxin serum levels are also mediated by the P-glycoprotein transporter. All known arrhythmias have been attributed to digitalis toxicity. Other signs and symptoms of digitalis toxicity include nausea, vomiting, diarrhea, headache, fatigue, and colored vision. Under anesthesia the first sign is usually an arrhythmia, frequently premature ventricular contractions (PVCs). Close monitoring of electrolytes should be performed in digoxin-treated patients receiving a preoperative preparation of the bowel. Calcium administration is contraindicated in digoxin-treated patients because it may lead to cardiac arrest. Preoperatively, in select patients, the serum levels of potassium and digitalis can be monitored.[114]

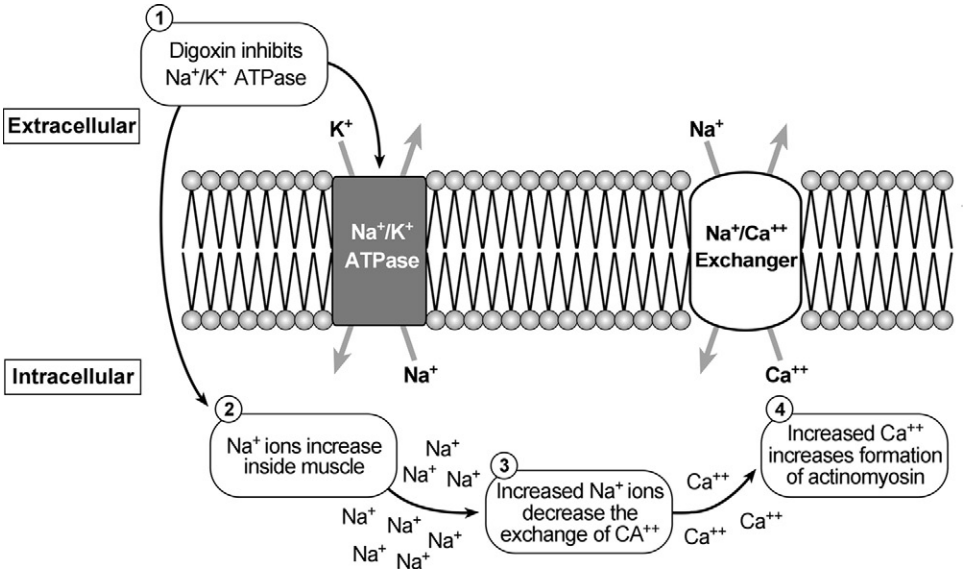

FIGURE **13-6** The mechanism of action of digitalis. *(1)* Sodium potassium ATPase is inhibited resulting in increased intracellular sodium; *(2)* increased intracellular sodium produces a decrease in the exchange of sodium and calcium; *(3)* intracellular calcium increases; and *(4)* muscle contraction is enhanced.

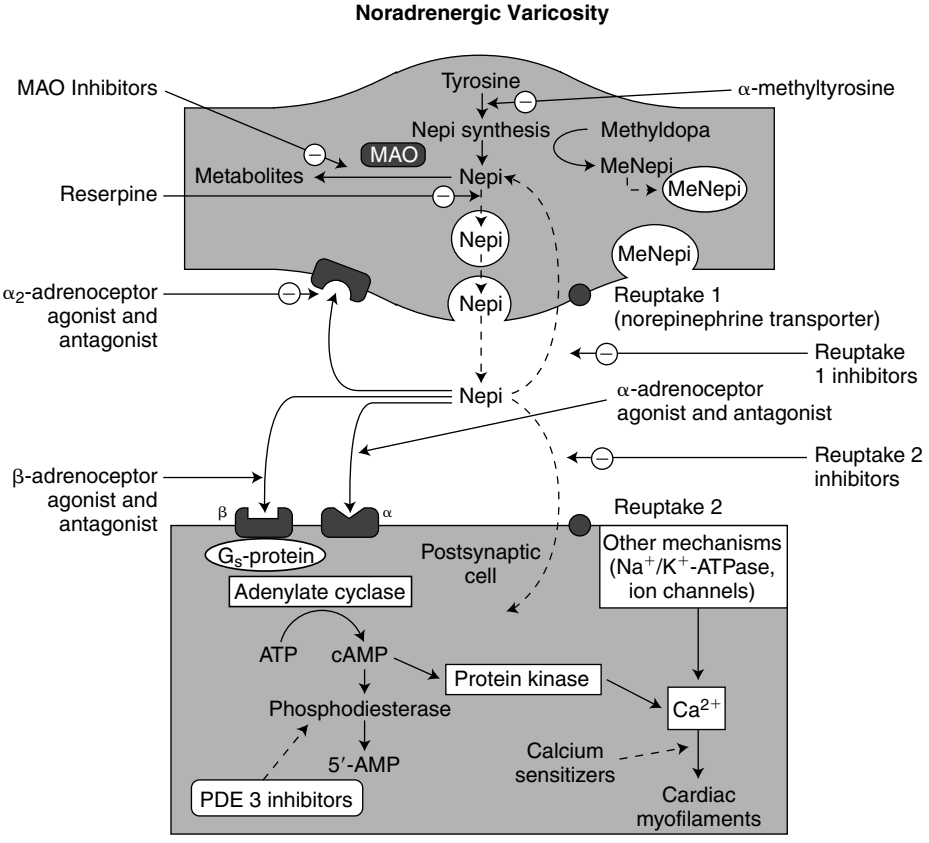

FIGURE **13-7** Common mechanisms for drugs affecting the sympathetic nervous system.

Some common mechanisms for drugs affecting the sympathetic nervous system are shown in Figure 13-7.

MANAGEMENT OF SPECIFIC DISEASES

In past decades, the treatment of cardiovascular diseases under anesthesia was difficult and limited. The lack of specific cardiac drugs and the limited selection of anesthetic agents warranted symptomatic therapy designed to facilitate surgery until the patient was in the postanesthesia care unit. Currently, with the vast array of cardiac drugs, the improved sophistication of anesthetic management, and monitoring that provides extensive hemodynamic information, the anesthesia provider is able to treat patients in a manner that is

BOX **13-2**

Clinical Predictors of Increased Perioperative Cardiovascular Risk

Major Risk Factors

Unstable Coronary Syndromes

- Acute or recent myocardial infarction with evidence of important ischemic risk by clinical symptoms or noninvasive study*
- Unstable or severe angina (Canadian class III or IV)

Decompensated Heart Failure

- New York Heart Association functional class IV; worsening or new onset heart failure

Significant Arrhythmias

- High-grade atrioventricular block
- Mobitz II atrioventricular block
- Third-degree atrioventricular block
- Symptomatic ventricular arrhythmias
- Supraventricular arrhythmias, including atrial fibrillation with uncontrolled ventricular rate greater than 100 at rest
- Symptomatic bradycardia
- Newly recognized ventricular tachycardia

Severe Valvular Disease

- Severe aortic stenosis with mean pressure gradient greater than 40 mmHg; aortic valve area less than 1 cm^2; or exhibiting symptoms
- Symptomatic mitral stenosis; progressive dyspnea on exertion, exertional presyncope, or heart failure

Intermediate Risk Factors

- Mild angina pectoris (Canadian class I or II)
- Previous myocardial infarction identified by history or pathologic Q waves
- Compensated or previous heart failure
- Diabetes mellitus (particularly insulin dependent)
- Renal insufficiency

Minor Risk Factors

- Advanced age
- Abnormal ECG (left ventricular hypertrophy, left bundle-branch block, ST-T abnormalities)
- Rhythm other than sinus (e.g., atrial fibrillation)
- Low functional capacity (e.g., inability to climb one flight of stairs with a bag of groceries)
- History of stroke
- Uncontrolled systemic hypertension

ECG, Electrocardiogram.
*The American College of Cardiology National Database Library defines recent myocardial infarction as having occurred more than 7 days previously, but less than or equal to 1 month (30 days); acute myocardial infarction is defined as having occurred within the last 7 days; may include "stable" angina in patients who are unusually sedentary.

BOX **13-3**

Cardiac Risk* Stratification for Noncardiac Surgical Procedures

High Risk (Reported Cardiac Risk Often Greater Than 5%)

- Aortic and other major vascular surgery
- Peripheral vascular surgery

Intermediate Risk (Reported Cardiac Risk Generally 1% to 5%)

- Carotid endarterectomy
- Head and neck surgery
- Intraperitoneal and intrathoracic surgery
- Orthopedic surgery
- Prostate surgery

Low Risk (Reported Cardiac Risk Generally Less Than 1%)†

- Endoscopic procedures
- Superficial procedures
- Cataract surgery
- Breast surgery
- Ambulatory surgery

From Fleisher LA, et al. 2009 ACCF/AHA focused update on perioperative beta blockade incorporated into the ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2009:54:e13-118.
*Combined incidence of cardiac death and nonfatal myocardial infarction.
†These patients do not generally require further preoperative cardiac testing.

appropriate for management of their diseases. Therapies can be chosen that fit into a patient's plan of care. The anesthetic process can safely and effectively continue the care management of the individual patient. To assist in predicting possible poor outcomes, ACCF/AHA and the European Society of Cardiology have classified the cardiovascular and surgical risks[115,116] (Boxes 13-2 and 13-3).

The drugs listed for therapy of the cardiovascular disorders that follow are presented not so much for their specific intraoperative use but as a means of continuing the patient's current drug profile. Patient treatment mirrors general nonoperative indications and considerations. Anesthetic techniques take into account the combined effects of cardiac drugs and anesthetic agents when administered together.

Congestive Heart Failure

In the United States, 4 to 5 million people have chronic CHF, with 600,000 to 700,000 new cases occurring each year. The incidence will undoubtedly increase as the population ages. Heart failure results in almost 1 million hospitalizations each year. It is the most common hospital discharge diagnosis in patients older than age 65 years. More than 280,000 patients die as a direct or an indirect consequence of heart failure each year, a sixfold increase during the past 40 years.[117] It is the only major cardiovascular disorder that is increasing in prevalence, with an estimated annual cost of $40 billion. Once cardiac failure has been diagnosed, 5-year survival rates are typically 25% to 40%, similar to the survival rates for cancer. Fortunately, recent data suggests that hospitalization and mortality rates are declining, which may indicate that aggressive interventions and management are yielding positive results.[118] The classification of heart failure is given in Box 13-4.

Heart failure is a major independent predictor of adverse perioperative outcome in noncardiac surgery.[119] Mortality estimates

BOX **13-4**

New York Heart Association Functional Classification for Heart Failure

Class I (Mild)
- No limitation of physical activity.
- Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea.

Class II (Mild)
- Slight limitation of physical activity.
- Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.

Class III (Moderate)
- Marked limitation of physical activity.
- Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.

Class IV (Severe)
- Unable to carry out any physical activity without discomfort.
- Symptoms of cardiac insufficiency at rest.
- If any physical activity is undertaken, discomfort is increased.

Adapted from Greenberg B, Kahn AM. Clinical assessment of heart failure. In: Bonow RO, et al. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*. 9th ed. Philadelphia: Saunders; 2012:507.

BOX **13-5**

Causes of Intraoperative Rhythm Disturbances

Structural Heart Disease
- Coronary artery disease
- Myocardial infarction
- Valvular and congenital heart disease
- Cardiomyopathy
- Sick sinus or long Q-T interval syndrome
- Wolff-Parkinson-White syndrome
- Heart disease secondary to systemic disease (e.g., uremia, diabetes)
- Sinus bradycardia
- Atrioventricular node heart block

Transient Imbalance
- Stress: electrolyte or metabolic imbalance
- Laryngoscopy, hypoxia, hypercarbia
- Device malfunction, microshock
- Diagnostic or therapeutic intervention (pacemakers, cardioverter-defibrillators)
- Surgical stimulation
- Central vascular catheters

Adapted from Atlee JL. *Complications in Anesthesia*. 2nd ed. Philadelphia: Saunders; 2007:319-335.

range from 3% to as high as 30% in patients undergoing abdominal surgery.[120] In patients with CHF and renal failure undergoing emergency surgery, mortality rates as high as 76% have been reported.

Congestive heart failure is a syndrome resulting from a cardiac malfunction that impairs the ability of the heart to eject blood and meet the circulatory demands of the body. It is defined as a complex clinical syndrome that can result from any structural or functional cardiac disorder that interferes with the ability of the ventricle to fill with or eject blood. Alterations associated with CHF include impairment-induced complex changes in the structure of the ventricle called *ventricular remodeling*, along with hormonal and physiologic alterations.[121] The chamber dilates, hypertrophies, and becomes more spherical. Substantial evidence suggests that activation of the body's endogenous neurohormonal systems, such as the renin-angiotensin system, plays an important role in cardiac remodeling and the progression of heart failure. Treatment is complex and tailored to the patient's age, current disease state, and associated concurrent disorders. It involves a polypharmaceutical approach that is referred to as triple therapy. This includes ACE inhibitors, β-blockers, and diuretics. Statins are usually added as well. Other agents useful in select patients may include digoxin, ARBs, nitrates, nesiritide, aldosterone, and hydralazine. Mechanical support devices may be added as well.[117]

In the perioperative period, anesthesia providers are faced with managing therapy for all degrees of severity of CHF. The goal can range from prevention of symptom progression to surviving an emergency procedure in life-threatening cases. When appropriate, regional nerve block techniques should be considered, but patients may have difficulty lying flat during surgery. No single general anesthetic technique has proven superior. Invasive arterial blood pressure monitoring and transesophageal echocardiography (TEE) are useful for guiding intraoperative decision making and fluid management. TEE is especially useful in diagnosing whether hypotensive episodes are the result of inadequate circulating blood volume, worsening ventricular function, or arterial vasoconstriction.

Drugs such as the inotropes, phosphodiesterase inhibitors, diuretics, and vasodilators are commonly used intraoperatively in acute episodes[114,120,122] (see Tables 13-3 and 13-9).

Arrhythmias

The incidence of serious arrhythmias requiring intervention during general anesthesia is relatively low. A large multicenter study found that not counting simple tachycardia, bradycardia, or clinically minor rhythm disturbances, the frequency of serious arrhythmias was 1.6% in a series of more than 17,000 patients who underwent general anesthesia.[123] It is surprising that the incidence is not higher, because several contradictory factors are involved; most drugs given during anesthesia are cardiac depressants; therefore they tend to be antiarrhythmic. However, patients with multiple drug profiles in combination with the anesthetics may experience drug interactions that lead to rhythm disturbances. Add to these pharmacologic factors the stresses of surgery and anesthesia, and a multitude of effects on cardiac rhythms may be expected.

In recent years, new pharmacologic and nonpharmacologic management approaches for cardiac arrhythmias have emerged. New drugs, implantable cardiac devices (ICDs), and ablation therapy are available for managing these disorders. The use of antiarrhythmic drugs in the United States is declining because of the increasing use of ablation therapy and implantable devices.[61] Some causes of intraoperative rhythm disturbances are listed in Box 13-5.

The goal of drug therapy for arrhythmias during anesthesia should be to treat immediate hemodynamic problems and prevent progression of serious arrhythmias. Treatment is similar to that in the nonoperative setting, with the caveat that most therapies should be carefully titrated to avoid unexpected proarrhythmic or excessive hypotensive outcomes. Some cautionary statements should precede any discussion on the use of antiarrhythmic agents during anesthesia:

- The cause of the arrhythmia should be explored before any treatment is instituted. A cardiology consult should be obtained when possible.

TABLE 13-10 Classification of Antiarrhythmic Drugs

Class	Electrophysiologic Effect	Drug
I	Depression of phase 0 depolarization (block sodium channels)	
IA	Moderate depression and prolonged repolarization	Quinidine, procainamide, disopyramide
IB	Weak depression and shortened repolarization	Lidocaine, mexiletine, phenytoin, tocainide
IC	Strong depression with little effect on repolarization	Flecainide, propafenone, moricizine
II	β-Adrenergic blocking effects	Esmolol, propranolol, metoprolol, timolol, pindolol, atenolol, acebutolol, nadolol, carvedilol
III	Prolongs repolarization (blocks potassium channels)	Amiodarone, bretylium, sotalol, ibutilide, dofetilide
IV	Calcium channel–blocking effects	Verapamil, diltiazem
Other		Adenosine, adenosine triphosphate, digoxin, atropine

- Adequacy of ventilation, depth of anesthesia, acid-base balance, and fluid and electrolyte balance must be verified before appropriate therapy can be formulated.
- Multiple-drug administration, which constitutes modern anesthesia practice, may result in unexpected drug interactions. Analysis of complex arrhythmias with the commonly used three- or five-lead electrocardiograph system during a surgical procedure is less than ideal for proper diagnosis and treatment. Nonetheless, rhythm disturbances that compromise hemodynamic stability or may progress to more severe dysfunction must be addressed.

Classification of antiarrhythmic drugs is given in Table 13-10. The drugs of choice for the common arrhythmias are given in Table 13-11.

Hypertension

Hypertension is a major health problem in the United States; an estimated 70 million Americans have hypertension or should be monitored for elevated blood pressure.[46] The classification of hypertension is given in Table 13-12. The optimal blood pressure is believed to be less than 120 systolic and less than 90 diastolic, although many clinicians consider less than 130 systolic to be adequate. Patients are categorized as having either prehypertension, or either stage 1 or 2 hypertension.[124] A large number of drugs are available for the treatment of high blood pressure. Those that are considered as initial therapy include diuretics, calcium channel blockers, ACE inhibitors, and angiotensin receptor antagonists (ARBs).[125,126] β-receptor blockers are frequently included as initial therapy but may not be preferred in uncomplicated hypertensive patients.[127,128] Most patients with hypertension are taking two or more drugs to control their blood pressure. The most important aspect of treatment is to reduce blood pressure to goal levels. Which drug combinations appear less important. Unfortunately, despite the remarkable progress in therapy, blood pressure remains inadequately controlled in more than half of patients with hypertension in the United States.[129,130]

Drugs available for the treatment of hypertension are listed in Table 13-5. Antihypertensive drugs that are safe for use during pregnancy are listed in Table 13-13.

Manipulation of the patient's blood pressure is an ongoing task during anesthesia, and many drugs are available to increase and decrease blood pressure when indicated. Improved monitoring and sophistication of anesthetic techniques has made control of blood pressure almost routine.

The problem of hypertension has varying significance in preoperative, intraoperative, and postoperative situations. Mild hypertension probably represents only a minor risk for anesthesia and surgery.[131] Patients with more severe hypertensive episodes are at greater risk and will benefit from acute therapy combined with postoperative long-term follow-up.[132] Hypertensive episodes during the perioperative period occur most often during emergence from anesthesia and may be associated with pain, airway stimulation, hypoxia-hypercarbia, hypothermia and shivering, bladder distention, withdrawal from preoperative medications, and intraoperative use of vasopressors. Drugs useful for the treatment of perioperative hypertension are listed in Table 13-9.

Ischemic Heart Disease

Ischemic heart disease (IHD) is the most common cardiac disease encountered in the operating room. Approximately 18 million people in the United States have either angina or a past myocardial infarction.[133,134]

The goal of any anesthetic in a cardiac-compromised patient is hemodynamic optimization tailored to each patient's unique disease and surgical profile. No single anesthetic technique or agent has been shown to be superior.[135] Finding a balance that avoids increases in myocardial work while maintaining proper perfusion is essential.[136,137]

The causes of coronary artery disease and management of patients with the disorder are discussed in detail in Chapters 23 and 24. The classification of angina pectoris is given in Table 13-14.

Usual pharmacotherapy includes nitrates, β-blockers, calcium channel blockers, aspirin, and lipid lowering or "statin" drugs (Table 13-15). Nitrates are given for symptomatic relief of acute anginal episodes. Positive benefits have been noted for perioperative statin use.[138] Preoperative statin use was associated with reduced cardiac mortality after primary, elective coronary artery bypass grafting. Postoperative statin discontinuation was associated with increased in-hospital mortality.[139] The β-blockers, ACE inhibitors, and calcium channel blockers are listed in Table 13-5. The HMG-CoA (3-hydroxy-3-methylglutaryl–coenzyme A) reductase inhibitors ("statins") are listed in Table 13-16.

PREOPERATIVE ADMINISTRATION OF CARDIAC DRUGS

Continuation of the patient's cardiac medications throughout the perioperative period is now considered routine practice. It is better to have the patient's disease state under proper control than to discontinue any medications before surgery and risk having the patient in unstable condition. Withdrawal after abrupt discontinuation of β-blockers and clonidine is especially severe. This also includes aspirin, which adds little bleeding risk to surgical procedures.

Aspirin is recommended as a lifelong therapy that should never be interrupted for patients with cardiovascular disease. The abrupt withdrawal of aspirin can cause a platelet rebound phenomenon and prothrombotic state leading to major adverse cardiovascular event.[140] Clopidogrel therapy is mandatory for 6 weeks after placement of

TABLE 13-11 Drugs of Choice for Common Arrhythmias

Arrhythmia	Drug of Choice	Alternatives	Remarks
Atrial fibrillation or flutter	*Rate control:* IV verapamil, diltiazem, β-blocker, or digoxin	IV procainamide or ibutilide; dofetilide; single large oral dose of propafenone or flecainide	Amiodarone also may slow ventricular response, and conversion to normal rhythm can occur, but generally after delay of several hours
Acute management	*Conversion:* DC cardioversion		Ibutilide infusion may increase effectiveness of DC cardioversion Incidence of atrial fibrillation following cardiac surgery can be reduced by preoperative sotalol, amiodarone, or a β-blocker
Chronic treatment	*Rate control:* Verapamil, diltiazem, a β-blocker, or digoxin *Maintenance of sinus rhythm:* Amiodarone, sotalol, flecainide, propafenone, or dofetilide	Quinidine, procainamide, disopyramide	Radiofrequency ablation may be effective in selected patients
Supraventricular tachycardias *Acute management*	IV adenosine, verapamil, or diltiazem	IV esmolol, another β-blocker, or digoxin for termination	Direct current cardioversion or atrial pacing may be effective for some patients; only rarely required
Long-term suppression	β-blockers, verapamil, diltiazem, flecainide, propafenone, amiodarone, sotalol, or digoxin	Quinidine, procainamide, or disopyramide	Radiofrequency ablation can cure many patients
Premature ventricular complexes (PVCs) or nonsustained ventricular tachycardia	*Asymptomatic patients:* Without structural heart disease: no drug therapy indicated *Symptomatic patients:* β-blocker	Lidocaine IV for acute suppression under anesthesia	No evidence that prolonged suppression with drugs improves survival; for post-MI patients, treatment with a β-blocker has decreased mortality, treatment with flecainide or moricizine has increased it
Sustained ventricular tachycardia	Amiodarone	Procainamide, lidocaine	Long-term therapy ICD, amiodarone
Ventricular fibrillation	*Prevention of recurrence:* Amiodarone	Procainamide, lidocaine	Long-term therapy ICD, amiodarone
Cardiac glycoside-induced ventricular tachyarrhythmias	Digoxin-immune Fab (digoxin antibody fragments—Digibind, DigiFab)		Self-limited if digoxin stopped; avoid direct current cardioversion, except for ventricular fibrillation or sustained ventricular tachycardia. A β-blocker or procainamide can make heart block worse
Drug-induced torsades de pointes	IV magnesium sulfate	Cardiac pacing, isoproterenol	Causative agents should be discontinued; magnesium sulfate may be effective, even in absence of hypomagnesemia; potassium should be used to raise serum K to 4.5 to 5.0 mEq/L

Adapted from Medical Letter Treatment Guidelines: Drugs for cardiac arrhythmias. *Med Lett.* 2007;5(58):51-58; Stone ME, et al. Perioperative management of patients with cardiac implantable electronic devices, *Br J Anaesth.* 2011;107(suppl 1):i16-26.
ICD, Implantable cardioverter device/defibrillator; *IV*, intravenous; *MI*, myocardial infarction.

bare-metal stents, 3 to 6 months after myocardial infarction, and at least 12 months after placement of drug-eluting stents. Elective surgery should be postponed for at least 6 weeks and optimally 3 months in a patient who has had a bare-metal stent placement and at least 1 year for a drug-eluting stent. Because of the hypercoagulable state induced by surgery, early withdrawal of antiplatelet therapy for secondary prevention of cardiovascular disease increases the risk of postoperative myocardial infarction and death. The risk of a cardiovascular event when stopping antiplatelet agents preoperatively is higher than the risk of surgical bleeding when continuing these drugs.

In surgical patients, antiplatelet therapy should be maintained in all situations in which the risk of surgical bleeding is low, which is usually the case in the ambulatory setting. The exception is surgery in a closed space such as intracranial or in the posterior eye chamber, middle ear, intramedullary spine, and possibly transurethral prostatectomy or surgeries associated with massive bleeding and difficult hemostasis.[140-142] A complete discussion of the anesthesia management of patients on antiplatelet drugs can be found in Chapter 34.

SUMMARY

Both advances in diagnostic and screening tests for heart disease and improvements in cardiac disease management continue to make impressive strides. Angioplasty is more effective and widely available, and electrophysiologic treatment of rhythm disorders is now considered routine. The number and diversity of cardiac medications we encounter in the perioperative period continues to grow in number and complexity. These advances require that anesthesia clinicians stay abreast of ever more complex clinical techniques but at the same time improve anesthesia quality and safety for our patients.

TABLE 13-12 Classification and Management of Blood Pressure for Adults

Blood Pressure Classification	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)
Normal	<120	and <80
Prehypertension	120-139	or 80-89
Stage 1 hypertension	140-159	or 90-99
Stage 2 hypertension	≥160	or ≥100

From Joint National Committee on Prevention, Detection and Treatment of High Blood Pressure: *Seventh Report of the National Committee on Detection, Evaluation and Treatment of High Blood Pressure* (JNC-7) (NIH Publication No. 03-5233). Washington, DC: U.S. Department of Health and Human Services; National Institute of Health; National Heart, Lung and Blood Institute; National High Blood Pressure Education Program, May 2003.

TABLE 13-13 Antihypertensive Drugs Used in Pregnancy*

Suggested Drug	Comments
Central α-agonists	Methyldopa is the drug of choice
β-Blockers	Atenolol, metoprolol, and labetalol
Diuretics	Diuretics recommended for chronic hypertension if prescribed before gestation or if patients appear to be salt sensitive; diuretics not recommended in patients with preeclampsia
Direct vasodilators	Hydralazine is the parenteral drug of choice, based on its long history of safety and efficacy

From Joint National Committee on Prevention, Detection and Treatment of High Blood Pressure: *Seventh Report of the National Committee on Detection, Evaluation and Treatment of High Blood Pressure* (JNC-7) (NIH Publication No. 03-5233). Washington, DC: U.S. Department of Health and Human Services; National Institute of Health; National Heart, Lung and Blood Institute; National High Blood Pressure Education Program, May 2003.
*Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers should not be used. Fetal abnormalities and death have been reported.

TABLE 13-14 Classification of Angina Pectoris

Class	New York Heart Association Functional Classification	Canadian Cardiovascular Society Functional Classification	Specific Activity Scale
I	Patients with cardiac disease but without resulting limitations of physical activity Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain	Ordinary physical activity, such as walking and climbing stairs, does not cause angina Angina with strenuous or rapid or prolonged exertion at work or recreation	Patients can perform to completion any activity requiring ≥7 or more metabolic equivalents, e.g., can carry 24 lb up eight steps; carry objects that weigh 80 lb; do outdoor work (shovel snow, spade soil); do recreational activities (skiing, basketball, squash, handball, jog or walk 5 mph)
II	Patients with cardiac disease resulting in slight limitation of physical activity They are comfortable at rest Ordinary physical activity results in fatigue, palpitations, dyspnea, or anginal pain	Slight limitation of ordinary activity Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, in cold, in wind, or when under emotional stress, or only during the few hours after awakening Walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions	Patient can perform to completion any activity requiring ≥5 or more metabolic equivalents but cannot and does not perform to completion activities requiring ≥7 or more metabolic equivalents, e.g., have sexual intercourse without stopping, garden, rake, weed, roller skate, dance foxtrot, walk at 4 mph on level ground
III	Patients with cardiac disease resulting in marked limitation of physical activity They are comfortable at rest Less than ordinary physical activity causes fatigue, palpitations, dyspnea, or anginal pain	Marked limitation of ordinary physical activity Walking one or two blocks on the level and climbing more than one flight in normal conditions	Patient can perform to completion any activity requiring ≥2 or more metabolic equivalents but cannot and does not perform to completion any activities requiring ≥5 or more metabolic equivalents, e.g., shower without stopping, strip and make bed, clean windows, walk 2.5 mph, bowl, play golf, dress without stopping
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest If any physical activity is undertaken, discomfort is increased	Inability to carry on any physical activity without discomfort—anginal syndrome may be present at rest	Patient cannot or does not perform to completion activities requiring ≥2 or more metabolic equivalents; cannot carry out activities listed above (Specific Activity Scale, class III)

From Goldman L, et al. Comparative reproducibility and validity of systems for assessing cardiovascular functional class: advantages of a new specific activity scale. *Circulation*. 1981;64:1227-1234.

TABLE 13-15 Drug Therapy for Angina

Drug	Comments
Nitrates	First-line therapy for acute attacks; mechanism is a decrease in oxygen demand via a reduction in preload and some beneficial redistribution in blood flow
β-Blockers	Cornerstone therapy for chronic prophylaxis; decrease cardiac demand via lower heart rate, blood pressure, and contractility
Calcium channel blockers	Especially effective in variant angina and in patients intolerant to β-blockers; reduce preload, afterload, and increase coronary flow
Antiplatelet drugs	Aspirin inhibits platelet and endothelial cyclooxygenase; reduces coronary thrombosis; clopidogrel (Plavix) may be substituted in patients with contraindications to aspirin
Statins	HMG-CoA reductase inhibitors, commonly referred to as *statins*; reduce C-reactive protein, thrombogenicity, and adverse cardiac events
Angiotensin-converting enzyme inhibitors	May be useful in patients with coronary artery disease and diabetes or other vascular diseases
Ranolazine	Ranolazine (Ranexa) is usually given in conjunction with the standard antianginal agents; blocks the late inward sodium current reducing intracellular calcium overload

HMG-CoA, 3-hydroxy-3-methylglutaryl–coenzyme A.

TABLE 13-16 HMG-CoA Reductase Inhibitors ("Statins")

Drug	Initial Dosage	Maximum Dosage	Comments
Atorvastatin (Lipitor)	10 mg once	80 mg once	Statins are generally tolerated better than other lipid-lowering drugs. Mild transient gastrointestinal disturbances, muscle pain, rash, and headache have occurred. Some patients have reported sleep disturbances. An increase in liver enzymes and creatine phosphokinase may occur with significant myalgia and muscle weakness.
Fluvastatin (Lescol)	20 mg once	40 mg bid	
Lovastatin (Mevacor)	20 mg once	80 mg once	
Pravastatin (Pravachol)	40 mg once	80 mg once	
Rosuvastatin (Crestor)	10 mg once	40 mg once	
Simvastatin (Zocor)	20 mg once	80 mg once	

Adapted from Medical Letter Treatment Guidelines: Drugs for lipids. *Med Lett*. 2011;9(103):13-20; *Mosby's Drug Consult*. St Louis: Mosby; 2007.
HMG-CoA, 3-hydroxy-3-methylglutaryl–coenzyme A.

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14 CHAPTER Chemistry and Physics of Anesthesia

◆ *Mark D. Welliver*

The dynamics of much of anesthesia practice lie within the framework of chemical and physical science. Chemistry, the study of matter composition, properties, and behavior at the atomic and molecular level, and physics, the study of motion, matter, and energy interaction, are two foundations for nurse anesthetist practice. Chemistry and physics explain such actions as pressure, flow, diffusion, expansion, contraction, and other processes that are intimately intertwined with the delivery of anesthetics. From the ancient philosophical beginnings of atomic theory and the proverbial falling apple of Newtonian physics (Sir Isaac Newton, 1642-1727) to current advances in quantum mechanics, discoveries have led to advances and application for anesthesiology. To understand these laws and theories is to understand the how and why of our practice, give us rationale for clinical interventions, and allow us the ability to manipulate dynamic processes to our patients' favor.

The dynamics of anesthesia herein are explained primarily by the atomic and kinetic molecular theories, Newtonian physics, thermodynamics, and the quantum mechanics of electromagnetic radiation. This chapter provides a short, concise resource that focuses on the chemistry and physics of anesthesia.

GENERAL CHEMISTRY: MATTER AND ENERGY

The universe is composed of two main constituents, matter and energy. Energy is explored more thoroughly in the section on physics. Matter is the tangible composition of the universe that may be solid, liquid, gas, or plasma. Solids are defined as material that resists changes in shape and volume. Liquids are fluids that exhibit minimal to no compressibility and may change volume with changes in pressure and temperature. Gases are also fluids but are compressible and easily change volume with changes in pressure and temperature. Plasma is a mixture of ionized gas and free-floating electrons. It has been postulated that more than 99% of the universe's matter is plasma.

International System of Measurement

When studying and interacting with matter and energy, it is necessary to have a system of standardized units of measurement. The Systéme International (SI) is a set of standardized units of measure based on the metric scale. The SI uses 7 base quantities for measurement (Table 14-1) and 12 standard prefixes for naming units of measure to denote quantity (Table 14-2). Other units or combinations of units may be used in addition to those shown. Additionally, temperature and pressure affect the behavior of matter, and a standardized reference has been established for both. The standard temperature and pressure (STP) is 100.00 kilopascals at 273 kelvin.

Elements

Elements are matter that possess similar atoms containing the same protons. The periodic chart of the elements lists these elements according to their chemical characteristics. Vertical columns known as *groups* list elements with similar properties. Horizontal rows are known as *periods*. Atomic size progresses up across rows from left to right. Atomic weights are listed with each element on the chart (Figure 14-1).

TABLE 14-1 Systéme International Seven Base Quantities for Measurement

SI Unit	Symbol	Quantity
meter	m	Length
kilogram	kg	Mass
second	s	Time
ampere	A	Electric current
kelvin	K	Temperature
candela	cd	Luminous intensity
mole	mol	Amount substance

TABLE 14-2 Systéme International Prefixes

Name	Symbol	Factor
tera-	T	10^{12}
giga-	G	10^{9}
mega-	M	10^{6}
kilo-	k	10^{3}
hecto-	h	10^{2}
deca-	da	10^{1}
deci-	d	10^{-1}
centi-	c	10^{-2}
milli-	m	10^{-3}
micro-	μ	10^{-6}
nano-	n	10^{-9}
pico-	p	10^{-12}

ATOMIC STRUCTURE

Atomic theory has its origins in the philosophical musings of the ancient Greek philosopher Democritus, who described indivisible building blocks of matter referred to as "atomos."[1] The orbital theory of atomic structure was later put forth by Ernesto Rutherford (1871-1937) and improved upon by Neils Bohr (1885-1962), who described electron orbits in terms of energy levels and ability to emit quantized energy by stimulated emission. The atomic theory describes atoms as having a central core, the *nucleus*, with orbiting particles called *electrons* (Figure 14-2). Electrons are negatively charged. The nucleus contains protons and neutrons. *Protons* have

1 H 1.008																	2 He 4.002
3 Li 6.941	4 Be 9.012											5 B 10.811	6 C 12.011	7 N 14.007	8 O 15.999	9 F 18.998	10 Ne 20.180
11 Na 22.990	12 Mg 24.305											13 Al 26.982	14 Si 28.086	15 P 30.974	16 S 32.066	17 Cl 35.452	18 Ar 39.948
19 K 39.098	20 Ca 40.078	21 Sc 44.956	22 Ti 47.867	23 V 50.942	24 Cr 51.996	25 Mn 54.931	26 Fe 55.845	27 Co 58.933	28 Ni 58.963	29 Cu 63.546	30 Zn 65.39	31 Ga 69.723	32 Ge 72.61	33 As 74.922	34 Se 78.96	35 Br 79.904	36 Kr 83.80
37 Rb 85.468	38 Sr 87.62	39 Y 88.906	40 Zr 91.224	41 Nb 92.906	42 Mo 95.94	43 Tc (98)	44 Ru 101.07	45 Rh 102.906	46 Pd 106.42	47 Ag 107.868	48 Cd 112.411	49 In 114.818	50 Sn 118.710	51 Sb 121.760	52 Te 127.60	53 I 126.904	54 Xe 131.29
55 Cs 132.905	56 Ba 137.327	57 La 138.905	72 Hf 178.49	73 Ta 180.948	74 W 183.84	75 Re 186.207	76 Os 190.23	77 Ir 192.217	78 Pt 195.08	79 Au 196.967	80 Hg 200.59	81 Ti 204.383	82 Pb 207.2	83 Bi 208.980	84 Po (209)	85 At (210)	86 Rn (222)
87 Fr (223)	88 Ra 226.025	89 Ac 227.028	104 Unq (261)	105 Unp (262)	106 Unh (263)	107 Uns (262)	108 Uno (265)	109 Une (266)	110 Uun (269)								

58 Ce 140.115	59 Pr 140.907	60 Nd 144.24	61 Pm (145)	62 Sm 150.36	63 Eu 151.965	64 Gd 157.25	65 Tb 158.925	66 Dy 162.50	67 Ho 164.930	68 Er 167.26	69 Tm 168.939	70 Yb 173.04	71 Lu 174.967
90 Th 232.038	91 Pa 231.036	92 U 238.029	93 Np 237.048	94 Pu (244)	95 Am (243)	96 Cm (247)	97 Bk (247)	98 Cf (251)	99 Es (252)	100 Fm (257)	101 Md (258)	102 No (259)	103 Lr (260)

FIGURE **14-1** The Periodic Table. (From Patton KT, Thibodeau GA. *Anatomy & Physiology*. 8th ed. St Louis: Mosby; 2013.)

a positive charge and are larger than electrons. *Neutrons* lack a charge and are similar in size to protons. The number of protons in an atom constitutes its *atomic number*. Electrons, much smaller than protons and neutrons, orbit around the nucleus and are negatively charged.

Electron Configuration

Atoms have electrons that orbit in shells around the nucleus. Each shell can contain only a set number of electrons. These shells have been designated K, L, M, N, O, P, Q. The corresponding maximal number of electrons that may occupy each shell is 2, 8, 18, 32, 32, 18, and 8. Electrons must fill lower shells before occupying higher shells. Quantum physics has refined the electron shell model by designating the K, L, M, N, O, P, Q shells with n-values 1, 2, 3, 4, 5, 6, and 7, which correspond with increasing energy levels. Electron shells are further divided into subshells with the designations s, p, d, f, and g. Subshells may hold only the following number of electrons: s(2), p(6), d(10), f(14), and g(18). Subshells are further subdivided into orbitals. Orbitals may only contain two electrons that spin in opposite directions. An s subshell has 1 orbital, a p subshell has 3 orbitals, a d subshell has 5 orbitals, and so forth. Electrons occupy lower energy level orbitals but may temporarily jump to higher level orbitals when they absorb energy. Electrons that jump to higher levels will emit their excess energy and return to their lower energy state. (See discussion on lasers later in this chapter.)

Angular Momentum/Spin

Nuclei and electrons have an angular momentum also known as *spin*. Atomic particles possess an intrinsic axis upon which they rotate (spin). Spin is analogous to the axis on which the earth rotates. The spin of an electron or proton is not directly measurable, but the uneven distribution of charge it produces is measurable. A magnetic moment is created and is essentially a minute electric current loop. (See discussion on magnetic resonance imaging later in this chapter.)

Ions

Ions are atoms that have gained or lost electrons from their natural composition. An atom that has gained an electron(s) is called an *anion*. Conversely, an atom that has lost an electron(s) is called a *cation*. Ions are important in chemical bonding and aqueous solubility. Mass number/atomic mass number is the amount of protons and neutrons in an atom. Isotopes of the same element have the same number of protons but different numbers of neutrons. Isotopes of the same element have differing mass numbers.

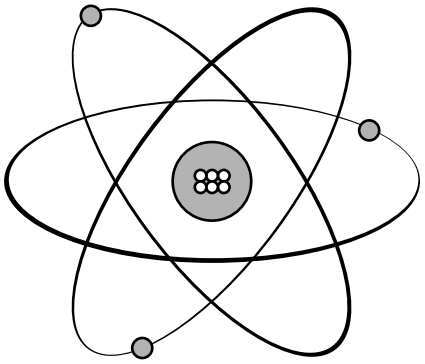

FIGURE **14-2** Atomic structure showing nucleus containing protons and neutrons with orbiting electrons.

MOLECULAR BOND TYPES

Molecules are composed of two or more bonded atoms. Electrons in the outermost shell are called *valence electrons* and are involved in molecular bonding. Molecular bonding may occur by direct sharing of electrons or by thermodynamic interaction due to distribution of electron charge. Atoms with unpaired valence electrons are reactive and tend to form bonds that will fill their outer shell. Covalent and electrostatic are two general types of bonds. Atoms may bond to atoms of the same element (e.g., oxygen) or to different element atoms (e.g., water). Compounds are bonded atoms of differing elements.

Covalent Bonds

The physical sharing of electrons between atoms constitutes a *covalent bond*. The sharing of one pair of electrons is called a *single bond*, sharing two pairs of electrons is a *double bond*, and sharing three pairs of electrons is a *triple bond*. Often covalent bonds are stronger than electrostatic bonds. Covalent bonding may be between same or different atoms that share similar electronegativity.

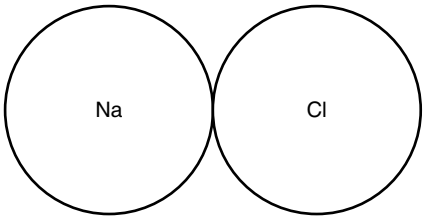

FIGURE **14-3** Ion-to-ion bond representation between sodium and chloride ions.

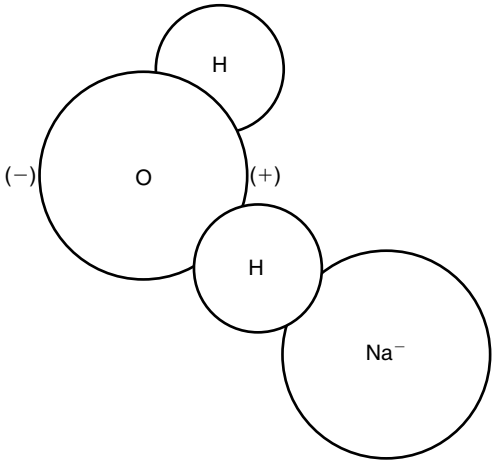

FIGURE **14-4** Ion-to-dipole bond representation between a water molecule and sodium ion.

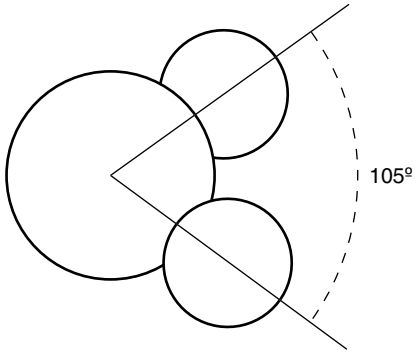

FIGURE **14-5** Hydrogen atoms' bond angle in a water molecule.

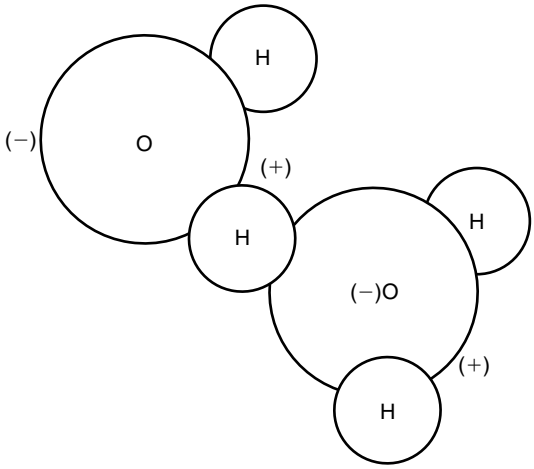

FIGURE **14-6** Dipole-to-dipole bond representation between two water molecules.

Electrostatic Bonds

Electrostatic bonds are made by attraction of electrons between atoms. Electrostatic bonding may be ion-to-ion interaction, ion-to-dipole interaction, or dipole-to-dipole interaction and follow the general rule of "opposites attract," with negative charges attracting positive charges.

Ion-Ion Bonding

Ion-to-ion bonds are the strongest of the electrostatic bonds. These bonds are not directional and occur anywhere along the outer electron shell of an atom. Molecules with ionic bonds have high melting and boiling points. Sodium chloride (table salt) is an example of ion-to-ion bonding (Figure 14-3).

Ion-Dipole Bonding

Ion-to-dipole bonds are weaker than ion-ion bonds, with only partial charges involved. Some molecules have structural arrangements that produce an uneven distribution of electrons. This uneven distribution of charges creates a dipole in which there is a more positive or more negative side to the molecule, although the molecule does not have a formal charge. An example of a molecule with an uneven charge distribution is water. The spatial arrangement of water's hydrogens toward one side of an oxygen atom causes that side to have a more positive character and the opposite side to have a more negative character. This dipole of water may bond to an ion of opposite charge. The ions of sodium and chlorine bond to water by ion-to-dipole interaction (Figure 14-4).

Dipole-Dipole Bonding

Water is an example of dipole-to-dipole molecular bonding. The spatial arrangement of water's hydrogens at a 105-degree angle to each other causes this molecule to be dipolar (Figure 14-5). The dipolar nature of water molecules allows them to form weak bonds with one another (Figure 14-6). The polar sides of water molecules also enable them to bond to ions and other polar molecules. For this reason, water is a convenient solvent for many substances such as drugs. Surface tension of water is a physical characteristic that is caused by water's dipole-to-dipole intermolecular attractions.

Some molecules may have *induced dipoles* caused by momentary uneven spatial distribution of electrons. Induced dipoles are not permanent. These temporary dipoles may lead to weak bonding between nonpolar molecules. Oils represent nonpolar molecules that display induced dipole bonding, often called *London dispersion forces*. London dispersion forces are the weakest of all molecular bonds. Despite this weakness, London dispersion forces at very low temperatures allow oxygen and nitrogen to become liquids.

Molecular Bonding Representations

There are several ways to denote bonding and electron distribution. The Lewis structure (electron dot structure) shows the valence electrons as they bond among atoms. Lewis structures may show dots or lines to represent electrons. Again, only outer shell valence electrons are represented and not lower, fully filled shells. Skeletal diagrams are another frequently used method to represent molecular bonding. In organic chemistry, skeletal diagrams use lines to show atom bonding often omitting the letter C for carbon (Figure 14-7).

The Valence Shell Electron Pair Repulsion diagrams (VSEPR) are more descriptive Lewis structures based on the theory of the same name. These diagrams represent electron repulsions, and the

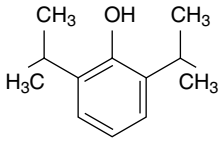

FIGURE **14-7** Skeletal diagram of diisopropyl phenol molecule.

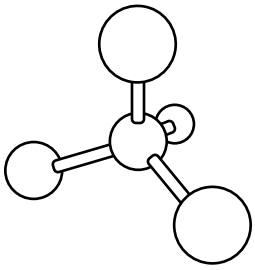

FIGURE **14-8** Valence Shell Electron Pair Repulsion (VSEPR) diagram of a tetrahedral-shaped molecule.

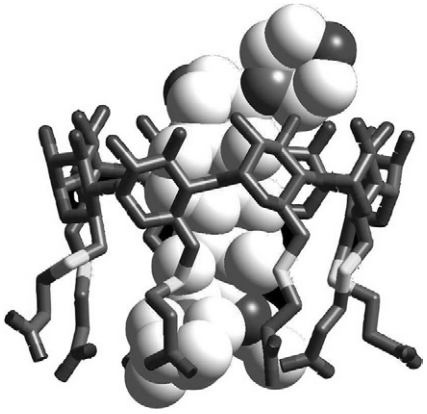

FIGURE **14-9** Molecular model of sugammadex encapsulating a rocuronium molecule. (From Zhang M-Q, et al. *Angew Chem Int Ed.* 2002;41(2):265. © Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.)

resultant approximation of the geometric distribution of atoms in covalently bonded molecules (Figure 14-8).

Molecular Modeling

Molecular models are detailed representations of molecules. Electrons are in constant "orbit" in an atom, and attempts have been made to graphically represent their space-occupying possible locations (Figure 14-9). Space-filling models reflect the "electron cloud" of specific atoms in a molecule. These models can appear as spherical, ball and stick, or ribbon-like representations of atoms and molecules that are affixed to one another. Molecular modeling is expanding our understanding not only of molecular geometries but also molecular behavior.[2]

Isomers

Isomers are molecules that have the same chemical formula but different structural formulas. The number and type of atoms and bonds are the same in isomers, but the arrangement of the atoms is different. Isomers may be *structural* or *stereoisomers*. Structural isomers have the same molecular formula, but their atoms are located in different places. Enflurane and isoflurane are examples of structural isomers. Structural isomers are truly different molecules with differing physical and chemical properties. Stereoisomers are molecules that have a similar geometric arrangement of atoms but differ in their spatial position. Stereoisomers may be *enantiomers* or *diastereomers*. Enantiomers are mirror images of one another, cannot be superimposed, and possess similar chemical and physical properties. Enantiomers are optically active and can rotate polarized light in a clockwise fashion (prefix + or dextro) or counterclockwise fashion (prefix − or levo). Racemic chemical compositions contain 50% of the levo form isomer and 50% of the dextro form isomer. Diastereomers are not mirror images and may have differing physical and chemical properties.

BOND BREAKING

Bond energy is the amount of energy needed to make or break a bond. Energy is released when a bond is formed, and energy is consumed with breaking a bond. The energy released when a bond is formed is the same amount of energy needed to break that same chemical bond. Short bonds, such as covalent bonds, tend to possess greater bond energies than longer, electrostatic bonds. When molecular bonds are broken, new molecular bonds are often formed and energy is released. An example of this is adenosine triphosphate (ATP) conversion to adenosine diphosphate (ADP). Energy is actually consumed in the process of breaking an ATP bond. A greater amount of energy is released when the free phosphate forms new bonds with hydrogen.[3] Bond energies are measured as an enthalpy change.

Enthalpy

Enthalpy is the total amount of energy possessed by a system. A system can be on the atomic scale or the macroscopic scale. The enthalpy of a system is the total of all kinetic and potential energy. The stored, or potential, energy includes its height in relation to the force of gravity and the energy stored in the bonds of molecules and atoms and even subatomic particles. All movement, as well as stored energy, must be accounted for and summated to know the enthalpy of a system. Thus the total amount of energy contained within a system is increasingly difficult to quantify, especially with increasing complexity of a system. The difficulty in measuring all the energy in a particular system requires a simpler method to evaluate energy involved in chemical reactions. Therefore, *change of energy (ΔH)* rather than total energy (enthalpy) of a system is measured.

ORGANIC COMPOUNDS

Organic chemistry is the study of carbon-containing molecules. Biological life on earth is based on carbon-containing compounds. Carbon is a unique atom that combines with many atoms in multiple arrangements, owing to its four valence electrons available for bonding. Carbon may make single, double, or triple covalent bonds with other atoms or molecules.

Hydrocarbons

Hydrocarbons are molecules composed entirely of carbon atoms with hydrogen atoms attached. These molecules are often found in straight chains, with or without branches. *Saturated hydrocarbons* are single-bonded carbon chains with all available carbon bonds attached to hydrogen. Hydrocarbons containing only single-bonded carbon atoms are called *alkanes*. The six-carbon hydrocarbon shown in Figure 14-10 is called a *hexane*. The *hex-* prefix denotes six carbons and the *-ane* suffix denotes an alkane with all single bonds.

Unsaturated hydrocarbons have one or more double or triple bonds between carbon atoms. Hydrocarbons containing double-bonded carbons are called *alkenes* and triple-bonded carbons are

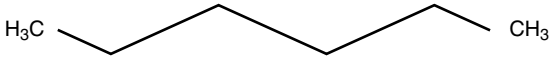

FIGURE **14-10** Hexane.

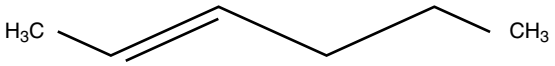

FIGURE **14-11** Hexene.

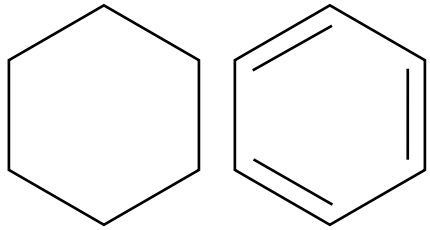

FIGURE **14-12** Hexane and benzene.

called *alkynes*. The six-carbon hydrocarbon containing a double bond is called *hexene* (Figure 14-11).

Cyclic hydrocarbons are carbon chains in a ring structure. They may contain multiple carbon atoms and may have single, double, or triple bonds. The cyclic hydrocarbons hexane and benzene (1,3,5 cyclohexatriene) are shown in Figure 14-12.

Saturated and unsaturated hydrocarbons that have hydrogens omitted are known as *alkyls*, are very reactive, and bond to functional groups. Cyclic hydrocarbons omitting a hydrogen on any carbon atom are called *aryls*, are reactive, and also bind with functional groups.

Functional Groups

Functional groups impart unique characteristics to molecules. There are many functional groups in organic chemistry, and several have importance in anesthesia.

Amines are derivatives of ammonia (NH_3) and have the general formula NR_3. Only one or two of the R groups may be hydrogen. All amines have a lone pair of electrons on the nitrogen.

Alcohols have the general formula ROH, where *R* represents any alkyl group. The hydroxyl group (OH) of alcohols is highly polar and easily forms hydrogen bonds with other polar molecules. The polarity of the hydroxyl group allows alcohols to dissolve many other polar molecules.

Phenols are similar to alcohols in that they both have the general formula ROH. The *R* in phenols instead represents an aryl group (benzene). A simple phenol is polar due to the hydroxyl group, but more complex phenols such as propofol (diisopropyl phenol) are not water soluble (Figure 14-13).

Ethers have the general formula ROR′, where *R* and *R′* are alkyl groups attached by oxygen. Ethers are inert and do not react with oxidizing or reducing agents but are highly flammable. The outdated anesthetic agent diethyl ether clearly shows both alkyl groups bonded to oxygen (Figure 14-14). Halogen substitution on ethers alters anesthetic characteristics, such as blood solubility and potency, while lowering flammability.

Several functional groups contain a structural arrangement of carbon double bonded to oxygen. This is known as a carbonyl group and structurally identified as C=O. The carbonyl group is polar, with the oxygen being more electrically negative. This polar characteristic is imparted to functional groups that contain a carbonyl group. The carbonyl group, though not a functional group

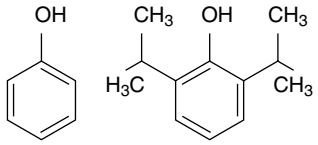

FIGURE **14-13** Phenol and disopropyl phenol molecules.

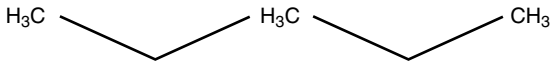

FIGURE **14-14** Diethyl ether.

by itself, is a key component of the following functional groups: aldehydes, ketones, carboxylic acids, esters, and amides.

- *Aldehydes* have the general formula RCHO.
- *Ketones* have the general formula RCOR′.
- *Carboxylic acids* have the general formula RCOOH.
- *Esters* have the general formula RCOOR.
- *Amides* have the general formulas $RCONH_2$, RCONHR, or $RCONR_2$.

SOLUBILITY

Solubility is the maximum amount of one substance (solute) that is able to dissolve into another (solvent). The factors that may affect solubility of solutes in solvents are the intermolecular interactions between the substances, temperature, and pressure.

Solids and Liquids

Solubility is enhanced by intermolecular interactions between substances that have similar electron configurations. "Like dissolves like" is often used to describe solubility. Salt (NaCl) in water is an example. The similar polarity of water and salt's constituent parts promote dissolving. Temperature also affects solubility. Energy is required to break the bonds of substances that are dissolving. Most often this is an endothermic reaction, which means it requires more energy than it produces. It consumes heat rather than produces heat. With endothermic reactions, solubility is increased with increased temperature; the additional energy (heat) drives greater dissolving. Most reactions of solids dissolving in liquids are endothermic. Occasionally the process may be exothermic, meaning energy is released in excess of the energy required to break the bonds of the solute. In this unique scenario, increases in temperature will decrease solubility. Pressure exerts little to no influence on solubility of solids and liquids.

Gases

Gas solubility in liquids is inversely related to temperature. As temperature increases, less gas is able to dissolve into a liquid. An increased temperature represents greater kinetic energy. Greater kinetic energy allows dissolved gas molecules to escape and prevents further dissolving. Lower temperature slows the kinetic energy of gas molecules, allowing them to dissolve into liquids. A clinical example of temperature affecting solubility is seen with the slower emergence of hypothermic patients receiving volatile-agent general anesthetics. The hypothermic patient retains anesthetic gases in the blood because of increased solubility related to temperature.[4] Gas solubility in a liquid is directly proportional to pressure and is described by Henry's law.[5]

Henry's Law

Henry's law (William Henry, 1775-1836) states "at constant temperature, the amount of gas dissolved in a liquid is directly

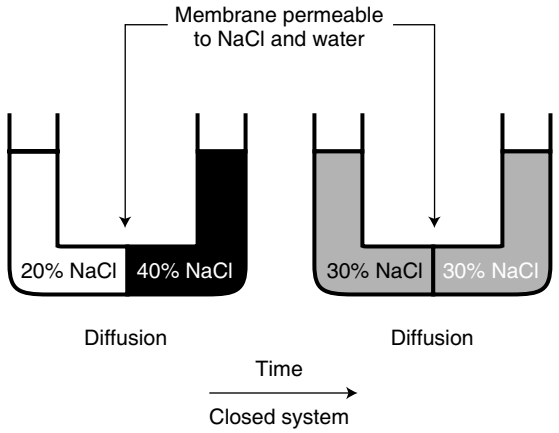

FIGURE **14-15** Diffusion of water and NaCl.

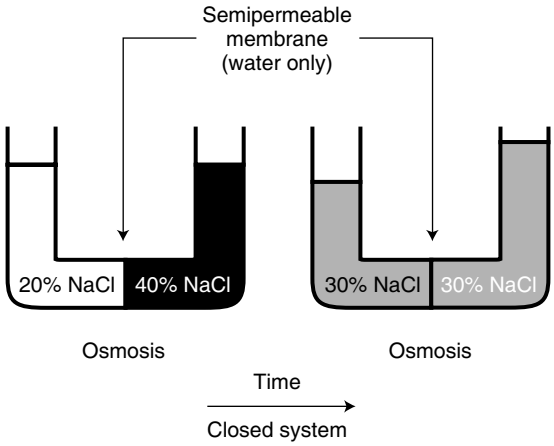

FIGURE **14-16** Osmosis of water through a semipermeable membrane.

proportional to the partial pressure of that gas at equilibrium above the gas-liquid interface." The formula is:

$$p = kc$$

where **p** is the partial pressure of the solute above the solution, **k** is Henry's constant, and **c** is the concentration of the solute in solution. Increasing the partial pressure of a gas above a liquid will increase the amount of gas that dissolves in the liquid. Increased delivery of oxygen (FIO_2) to patients to improve arterial oxygenation (PaO_2) and overpressurizing (high concentration) anesthetics reflect the direct relationship of pressure and solubility described by Henry's law. "Overpressurizing" is the process of significantly increasing a volatile anesthetic concentration (partial pressure) delivered to a patient to increase the alveolar concentration, and therefore the amount dissolved in the blood, to speed uptake.

DIFFUSION

Diffusion is the process of net movement of one type of molecule through space as a result of random motion intended to minimize a concentration gradient (Figure 14-15). This basic process occurs by Brownian (Robert Brown, 1773-1858) motion, which is driven by the inherent kinetic energy of the molecules.[6] Temperature is directly proportional to kinetic energy. Kinetic energy allows molecules to move freely in a fluid, and therefore mixtures of fluids tend to evenly distribute. The velocity at which a molecule may distribute is determined by its molecular weight. Every molecule at a given temperature will have the same kinetic energy, independent of its size, but its velocity may differ. From the formula for kinetic energy, KE = (½) mv^2, we can determine that if the mass of a molecule is changed, there must be an opposite change in velocity. Greater velocity correlates with faster diffusion. Thus, molecules with smaller mass will diffuse faster.

Graham's Law

Thomas Graham (1805-1869) determined that the rate of effusion (gas diffusion through an orifice) of a gas is inversely proportional to the square root of its molecular weight. The formula is:

$$r = 1/\sqrt{mw}$$

where **r** is the rate of diffusion, and **mw** is the molecular weight. Graham's law determines the faster diffusion of smaller molecules compared to larger molecules. Graham's law is helpful in understanding the effect of molecular weight on diffusion but is limited in fully describing all the factors influencing diffusion.

Diffusion Through Permeable and Semipermeable Membranes

Diffusion may occur through open space or through permeable membranes (tissues). If a fluid (gas or liquid) is permeable through a membrane, then the diffusion that occurs is dependent on five factors. These factors include concentration gradient, tissue area, and fluid tissue solubility, which are all directly proportional to diffusion. Membrane thickness and molecular weight are factors that are inversely proportional to diffusion.

Osmosis

Osmosis is the movement of water across a semipermeable membrane to equilibrate a concentration gradient (Figure 14-16). Semipermeable membranes are permeable to water only and not to solute. *Osmotic pressure* is the force needed to stop osmosis from occurring. *Oncotic pressure* is the osmotic pressure by plasma proteins and electrolytes in capillaries. Oncotic pressure balances the hydrostatic pressure tendency to push water out of capillaries. Normal oncotic pressure is approximately 28 mmHg. Our vascular system is a semipermeable membrane that responds to intravascular delivery of colloids by sequestering fluid.[7,8]

Diffusion in Anesthesia

Diffusion is a passive process driven by entropy (see Entropy in this chapter). The diffusion of oxygen and nitrous oxide represents both positive and negative consequences of this process. Nitrous oxide diffuses into air-filled cavities; therefore, delivery of nitrous oxide is contraindicated in patients with pneumothorax or where air-filled cavity expansion is undesirable.[9] Nitrous oxide expansion of endotracheal cuffs may cause tracheal mucosal damage.[10,11] Distention of bowel during nitrous oxide delivery also has been documented.[12,13] Apneic oxygenation is well known and exemplifies the beneficial process of diffusion.[14] An intubated patient who has previously been ventilated with 100% oxygen and remains connected to the ventilation circuit with 100% oxygen flow will maintain an acceptable PaO_2 if ventilation is ceased. The continual diffusion of oxygen into the blood is driven by a concentration gradient that continually diffuses oxygen into the alveoli via the ventilator circuit. The diffusion of gases across biological tissues is expressed by Fick's law.

Fick's Law

Fick's law for diffusion of a gas across a tissue plane is an encompassing law that accounts for molecular weight, concentration gradient, solubility, and membrane interactions. Fick's law states that diffusion

of a gas across a semipermeable membrane is directly proportional to the partial pressure gradient, the membrane solubility of the gas, and the membrane area and is inversely proportional to the membrane thickness and molecular weight of the gas. Specific application of the Fick equation for diffusion of respiratory gases is as follows:

$$J = \alpha D / \Delta x (Pao_2 - Pcapo_2)$$

where **J** is diffusion flux, **α** is the solubility constant for oxygen, **D** is diffusivity, **Δx** is the membrane thickness, and **(Pao_2 − $Pcapo_2$)** is the alveolar-capillary oxygen partial pressure difference. Fick's equation allows determination of pulmonary gas exchange.[15,16] The diffusion hypoxia that occurs after the delivery of nitrous oxide is discontinued, and low inspired oxygen is administered as explained by Fick's equation.[17]

NEWTONIAN PHYSICS

GRAVITY

All life on earth is well aware of gravity. From our first steps to our last, gravity affects every facet of our daily lives. It is a unidirectional force pulling objects down toward earth's center. Gravity appears to pull on heavy objects with greater force than lighter objects, but this is not necessarily true. Aristotle saw gravity this way and felt it was due to an object's desire to return to its natural position at rest on the earth. It took 2000 years to change that perspective. Gravity pulls on all objects with a force of 9.81 m/sec/sec (32 ft/sec/sec). Sir Isaac Newton's law of gravity derived that, "Each particle of matter attracts every other particle with a force which is directly proportional to the product of their masses and inversely proportional to the square of the distance between them." The formula for gravity is:

$$\text{Gravitational force} = (G \times m1 \times m2) / (d^2)$$

where **G** is the gravitational constant ($6.67 \times 10^{-11} Nm^2/kg^2$), **m1** and **m2** are the masses of the two objects for which you are calculating the force, and **d** is the distance between the centers of gravity of the two masses. Remember that mass and weight are not the same. Mass is the total of all matter in an object—the sum of all the electrons', protons', and neutrons' equal mass. Weight is the total effect of gravity pulling on all these electrons, protons, and neutrons of an object. An example often cited is that you may weigh 70 kilograms on earth due to the gravitational pull on all your atoms, but you would weigh less on the moon, which has less gravitational pull. Your mass or total amount of matter remains the same on earth or the moon.

$$\text{Mass} \times \text{force of gravity} = \text{weight}$$

The earth attracts all other objects around it with a force of 9.81 m/sec/sec, and those objects in turn attract the earth in relation to their mass and distance from the planet. The formula for gravitational acceleration is:

$$g = GM_e / r^2_e$$

where **g** is gravitational acceleration, **G** is the gravitational constant, $\mathbf{M_e}$ is the mass of earth, and $\mathbf{r^2_e}$ is the mean radius of earth. Earth's attraction for objects is proportional to mass for all objects at the same distance. One might want to say that larger-mass objects would accelerate or be pulled faster to earth, but objects also resist movement proportional to their mass (third law of motion). Gravity pulls on one atom of carbon with 9.81 m/sec/sec force, and the carbon atom resists this pull with a force of *x*. Gravity pulls on two carbon atoms with a force of 9.81 m/sec/sec on each atom for a total gravitational force of 9.81 m/sec/sec × 2, or 19.62 m/sec/sec. Two carbon atoms resist movement twice (2×) as much as one carbon atom, thus the net gravitational effect (falling) is the same. This is how greater-mass objects are pulled by gravity with the same force and fall at the same acceleration as lesser-mass objects.

This equal attraction on objects is often hidden in everyday life, owing to the effect of air molecules interacting with falling objects. Assuredly, all objects fall due to gravity at the same speed in a vacuum that is devoid of other molecules. Air molecules possess energy, move about, and interact with other matter. This causes friction. Greater friction equals greater force against the pull of gravity and slowing of a fall, but in a vacuum all objects fall equally at equal velocities.

NEWTON'S LAWS OF MOTION

- *Newton's first law* (law of inertia): A body in motion tends to stay in motion unless acted upon by another force.
- *Newton's second law* (law of acceleration): Acceleration of a body is in the direction of and proportional to the force (**F**), and that acceleration (**a**) is inverse to the mass (**m**) of the body, **F = ma.** If multiple forces exist, the direction and acceleration are proportional to the sum of all the forces. These are called *vectors*.
- *Newton's third law* (law of reciprocal action): For every action, there is an equal and opposite reaction. It states that objects exert equal but opposite forces on one another.[18] Example: An apple on a desk pulls down with a gravitational force equal to the force that the table resists.

FORCE

Force is the amount of energy required to move an object. From the understanding that the force of gravity pulls equally on all objects proportional to mass, a standardization of force became possible. Because we know that gravity pulls (accelerates) all objects with a force of 9.81 m/sec/sec, this force would also be 9.81 m/sec/sec if applied to any given weight. The force of gravity applied to 1 kg weight creates a standard by which other forces may be compared, quantified, and measured. Thus the force required to accelerate a 1 kg weight 1 meter per second became known as the *newton*.

The newton is the standard measure of force derived from the force of gravity.

$$\text{newton} = 1 \text{ meter} / \text{sec} / \text{sec}$$
$$= 1 / 9.81 \text{ kg weight or } 102 \text{ g weight}$$
$$\text{gravity} = 9.81 \text{ meter} / \text{sec} / \text{sec}$$

One newton is equivalent to 1/9.81 kg weight or 102 g weight. Force is mass multiplied by acceleration. The formula for force is:

$$F = ma$$

where **F** is force, **m** is mass, and **a** is acceleration. Often in settings of small measures of force, the newton is too large. A dyne is 1000th of a newton. A dyne is the force required to move a 1-g weight 1 cm per second. Dynes are used in calculating systemic and pulmonary vascular resistance.[19,20]

Pulmonary vascular resistance (PVR) is the measure of the pulmonary vascular system's resistance to flow from the right ventricle. Normal PVR is 100 to 200 dyne sec/cm^5. Systemic vascular resistance (SVR) is the measure of the peripheral vascular system's resistance to flow that must be overcome for flow to occur. The left ventricle must therefore pump blood with a force greater than the resistance of the vascular system. The formula for calculating SVR is 80 × (MAP − CVP)/CO = SVR. Normal SVR is 900 to 1200 dyne sec/cm^5.

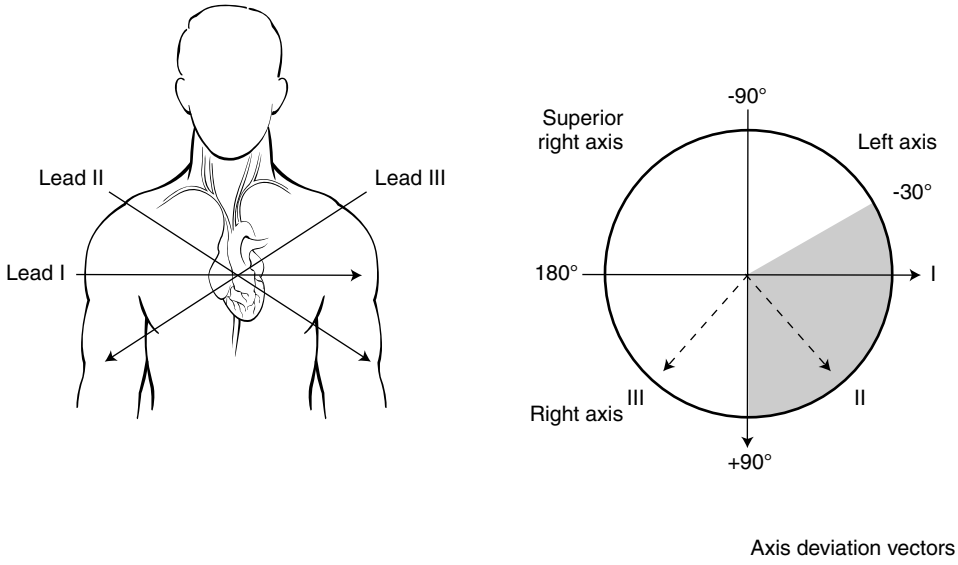

FIGURE **14-17** Electrocardiogram lead placement with vector direction and location of normal and abnormal axes.

Another application of force measurement in anesthesia is the technology of accelerometry used to measure the degree of neuromuscular blockade.[21,22] Accelerometry uses a piezoelectric disk to generate an electric current in proportion to acceleration (see Piezoelectric Effect in this chapter). An accelerometer measures the acceleration caused by the contraction of the adductor pollicis muscle after ulnar nerve stimulation. A comparison of baseline stimulated muscle twitches (forces) to twitches suppressed by neuromuscular blocking agents allows the quantification of the degree of neuromuscular blockade.[23] Accelerometers provide objective twitch data referenced to the patient's baseline twitch response.[24] Visual or tactile assessment of twitch heights is subjective and less reliable than accelerometry.[24,25]

Force is a basic phenomenon of physics that permeates the universe. Because all matter possesses mass, and all mass has some degree of acceleration, force exists everywhere. All forces possess direction. The study of force direction is explored with vectors.

Vectors

Two basic types of values describe our physical world: *scalar* and *vector*. Scalar values are fully described by magnitude alone, they possess no motion, and they include mass, energy, and work. Vector values are fully described by magnitude and direction. Vectors express motion and are described by the mathematics of force, speed, velocity, acceleration, distance, and displacement. Vector diagrams are scaled representations of vectors, with an arrow starting at a given magnitude and pointing in the direction of the force summation.

An electrocardiogram (ECG) is an example of a type of vector diagram that allows us to calculate the predominant direction of electrical force in the myocardium. An ECG records electrical flow as an upward or downward deflection on graph paper. When the flow is toward the positive electrode, an upward deflection will record. When the flow is away from the positive electrode, a downward deflection will record. Twelve-lead ECGs are scaled graphs with multiple points of reference used to measure the force direction of the electrical conductance. As multiple points of reference are recorded, direction of electrical flow predominance may be determined (vector summation). This is the principle behind determining axis deviation of the heart.

TABLE **14-3** Axis Deviation Determination Methods

Vector Method	Inspection Method	Grant Method
I+, aVF+ = Normal axis	I+, III+ = Normal axis	I+, II+ = Normal axis
I–, aVF– = Superior right	I– = Right axis	I+, II– = Left axis
I–, aVF+ = Right axis	III–, II– = Left axis	I–, II+ = Right axis
I+, aVF– see lead II (if II+ = Normal; if II– = Left axis)		I–, II– = Superior right

TABLE **14-4** Axis Deviations from Normal

Normal Axis	–30 to +90 degrees
Left axis deviation	–30 to –90 degrees
Right axis deviation	+90 to ±180 degrees
Superior right axis deviation	–90 to ±180 degrees

Axis deviation estimates the summation of forces that shift from the normal direction of electrical flow in the heart. Electrocardiogram vector diagrams are scaled clockwise from 0 degrees in the east position. The normal axis of electrical flow summation in the heart is between −30 degrees and +90 degrees. The axis determination steps that follow are based on identifying the positive (upward) deflections of the 12-lead electrocardiogram, which represents electrical flow toward the positive electrode. Because the normal axis of electrical flow is between −30 and +90 degrees, positive deflections in leads I and II would represent electrical flow in the normal direction. Negative deflections in lead I or lead II would reflect a deviation of normal axis and requires determination of the electrical flow vector. Vector deviations are described as *left*, *right*, or *right superior*. Several methods are available for quick determination of myocardial electrical axis deviation. Figure 14-17, Table 14-3, and Table 14-4 offer help in determining axis deviation.

PRESSURE

Pressure is defined as force over area, where **P** is pressure, **f** is force, and **a** is area.

$$P = f/a$$

Increasing the area in which a given force is applied will result in a lower pressure. The smaller the area to which the set force is applied, the greater the pressure. The standard unit of measurement for pressure is the pascal (Pa). A pascal is the force of 1 newton (N) over 1 square meter.

$$Pa = 1\ N/1\ m^2$$

A pascal equals 102 g weight acting over an area of 1 square meter. Remember, a newton equals 102 g weight. This is a very small unit of pressure. As the newton was fractionalized to the dyne for the purpose of establishing a more convenient unit of force measurement, the pascal was increased a thousand times to create the kilopascal (kPa) unit. A kilopascal is more convenient to use for measuring pressures. A kilopascal equals 1000 N or 102 kg acting over an area of 1 m^2.

$$Pa = 102\ g/m^2$$

$$kPa = 102\ kg/m^2$$

Syringes represent an example of the pressure generated by a force over a given area. Equal force (20 N) applied to the plungers of different syringes generates different pressures, depending on the area over which the force was applied. The force applied will cause greater pressure on injection with a tuberculin (TB) syringe (plunger area = 8.55×10^{-6} m^2) than with a larger 10-mL syringe (plunger area 3.42×10^{-5} m^2). As you increase the area to which a fixed force (20 N) is applied, the product of the equation, pressure (in atmospheres), becomes smaller.

$$P = f/a$$

$$\text{TB syringe: } 20\ N/8.55 \times 10^{-6}\ m^2 = 2339.18\ kPa,\ 17,543.94\ mmHg,\ \text{or } 23.08\ atm$$

$$\text{10-mL syringe: } 20\ N/3.42 \times 10^{-5}\ m^2 = 584.79\ kPa,\ 4386.28\ mmHg,\ \text{or } 5.77\ atm$$

$$\text{30-mL syringe: } 20\ N/5.99 \times 10^{-5}\ m^2 = 334.16\ kPa,\ 2506.40\ mmHg,\ \text{or } 3.29\ atm$$

These calculations show the extremely high pressures that can be generated by exerting a force over a small area. The tuberculin syringe generates more than 20 atmospheres of pressure and can rupture catheters if used to flush or dislodge blockages. Larger syringes are recommended for flushing or unclogging enteral feeding tubes because of the potential for generating high pressures with smaller syringes.[26-28]

Atmospheric Pressure

As previously discussed, gravity pulls on all objects, including the atoms and molecules of the atmosphere. Because these atoms and molecules have low mass, they have low gravitational pull but nonetheless are pulled toward Earth. The cumulative effect of gravity on atmospheric gases gives rise to atmospheric pressure. Atmospheric gases are less concentrated at altitude and more concentrated at sea level. Atmospheric pressure is the column of gravitational force on gases over a given area. This can be measured and is equivalent at sea level to 100 kPa (or 14.7 lb per square inch, 1020 cm of H_2O, or 760 mmHg—all equivalent to one another). *Standard pressure* in the SI is 100 kPa. Other units of pressure measurement include the following with their equivalents. It is best to memorize these:

1 torr = 1 mmHg
1 kPa = 10.2 cm H_2O = 7.5 mmHg

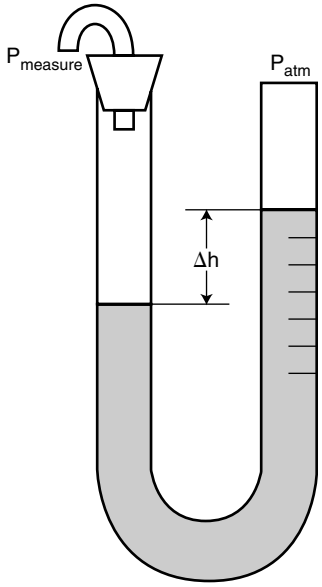

FIGURE **14-18** Manometer showing change in liquid column height *(Δh)* related to pressure applied.

1 atm = 760 mmHg = 760 torr = 1 bar = 100 kPa = 1020 cm H_2O = 14.7 lb/$inch_2$

Pressure Measurement

The simplest method for determining pressure is the manometer. A manometer is a liquid-filled tube that is open to atmospheric pressure on one end and exposed to a pressure for measurement on the other end (Figure 14-18). A pressure greater than atmospheric pressure (760 mmHg) will displace the column of liquid proportional to the pressure difference (Δh). Calibrating the column of liquid allows for quantification of the pressure.

A sphygmomanometer uses an inflatable cuff connected to a mercury-filled manometer to measure blood pressure. As the inflated cuff is slowly deflated, the arterial flow resumes, causing a pressure wave that is transmitted to a mercury column. The mercury column is calibrated to show the measured pressure in millimeters of mercury. A more recent advancement in blood pressure measurement is oscillometry. Oscillometry automates noninvasive blood pressure measurements by recording the oscillations in pressure caused by arterial pulsation.[29] As an inflated cuff is deflated, multiple measurements are made of these oscillations. Oscillations increase at systolic pressure and are maximal at the mean arterial pressure. Algorithmic computation of systolic and diastolic pressures is derived from the mean arterial pressure. Often these noninvasive automated blood pressure monitors use the piezoelectric principle to record the pressure oscillations and a microprocessor to derive the systolic and diastolic measurements.[30] Invasive blood pressure monitors use a piezoelectric transducer that converts pressure waves into electrical signals. Blood pressure measurements are gauge pressures that are zeroed to atmospheric pressure.

Gauge and Absolute Pressure

Different pressure measurements may use different zero reference points. The zero reference point may be a complete vacuum devoid of all molecules and molecular collisions that impart pressure. This is true zero pressure and is the reference point used when measuring absolute pressure. Absolute pressure is atmospheric pressure plus gauge pressure. Gauge pressure is zero

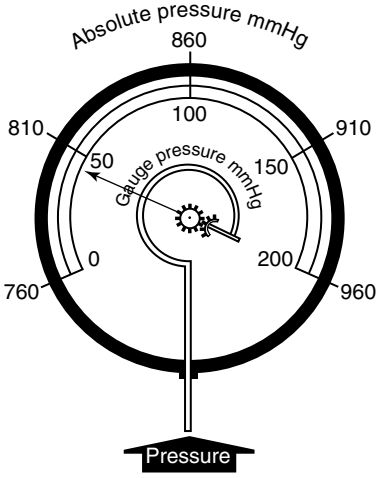

FIGURE **14-19** Bourdon gauge showing gauge pressure *(inside pressures)* referenced to absolute pressure *(outside pressures)*.

referenced at atmospheric pressure and reads zero at 760 mmHg at sea level. Gauge pressure is absolute pressure minus atmospheric pressure.

Bourdon gauges are often used in anesthesia to measure high pressures, such as in gas cylinders, and are zero referenced to atmospheric pressure (Figure 14-19). Bourdon gauges contain a coiled tube that expands as pressure is applied. A linkage connects the coil to a rotating arm that records the pressure. The American Society for Testing Materials International mandates that the zero reading of Bourdon gauges lie between the 6 o'clock and 9 o'clock positions. Other methods of pressure measurement in anesthesia include manometers.

THERMODYNAMICS

The three laws of thermodynamics explain the relationship between heat and energy and their exchange during work processes:

1. *Law of conservation of energy.* Energy cannot be created or destroyed. The increase in the internal energy of a thermodynamic system is equal to the amount of heat energy added to the system minus the work done by the system on the surroundings.
2. *Energy moves toward greater entropy or randomness*. The entropy of an isolated system not in equilibrium will tend to increase over time, approaching a maximum value at equilibrium.
3. *Absolute zero (0° K or −273.15° C) is void of all energy.* Absolute zero is theoretical, because it has been impossible to achieve. As a system approaches absolute zero of temperature, all processes cease, and the entropy of a system approaches a minimum value.

ENERGY

Energy can be defined as the exertion of force (kinetic) or the capacity (potential) to do work. Energy can be expressed as mechanical work, chemical reactions, or heat. The unit of measurement for energy is the joule. A joule is the force of 1 newton that moves its point of application 1 meter in the direction of that force. Two types of energy are potential and kinetic. Potential energy is energy waiting to be used. It is energy that is stored and available to be converted into power. Potential energy is defined as mass (**m**) times gravity (**g**) times height (**h**).

$$PE = mgh$$

Kinetic energy is energy of movement. *Kinetic* means movement. *Kinetic energy* is defined as one half the product of mass times the velocity squared.

$$KE = (1/2)\, mv^2$$

ENTROPY

Entropy is the universe's trend to equilibrate all things. It is the process that allows everything from ice melting to gas expansion. Sleep and the induction of general anesthesia have been proposed to be entropic processes.[31-34] All of these processes involve the equilibration of energy. Even matter is a form of energy. Entropy is unidirectional; it is the movement of energy from high concentration to lower concentration. It moves because of a gradient. The difference in the gradient influences the speed of the flow. Greater difference usually equals greater flow, and always from higher concentration to lower concentration. All energy and matter tend to follow this rule. An example of this unidirectional action is ice added to lemonade. Ice does not make lemonade colder, lemonade makes ice warmer. Diffusion, which will be covered later, is also a process driven by entropy. Entropy ends when all energy is equally distributed. Entropy is the underlying process promoting spontaneous and elicited movement in our everyday lives and the universe in general. Essentially, entropy drives the universe. This process should be kept in mind when learning or reviewing any dynamic concepts of anesthesia.[35]

TEMPERATURE

Matter may change form with the addition of greater heat energy. An example we see every day is the melting of an ice cube into liquid water, and liquid water into vapor with the addition of greater heat energy. Liquid water, with the addition of heat energy, expands. This is due to the water molecules moving apart with greater kinetic energy that ultimately allows them to escape individually as a vapor. Another liquid, mercury, also expands with the addition of heat energy. When placed in the bottom of a closed glass cylinder, the expansion is limited to one direction in relation to the energy applied. This is a simple application of heat energy (kinetic energy) interacting with matter to allow analysis of the thermal state: a thermometer.

Temperature is the measurement of the thermal state of an object. Heat is thermal energy; temperature is the quantitative measurement of that energy. Several temperature scales exist: Fahrenheit, Celsius, and Kelvin (Figure 14-20). Gabriel Daniel Fahrenheit (1686-1736) is credited with inventing the mercury thermometer (1714) and devising the Fahrenheit temperature scale. The Celsius (Anders Celsius, 1701-1744) or centigrade scale is the primary scale used for everyday temperature measurements. The Kelvin scale (William Thompson Lord Kelvin, 1824-1907) was developed to better reflect mathematically the temperature/pressure relationship of gases and is used when calculating their behaviors. Water freezes at 273.15° K and boils at 373.15° K. Conversion among temperature scales is as follows:

Celsius to Kelvin: °K = °C + 273
Celsius to Fahrenheit: °F = 1.8 (°C) + 32
Fahrenheit to Celsius: °C = (°F − 32)/1.8
Standard temperature is 273.15 K (0° C)

Heat Loss

Heat and energy are the same. Heat loss (energy loss) of a system, as discussed previously, is unidirectional from higher concentration to lower concentration, from hotter to less hot. Even ice possesses heat (energy). Remember absolute zero, 0° K (−273.15° C

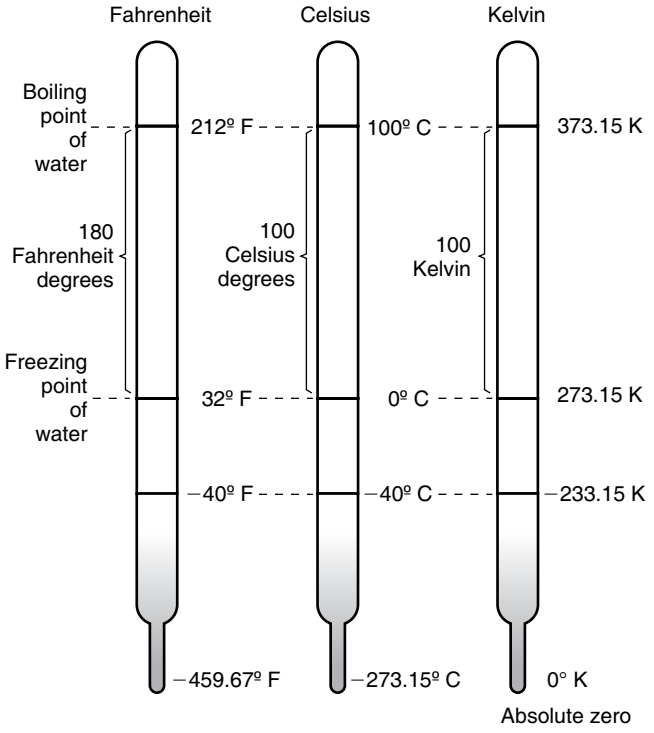

FIGURE **14-20** Temperature scales referenced to Kelvin.

or −459.67° F), is the absence of all energy and therefore absence of all heat. The human body is a system that contains energy. Much of this energy is in the form of heat. Our bodies continually exchange heat with the environment from high concentration to lower concentration. On a very hot day or in a very hot room, we could become hyperthermic. Similarly, in a cool room our bodies could become hypothermic, especially with exposed body surface. We will focus on heat loss in the cool operating room environment. Clothes, hair, skin, and fat insulate us from heat loss. Protective mechanisms exist that further lessen heat loss.

Vasoconstriction of peripheral vessels slows heat loss from our bodies. An example is the vasoconstriction seen in our limbs when exposed to a cold environment. The reverse thermoregulatory mechanism to promote heat loss is vasodilation when exposed to a hotter environment. The directing of blood to or away from our periphery aids in the removal or conservation of our body's heat energy. This thermoregulatory mechanism is disrupted under anesthesia by vasodilating drugs, specifically volatile anesthetics. Volatile and regional anesthetics vasodilate vessels, including those in the periphery, causing greater blood flow to the surface of our bodies.

Core Temperature Redistribution

Core temperature redistribution is the process of increased heat loss from the body resulting from the vasodilating effects of volatile and regional anesthetics, which cause greater blood flow and therefore heat flow to the body's surface from the core.[36-38] A patient's core temperature can quickly drop by the vasodilating actions of anesthetics, with the greatest decrease in the first hour.[37] It is imperative that one be cognizant of this heat loss mechanism and take measures to decrease it.[39-41] Covering all exposed areas of a patient minus the surgical site, wrapping the head in blankets, and warming the operating room all decrease heat loss. The use of forced warm air devices is effective at decreasing heat loss in the operating room environment.[42-44]

Blood flow to our body's surface encourages heat loss by four primary processes. In decreasing order they are:

1. Radiation
2. Convection
3. Conduction
4. Evaporation

Radiation

Radiation is the most significant mechanism of heat loss by our bodies, especially by patients under anesthesia. Radiation of the infrared electromagnetic wavelength transfers heat energy from our warm bodies to the less warm operating room environment (walls, ceiling, equipment, etc.). Electromagnetic radiation is pure energy. (See discussion on this later in the chapter.) Infrared radiation from our bodies is greatest in areas of highest blood flow. Our heads lose the greatest amount of heat due to the high percentage of blood flow. Blood carries body heat, and the greater amount of blood and heat transported to the head facilitates greater heat loss by radiation.

Convection

Convection is the process of creating air currents by heat. Our bodies transfer kinetic energy to air molecules on the surface of our skin. The heated air molecules then move about with greater kinetic energy, rise, and are replaced by colder (less kinetic energy) air molecules. Our bodies then transfer more kinetic energy to these molecules, they rise, and again are replaced by cooler air molecules. When thinking of convection, it helps to think in terms of *currents*.

Conduction

Conduction is the transfer of heat by physically touching a less warm object. Where two objects are in direct contact, heat exchange occurs from high concentration to lower concentration (entropy). An example would be holding a cold soda can. The sensation of cold is the direct loss of heat from your hand to the can. Cold is not transferred to your hand; heat is transferred to the can. A patient on a cold operating room table will conduct his or her heat to the less hot table wherever physical contact is present. This is not a significant process in adult patients, but for pediatric patients who have large body surface area to mass, it is quite significant. Use of warming blankets on operating room tables stops or reverses this heat transfer. Warming blankets may add heat energy to a patient, depending on the temperature and establishment of a thermal gradient.

Evaporation

Evaporation is not usually a large contributor to patient heat loss. Heat loss from evaporation includes moisture evaporated from the patient's skin, as well as exhaled water vapor. The process of evaporation, causing a phase change from liquid to gas, requires energy. The source of energy needed for this process comes from the surrounding environment of the evaporating substance. *Latent heat of vaporization* is the amount of heat energy per unit mass required to convert a liquid into the vapor phase. The energy withdrawn from the environment to convert one gram of water into vapor is 2500 joules, or approximately 600 calories. An example of this is the cooling off we feel after getting out of a swimming pool. The energy used to change the water into a vapor comes mostly from our bodies. Our body loses heat energy to this process, and we experience a state of lower thermal energy. Patients who have areas of their bodies surgically prepped with liquids (e.g., isopropyl alcohol, povidone-iodine, and chlorhexidine gluconate) experience heat

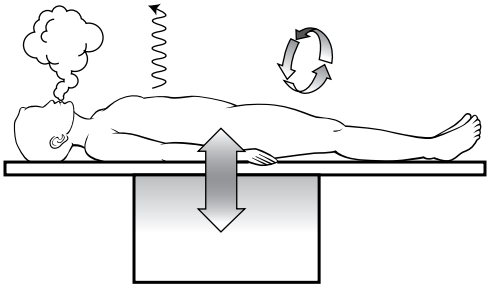

FIGURE **14-21** Heat loss mechanisms of radiation, convection, conduction, and evaporation in patients under anesthesia.

loss by this method. The process of breathing also causes heat loss through exhaled water vapor. This is not usually a high heat loss method in adult patients, but may become significant in pediatric patients when using high carrier gas flow rates. Lower carrier gas flows, when appropriate, and use of in-line humidifying apparatus decrease the evaporation of pulmonary water content and limit heat loss by this mode. One should consider these interventions with all intubated general anesthetics to prevent not only heat loss but also the pulmonary drying effects of dehydrate carrier gases.

Heat loss from patients is primarily due to radiation of infrared electromagnetic radiation.[45] Convection is the second largest method of heat loss in anesthetized patients.[45,46] Conduction and evaporation cause heat loss to lesser extents but remain a concern. Prevention of heat loss is extremely important to decrease higher morbidity experienced by hypothermic patients.[47-49] As Figure 14-21 illustrates, the use of forced warm air devices, lower gas flow rates, humidification systems, warming the operating room, and covering and insulating patients all are effective methods to decrease patient heat loss.[43,50]

Vaporization. Vaporization is the process of converting liquids or solids into vapors. Evaporation is the specific process of vaporizing liquids. Vaporization requires energy. As stated previously, the latent heat of vaporization is the energy needed to transform a given amount of liquid into a gas and is measured in kilojoules (kJ). The temperature at which the bulk of a liquid at a given pressure converts to a vapor is the *boiling point*. The temperature of a liquid will not rise above its boiling point; instead, the energy is used to transform the liquid into gas. Heating a liquid to its boiling point increases the kinetic energy of the liquid's molecules. Further addition of heat energy, above the boiling point, is transferred to molecules so they may break away from the surface and become a gas. "The rate of vaporization depends only on the temperature, the vapor pressure of the liquid, and the partial pressure of the vapor above the evaporating liquid."[51] As gas molecules escape the liquid, they exert a pressure known as *vapor pressure*, measured in millimeters of mercury. Increasing heat will increase molecular kinetic energy, which will increase the rate of vaporization. In a closed container, equilibrium will be achieved between molecules in the gaseous phase and those in the liquid phase.

All liquids that have high vapor pressures at room temperatures are known as *volatile liquids*. Vapor pressure and boiling points are inversely related. Vapor pressures of the volatile anesthetics at standard temperature and pressure (STP) are as follows:

- *Isoflurane:* 238 mmHg
- *Sevoflurane:* 160 mmHg
- *Desflurane:* 660 mmHg

Vapor pressures are unique characteristics of liquids that depend solely on temperature. Different liquids exert different vapor pressures at a given temperature. Because different volatile anesthetics have differing vapor pressures, vaporizers must be calibrated for each specific agent. Placing the wrong agent into a vaporizer will cause a greater or lower delivered concentration than dialed. If a high-vapor-pressure volatile anesthetic agent is placed inside a vaporizer calibrated for a lower-vapor-pressure volatile anesthetic, the output of that vaporizer will be higher than indicated on the control dial. If a volatile anesthetic agent with a lower vapor pressure is placed inside a vaporizer calibrated for a higher-vapor-pressure anesthetic, the output of that vaporizer will be lower than indicated on the control dial.[52]

Absolute Zero

The preceding discussion has covered the first and second laws of thermodynamics, with examples applied to the practice of anesthesia. With a unidirectional perspective and an understanding that energy cannot be created nor destroyed, the third law becomes self-evident. Absolute zero is the theoretical state devoid of all energy. No matter how much energy is distributed, it will still be present. Entropy to its universal maximum distribution will possess energy, even though it would be very low. There is energy in the universe, and therefore it will always be present in some form and to some degree. The absolute absence of energy is therefore impossible. That does not prevent us from calculating the theoretical temperature that would be devoid of energy. The theoretical temperature of absolute zero is −273° C (0° K, −460° F).

KINETIC MOLECULAR THEORY

Thermodynamics set the foundation for explaining the overall action of a system's energy. The kinetic molecular theory builds on Newtonian physics and thermodynamics and focuses on molecular movement (energy) and forces between these molecules. This theory explains how molecules behave as they follow the previously described laws of thermodynamics. Kinetic molecular theory was created to have a conceptual framework that encompassed the findings of Charles, Boyle, and Gay-Lussac and the *universal gas law* that unified their studies. A review of basic matter characteristics is as follows:

- *Matter* is composed of small particles called *molecules* and molecules are composed of atoms. Matter can take the form of solid, liquid, or gas.
- *Solids*—Molecules in a solid are held close together by intermolecular forces. They may move about slightly and vibrate.
- *Liquids*—Molecules in a liquid are held together by intermolecular forces and may slide or flow by one another.
- *Gases*—Molecules in a gas move linearly, and the attractive forces between molecules are less than their kinetic energy. They move almost completely free of one another.

The kinetic molecular theory, which best describes the action of gases, makes some generalized assumptions for simplicity:

1. Molecules have no volume.
2. Gas molecules exert no force on each other unless they collide.
3. Collisions of molecules with each other or the walls of the container do not decrease the energy of the system.
4. The molecules of a gas are in constant and random motion.
5. The temperature of a gas depends entirely on its average kinetic energy. The energy of a gas is entirely kinetic.

The kinetic molecular theory was created to explain the ideal gas law. Though the ideal gas law adequately explains the general behavior of gases, it does omit a gas molecule's small volume and intermolecular interactions. These flaws are further addressed in the section covering Van der Waal's equation.

TABLE 14-5 Gas Laws: Gas Properties and Relationships

Property Constant	Studied Properties	Property Relationship	Law
Pressure	Temperature, volume	Directly proportional	Charles
Temperature	Pressure, volume	Indirectly proportional	Boyle
Volume	Pressure, temperature	Directly proportional	Gay-Lussac

GAS LAWS

The foundations for the kinetic molecular theory were based on the discoveries of three scientists, Jacques Charles (1746-1823), Robert Boyle (1627-1691), and Joseph Louis Gay-Lussac (1778-1850). They each studied isolated components of pressure, volume, and temperature to explore the relationship of these components. Charles studied the relationship of volume and temperature when pressure is maintained constant. He found that the volume-to-temperature relationship is directly proportional. This means that at a constant pressure, volume will increase as temperature increases and vice versa. Boyle studied the relationship of pressure and volume when temperature is maintained constant. Boyle found that the pressure-to-volume relationship is indirectly proportional. Thus at a constant temperature, pressure will increase as volume decreases and vice versa. Gay-Lussac studied the relationship of pressure and temperature when volume is maintained constant. Gay-Lussac found that the pressure-to-temperature relationship is directly proportional. As pressure increases, temperature will increase and vice versa. The gas laws allow us to calculate the behavior of gases when one of the three factors of pressure, volume, or temperature is maintained unchanged. The clinical significance of these laws is expressed by the ability to calculate the available liters of oxygen from a cylinder of any known pressure. This and other examples are available at the end of the chapter. Table 14-5 summarizes the laws and the interrelationship of pressure, volume, and temperature.

Universal Gas Law

As the universal gas law unified the findings of Charles, Boyle, and Gay-Lussac, it also became known as the *unified gas law* or *ideal gas law*. The formula is as follows:

$$PV = nrT$$

where at standard temperature, **P** is pressure, **V** is volume, **n** is the number of moles, **r** is the constant 0.0821 liter-atm/K/mole, and **T** is temperature. A *mole* is a gram molecular weight of a gas. Atomic, or molecular, weight is the addition of all atomic particles, protons, neutrons, and electrons in an atom or molecule. An example is a mole of helium. Helium has a molecular weight of 4. Placing "gram" after helium's atomic weight gives us a "mole" of helium. Four grams of helium is a mole of helium. This amount of gas establishes a standard reference for calculations.

Using the universal gas law, you can calculate the volume for which 1 mole of a gas will expand at any given temperature or pressure. In the example given, we will calculate the volume in liters that 1 mole of oxygen will expand to at 1 atmosphere pressure at standard temperature (0° C). Celsius is converted to Kelvin.

$$1 \text{ atm } (x) = 1 \text{ mole } (0.0821 \text{ L atm / mol K}) (273 \text{ K})$$
$$x = 22.4 \text{ L}$$

One mole of any gas at 0° C will expand to 22.4 liters volume.

As this is a conceptual text, it is easier to view the universal gas law as PV = T to focus on the relationship between pressure, volume, and temperature. It is easy to see mathematically how increasing or decreasing any value would affect the other values as described previously. The universal gas law can be rearranged as follows:

$$PV = T \text{ or } T/P = V \text{ or } T/V = P$$

Increasing one value will increase or decrease the other values to maintain balance in the formula. The universal gas law allows understanding and quick determination of such things as: How much oxygen is available to be released from a partially full oxygen cylinder, and at what temperature will a full oxygen cylinder exceed its recommended pressure when heated?

Avogadro's Number

Amedeo Avogadro (1776-1856) was able to show that in a mole of any gas there are 6.023×10^{23} molecules. A mole of gas is equal to the molecular weight of the gas expressed in grams. A mole of helium would be 4 g and contain 6.023×10^{23} atoms. Similarly, a mole of oxygen (O_2) would be 32 g and contain 6.023×10^{23} molecules of oxygen. Oxygen is a molecule composed of two oxygen atoms bonded together, and therefore the molecular weight of the diatomic oxygen molecule is 32, not 16.

Van der Waal's Forces

Unfortunately, the simplicity of the universal gas law is not 100% accurate in fully describing the interaction of gases with their environment. The universal gas law is also called the *ideal gas law* because it explains the behavior of gases if they were "ideal." An ideal gas would possess molecules that occupy no volume and never interact with other molecules. Gas molecules do have volume and do occupy space, and therefore the volume they occupy must be taken into account when calculating a gas's expansion or contraction. The universal gas law does not account for gas molecule volume because Charles, Boyle, and Gay-Lussac did not account for this in their studies. (Remember, the universal gas law unified the work of Charles, Boyle, and Gay-Lussac.) An ideal gas also assumes no intermolecular forces. However, molecules do interact with one another, and this behavior alters the net effect of kinetics as calculated by the universal gas law. Van der Waal's (Johannes Diderik van der Waal, 1837-1923) equation corrects the universal gas law and accounts for molecular volume and molecular interaction in a gas. Van der Waal's equation is as follows:

$$(P + n^2a/V^2)(V/n - b) = RT$$

where **P** is the pressure of the fluid, **V** is the total volume of the container containing the fluid, **a** is a measure of the attraction between the particles, **b** is the volume excluded by a mole of particles, **n** is the number of moles, **R** is the gas constant, and **T** is the absolute temperature.

Because the deviations are not clinically significant, the universal gas law and molecular kinetic theory become immensely valuable in their simplicity to describe the behavior of gases.

Dalton's Law of Partial Pressures

Pressure in the kinetic molecular theory is purely the result of molecular collisions on the walls of a container. If there are more molecules in a container, there will be more collisions and thus greater pressure. Dalton's law (John Dalton, 1766-1844) states that the total pressure of a system is the additive pressures of each

individual gas in a mixture. Multiple gases in a mixture each will exert a pressure in proportion to its percentage in the mixture. The total pressure is the summation of individual molecular collisions upon the walls of a container.

$$P_t = P_1 + P_2 + P_3 + P_4 + P_5 + \ldots$$

An example is the mixture of gases that compose medical air at atmospheric pressure:

79% Nitrogen: 0.79 × 760 mmHg = 600.4 mmHg partial pressure nitrogen

21% Oxygen: 0.21 × 760 mmHg = 156.6 mmHg partial pressure oxygen = 760 mmHg total atmospheric pressure

Adiabatic Changes

Entropy in any system takes time. Rapid expansion or compression of gases may exceed the speed of energy equilibration with the surrounding environment. A rapid expansion or compression of a gas without equilibration of energy with the surrounding environment is called an *adiabatic* process and entails no increase or decrease in a system's energy.

Remember that the energy of a gas is almost entirely kinetic. Temperature is the measurement that quantifies the energy distribution among the molecules in a system. One could think of temperature measurement as a quantification of a system's kinetic energy per area. An example would be the experience of placing your hand into sunlight. The surface area of that sunlight measured is equal to the surface area of your hand. It is warm. Now place a magnifying glass of surface area equal to your hand into the sun and focus that same amount of sunlight energy onto a pinpoint area of your hand. Ouch! The same amount of energy experienced over less area is measured as a higher temperature. The temperature measurement is higher, but the system's energy total has not increased or decreased. The total sunlight energy hitting your hand is the same but distributed over different areas.

Energy Concentration Effect

Compressing a gas quickly will intensify the kinetic energy (molecular movement) such that the thermal measurement of the gas will be higher. This quick compression of the gas's area does not allow the system's energy to dissipate into the surrounding environment. Thus the temperature will quickly rise, proportional to the decreased volume. Although the temperature will be higher, the total energy of the system has not increased. A gas that is compressed quickly has little time to distribute any of its energy, so the thermal measurement becomes higher. This is the mechanism a diesel engine uses to ignite diesel fuel. Quick compression of fuel vapor intensifies the kinetic energy of the gas, with a corresponding increase in temperature, until the ignition temperature is achieved and spontaneous ignition occurs. This effect, though unlikely, could happen with a compressed gas cylinder that is quickly opened. The rapid reexpansion and recompression of gas as it rushes through the outlet channels of a cylinder could increase the temperature significantly. The high temperature generated could cause a burn or ignite any grease placed on the O-ring. Oil or grease is not recommended for use on any cylinder of compressed gas. Usually, rapid recompression in the cylinder stem is not a concern. It is possible and has occurred, but more likely the opposite will occur with rapid expansion of the gas as it leaves the cylinder.

Energy Dilution, Joule-Thompson Effect

The Joule-Thompson effect, named after James Prescott Joule, (1818-1889) and William Thompson Lord Kelvin, explains the cooling effect that occurs with adiabatic expansion of a gas. Rapid expansion of a gas causes the temperature measurement to decrease in the exact opposite process as explained previously. When we lower the pressure of a gas (increase its volume) quickly, we lower the energy per area. The temperature measurement will be lower when the volume is rapidly expanded. The total energy of the gas has not changed, but the expression, or thermal measurement, is decreased related to the increased volume. The temperature may be so low that frosting may occur at the cylinder outlet. Potentially, one could suffer a freeze injury. So why does this not always occur? If done slowly, energy from the environment will move into the gas, and ambient temperature will equalize with the less kinetic energy per area of expanding gas. The second law of thermodynamics, entropy, explains the maintenance of temperature when opening a gas cylinder slowly. Opening a cylinder slowly, therefore, would not be an adiabatic process. The slow opening of a gas cylinder allows the expansion of gas to draw energy from the environment to maintain an equal distribution of energy, and we observe no changes in temperature of the gas.

FLUID FLOW

Basic Principles of Fluid Mechanics

Fluids are defined by their response to stress. Stress is the distribution of force per unit area. The stress, or force distribution, may be tangential, and thus designated a shear stress, or it may be perpendicular and designated as a normal force. Strain is the deformation caused by stress. Fluids continuously change shape (flow) when subjected to shear stress, and respond in one of two ways to perpendicular forces:

1. Resist compression (e.g., liquids)
2. Become compressible and easily expandable (e.g., gases)

Both liquids and gases are fluids. Forces associated with fluids are gravity, pressure, and friction. Friction is resistance to flow from surface interaction and is proportional to viscosity. Viscosity is the physical property of a fluid that relates shear stress to rate of strain. Viscosity is the inherent property of a fluid that resists flow. Flow is the result of pressure forces in a fluid established by differences in pressure from one point to another, which creates a pressure gradient. All flow moves from higher pressure, or resistance, to lower. The following laws and principles apply to both compressible (gas) and incompressible (liquid) fluids. *Flow* is defined as the quantity of a fluid passing a point per unit of time, where **F** is the mean flow, **Q** is quantity, and **t** is time.

$$F = \frac{Q}{t}$$

Types of Flow

The three types of flow that occur through tubes and orifices are laminar, turbulent, and transitional. Laminar flow is a type of flow in which all molecules of a fluid travel in a parallel path within the tube. The molecules in the center of the tube encounter the least adhesive force of the walls of the tube and therefore move at a velocity twice that of the mean flow. Flow decreases approaching the walls and ceases at the wall. True laminar flow predominates in the smallest airways (terminal bronchioles). Transitional flow is a mixture of laminar flow along the walls of a tube with turbulent flow in the center. Turbulent flow is described as chaotic with irregular eddies throughout. Laminar, transitional, and turbulent airflow are illustrated in Figure 14-22.

Poiseuille's Law

Laminar flow is described mathematically by Poiseuille's law (Jean Louis Marie Poiseuille, 1797-1869). Poiseuille's law is:

$$F = (\pi r^4 \ \Delta P) / (8 \ n \ l)$$

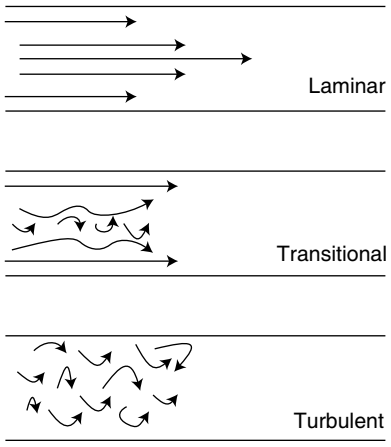

FIGURE **14-22** Three types of flow: laminar, transitional, and turbulent.

where **F** is flow, π is the constant *pie*, $\mathbf{r^4}$ is radius to the fourth power, **ΔP** is the pressure gradient, **n** is viscosity of fluid, and **l** is the length of tube. According to Poiseuille's law, radius will have the most dramatic effect on flow. Doubling the radius will result in a 16-fold increase in flow. A tripling of the radius increases flow 81-fold. Therefore, flow through a 16-gauge (1.65 mm) intravenous catheter is much greater than through a 20-gauge (0.89 mm) catheter. If the viscosity of a fluid is increased, flow decreases. Patients with polycythemia have decreased blood flow due to increased viscosity of blood. Increasing the length of a tube decreases the flow. If the length of a tube is decreased by 50%, there will be a corresponding doubling of the flow. If the length of a tube is doubled, flow decreases by half.

Clinical application of Poiseuille's law in anesthesia is exemplified as follows. To improve flow when delivering a unit of packed red blood cells, a large-diameter intravenous catheter (18 gauge or larger) is recommended, a pressure bag may be placed on the unit of packed red blood cells to increase the driving pressure (pressure gradient), and the packed red blood cells may be diluted with normal saline to lower viscosity.[53] These interventions are a direct manipulation of the factors associated with Poiseuille's law and significantly improve flow. Of all the changes that may be made, increasing the diameter of the intravenous catheter will have the most dramatic improvement of flow. Large-bore intravenous lines, such as an introducer central line, are best for rapid, large-volume infusion.

Mechanical ventilation of patients also reflects the factors associated with Poiseuille's law. The larger the endotracheal tube, the better flow of gas for ventilation. Delivery of β_2 receptor agonists, such as albuterol, have the effect of increasing the diameter of the bronchial tubes of the lungs to improve flow. Increasing the peak inspiratory pressure establishes a higher pressure gradient, which improves flow and delivered tidal volumes. Increases in the pressure gradient and flow velocity may initially improve flow but risks converting that flow to turbulent flow. Turbulent flow also may result when molecules of a fluid encounter rough, irregular walls or angles greater than 25 degrees. Turbulent flow often occurs in medium to large airways of the lung and predominates during periods of peak flow, coughing, and phonation. Orifice constrictions, such as glottic closure, cause laminar flow to become turbulent. Smaller bronchial tubes of the lung have slower velocities, and laminar flow is maintained. The presence of laminar, turbulent, or transitional flow is determined by Reynolds number.

Reynolds Number

Reynolds number (Osborne Reynolds, 1842-1912) is an index that incorporates the factors of Poiseuille's law with the addition of a fluid's density to determine whether a given flow will be laminar or turbulent. Reynolds number is directly proportional to the density of the fluid, linear velocity of the flow, and tube diameter; flow is inversely proportional to fluid viscosity. The equation is:

$$\text{Reynolds number} = \frac{vpd}{\eta}$$

where **v** is the linear velocity of fluid, **p** is density of fluid, **d** is diameter of tube, and **η** is viscosity. A calculated Reynolds number greater than 2000 will reflect a predominantly turbulent flow. Conversely, a Reynolds number less than 2000 will reflect predominantly laminar flow. Delivery of helium-oxygen mixtures to status asthmaticus patients, who are refractory to standard treatments, is based on the understanding of density's role in reestablishing laminar flow.[54] Helium, which has a significantly lower density (0.1786 g/L at STP) than nitrogen, (1.251 g/L at STP) improves flow by restoring laminar flow through the significantly narrowed airways of a severe asthma attack.

Bernoulli's Principle

Bernoulli's principle (Daniel Bernoulli, 1700-1782) describes the effect of fluid flow through a tube containing a constriction. As flow passes through a narrowing in a tube, the velocity of that flow increases and there is a corresponding decrease in pressure at the area of narrowing (Figure 14-23, A). This drop in pressure is explained by the conservation of energy law. For a steady flow of incompressible fluids, the sum of pressure, potential energy, and kinetic energy per unit of time must remain constant. The relationship of the pressure gradient to mass flow requires the pressure to decrease when the velocity increases. The Bernoulli equation is:

$$P + \tfrac{1}{2}\,\Delta V^2 + pgh = \text{constant}$$

where **p** is pressure, **Δ** is density, **V** is velocity, **g** is gravitational acceleration, and **h** is height. Bernoulli's equation is useful in determining flow through tubes that narrow, but it does not account for friction and assumes no changes in density or flow rate. The simplicity of this equation allows an explanation of the pressure velocity relationship if fluid flows across a constriction. The velocity of a fluid is the product of the flow rate divided by the area of flow.

$$\text{Velocity} = \frac{\text{Quantity of flow per unit of time}}{\text{area}}$$

If a given quantity of flow is 4 liters per minute over an area (tube) of 2 liters volume, the fluid velocity would be 2 liters per minute. If this flow meets a narrowing in its path that decreases the cross-sectional area to 1 liter volume, the fluid velocity would increase to 4 liters per minute.

$$V1 = \frac{4\ \text{L/min}}{2\ \text{L/min}} = 2\ \text{L/min}$$
$$V2 = \frac{4\ \text{L/min}}{1\ \text{L/min}} = 4\ \text{L/min}$$

This shows the increase in velocity associated with a narrowing in a tube for a given fluid flow (assuming no changes in density or height), and the conservation of energy law dictates there must be a corresponding decrease in pressure. The energy of the flowing system does not change because of a constriction, but rather the expression of that energy has changed. Essentially, more energy is imparted toward velocity as opposed to pushing on the walls of

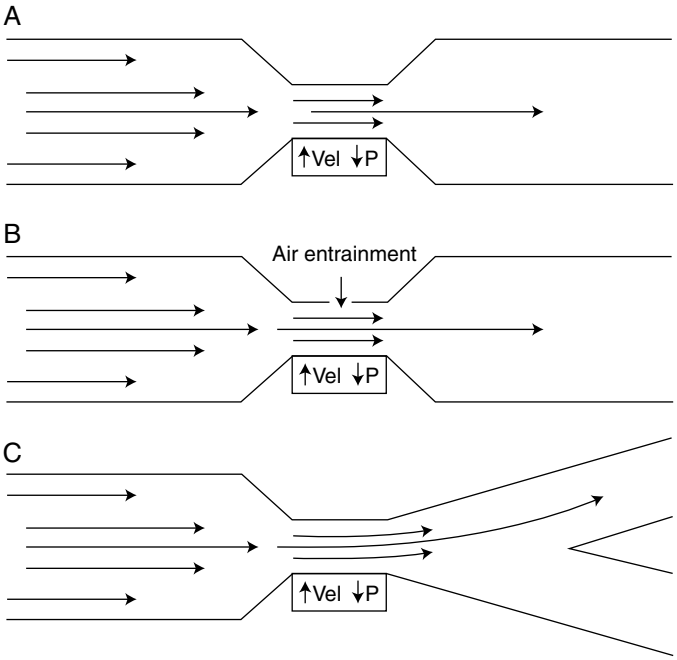

FIGURE **14-23** **A,** Bernoulli principle; **B,** Venturi effect; **C,** Coanda effect. *Vel,* Velocity; *P*, pressure.

the tube (pressure). Thus velocity increases and pressure drops to maintain conservation of energy.

Metered-dose inhalers (MDIs) use the Bernoulli principle to create a jet past a constriction that aerosolizes a drug in the expanding flow of gas. The necessity for large and sometimes cumbersome equipment is obviated by MDIs, which are able to consistently deliver aerosolized particles of medication into a fluid stream.[55] A more applicable example of the Bernoulli principle is the advantage taken of the pressure drop across the narrowing in a tube of fluid flow. The Venturi effect relies on the lower pressure at a constriction to entrain air or fluid into a fluid path.

Venturi Effect

The Venturi effect (Giovanni Battista Venturi, 1746-1822) utilizes the pressure drop across a narrowing in a tube. By placing an orifice at the narrowed region of flow, air is allowed to be entrained and enter the flow (see Figure 14-23, *B*). Air may be entrained into a flow of liquid, or a liquid may be entrained into the flow of a gas.[56] Jet ventilation uses this entrainment of air to augment lung ventilation volumes.[57-59] Nebulizers use the Venturi effect to deliver both humidification and medications such as albuterol.[60] Nebulizers effectively deliver medications into fluid paths, such as ventilator circuits, but have been replaced to a large extent by MDIs.

Coanda Effect

The Coanda effect (Henri Coanda, 1885-1972) explains the tendency of a fluid flow to follow a curved surface upon emerging from a constriction (see Figure 14-23, C). This may cause a preferential flow in one tube at a bifurcation just past a narrowing in a tube.[61] Beyond a narrowing in a tube, pressure will increase corresponding with a decrease in velocity of the fluid flow. If at a widening in a tube there is a division of flow with different angles, the return to a higher pressure will be at different points along the bifurcated tube. The bifurcated tube with the delayed reestablishment of higher pressure (and corresponding lower velocity) may preferentially attract a greater percentage of the total flow toward its path. The path with the greater flow will be at the expense of the other path. In situations in which the flow is blood in vessels or gas flow in the lungs, this diversion of flow could be consequential.[62-64]

Laplace's Law

Laplace's law (Pierre Simon Laplace, 1749-1827) describes the relationship of wall tension (**T**) to pressure (**P**) and radius (**r**) in cylinders and spheres.

- Cylinders: $T = Pr$
- Spheres: $2T = Pr$

Tension is a stress force exerted over a given area. It is measured in newtons per centimeter (N/cm). In cylinders, wall tension is increased with increased radius; similarly, increasing pressure will increase wall tension.[65] Laplace's law shows why smaller-diameter capillaries do not burst during periods of hypertension and larger vessels or aneurysms may. An abdominal aorta maintains a mean arterial pressure along its length, including an aneurysm if present. Aneurysms, which have a greater radius than the rest of the aorta, have a corresponding greater tension and are more likely to rupture. Laplace's formula, when rearranged, reflects the direct relationship of tension to radius in both the aorta and an aortic aneurysm at a constant pressure.

$$P = \frac{T}{r}$$

Example 1—Cylinders: If the mean aortic pressure is 100 mmHg with a normal radius of 2 cm and an aneurysm radius of 4 cm, the tension calculates as follows:

$$Pr = T$$

1. Normal aorta: 100 mmHg (P) × 2.0 cm (r) = (T)
   1.33 N/cm^2 (100 mmHg) × 2.0 cm = 2.66 N/cm
2. Aortic aneurysm: 100 mmHg (P) × 4.0 cm (r) = (T)
   1.33 N/cm^2 (100 mmHg) × 4.0 cm = 5.32 N/cm

The aortic aneurysm in this example has twice the wall tension of the normal aorta. (Millimeters mercury were converted to newtons in the formula). Any increases in blood pressure will increase the already high wall tensions of an aneurysm, and wall failure may result in dissection or rupture.[66]

In spheres, wall tension is increased twice as much, with increasing radius compared to cylinders. Applying Laplace's law to saccular aneurysms shows the relationship of increasing tension with increasing radius:

Example 2—Spheres: If the mean saccular aneurysm's pressures are 100 mmHg, with one radius 0.5 cm and the other 1 cm, the tension for each calculates as follows:

$$Pr = 2T$$

1. Small saccular aneurysm:

$$100\ \text{mmHg (P)} \times 0.5\ \text{cm (r)} = (2\ T)$$
$$1.33\ \text{N/cm}^2 (100\ \text{mmHg}) \times 0.5\ \text{cm} =$$
$$2 \times 0.665\ \text{N/cm} = 1.33\ \text{N/cm}$$

2. Large saccular aneurysm:

$$100\ \text{mmHg (P)} \times 1.0\ \text{cm (r)} = (2T)$$
$$1.33\ \text{N/cm}^2\ (100\ \text{mmHg}) \times 1.0\ \text{cm} =$$
$$2 \times 1.33\ \text{N/cm} = 2.66\ \text{N/cm}$$

Greater wall tension would be present in a large saccular aneurysm versus a small saccular aneurysm, and any increases in pressure would risk further increases in wall tension and rupture. Decreasing pressure will have the effect of decreasing wall tension across both cylinders and spheres and is the rationale for controlling blood pressure in patients with aneurysms.[67]

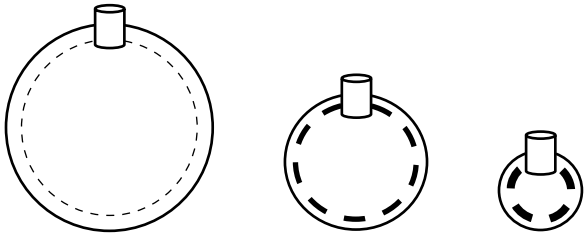

FIGURE **14-24** Increased surfactant concentration *(dashed line)* with decreasing alveolar size.

Laplace's law applied to a cardiac ventricle of increasing size explains the necessary inotropic response but eventual failure of contractility with increasing wall tension and pressure:

$$Pr = 2T$$

Increased pressure = Increased wall tension
Increased radius = Increased wall tension
Increased wall tension = Increased contractility (Frank-Starling curve)

Surfactant is a substance that lowers surface tension in alveoli to prevent the effects observed with Laplace's law. By lowering surface tension, the pressure in alveoli is lowered. Surfactant lowers surface tension more in smaller alveoli than in larger alveoli, owing to the effect of concentration when an alveolus contracts.[68] Greater surfactant concentration has greater surface tension–lowering ability. Surfactant therefore has the ability to equilibrate surface tension among different-sized alveoli and create stabilized alveolar pressures (Figure 14-24).

WAVES

Waves are a very important phenomenon in everyday life, as well as in anesthesia. Waves exist macroscopically, such as ocean waves and sound waves. They also exist within the atom and as light energy. Waves surround us and exist within us. To understand waves and wave action is to hold one key to understanding the basic ripple that permeates the universe. That basic ripple is energy. Waves are a periodic disturbance or motion. Waves are essentially the movement of energy. The "disturbance" is energy, and that is what is transported, or moved, along the wave front.

Wave Types

The two basic types of waves are transverse and longitudinal. *Transverse waves* are composed of up-and-down movement. In a transverse wave, the medium particles move perpendicular (up and down) to wave direction. *Electromagnetic radiation waves are transverse*. *Longitudinal waves* are composed of back-and-forth movement along the direction of the wave. In a longitudinal wave, the medium particles move forward parallel to the wave direction (propagation). There is no up-and-down motion in longitudinal waves. The wave energy causes only compression and decompression (rarefaction) to occur along its path. These are pressure fluctuations. *Sound waves are longitudinal.*

Wave characteristics:

- *Frequency*—Waves per second; measured in cycles per second called *hertz* (Hz)
- *Wave length*—Distance from one wave top (crest) to the next
- *Period or phase shift*—Describes how far the wave "slides"
- *Amplitude*—Height of wave
- *Speed*—Measured in meters per second
- *Wave part*—Crest is the wave top, trough is the wave bottom
- *Pressure waves*—Can be reflected, refracted, diffracted, or absorbed (interfered) by other waves
- *Reflection*—Waves reflect off of a medium in the same but opposite angle. The angle of incidence is the angle at which a wave strikes a medium.
- *Refraction*—Redirected in a new direction by contact with a new medium
- *Diffraction*—Spread or scattered; bending around an object
- *Absorption or interference*—Waves may interfere with other waves or be absorbed by matter. When waves interfere, amplitudes are additive. Constructive interference is when the *crest* of one wave passes through the *crest* of another wave or the *trough* of one wave passes through the *trough* of another wave, and the resultant wave is greater. Addition of two positive amplitudes or two negative amplitudes is a greater value or wave height. Destructive interference is when the *crest* of one wave passes through the *trough* of another wave. Amplitudes from one crest are added to the negative amplitudes from the other wave's trough, and the resultant wave is less.

Pressure Waves (Sound Waves)

Sound waves are pressure fluctuations that deviate from ambient pressure and are measured in pascals (Pa). Sound pressures are measured on a sound pressure level (SPL) that uses a logarithmic decibel scale to narrow the wide range (20 Hz to 20 kHz) of amplitudes audible to the human ear. Sound waves are longitudinal waves that propagate through matter (solid, liquid, gas) at varying speeds determined by the medium's elastic modulus (stiffness), density, and temperature. The speed of sound through air at 0° C is 740 miles per hour. In the absence of matter, there are no sound waves. Sound waves do not exist in a vacuum and only travel through matter.

Ultrasonography. Sound waves above the auditory limit of the human ear (20 kHz) are known as *ultrasound*. Ultrasonography uses ultrasound waves to construct a visual image of internal structures by examining the reflection of sound. Ultrasonography is useful for assisting simple procedures such as intravenous catheter insertion or for more invasive diagnostic assessment such as transesophageal echocardiography.[69-73] Ultrasonography uses a signal generator that transmits sound waves through tissues and a transducer to record the time delay for the returning reflected sound waves. The speed of sound waves in tissues is unique and constant to specific tissue compositions, and therefore the time delay of the returning reflected sound waves allows calculation of the location of different internal structures. Not all sound waves are reflected back to the transducer; some sound waves will have been refracted in a new direction, diffracted in multiple directions, or interfered with by tissues that cause attenuation or conversion to heat and resultant dissipation. The fraction of the original signal that is reflected back to the transducer must be amplified and processed into a visual display. The introduction of ultrasonography has been made possible by piezoelectric crystals that act as both signal generators and signal transducers (see Piezoelectric Effect). The process of a burst of ultrasound pressure waves followed by measurement of the reflected waves is done many times a second, permitting real-time imaging of internal structures by computational analysis.

Piezoelectric Effect. Piezoelectric crystals are unique quartz, ceramic, or polymer compositions that contain a matrix of polarized molecules that (1) respond to electric current by changing shape and (2) respond to mechanical stresses by generating an electric current. Piezoelectric crystals derive their name from the

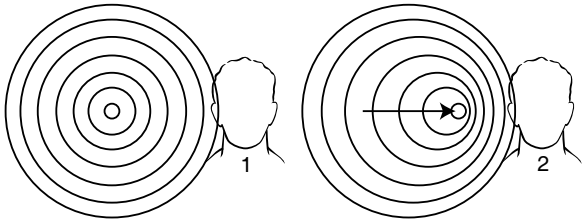

FIGURE **14-25** Doppler effect.

Greek prefix *piezein*, which means "to press tight or squeeze." The shape change caused by an electric current creates a pressure fluctuation around the crystal; this is a pressure wave. If a piezoelectric crystal is subjected to an alternating electric current, it will vibrate, creating many pressure waves in quick succession. The rate at which the crystal vibrates is called its *resonant frequency*. When not responding to an electric current, piezoelectric crystals are at rest and respond to the mechanical stress of the pressure waves by creating a small electric current.

Doppler Effect. The Doppler effect (Christian Johann Doppler, 1803-1853) describes the change in frequency of a propagated wave from a moving object. The sound of a siren changes to a higher frequency as it approaches a listener and lowers in frequency as it departs. Listener 1 in the Doppler effect figure (Figure 14-25) will hear a sound emitted from a stationary object with a fixed frequency. Listener 2 will hear a sound emitted from a moving object with increasing frequency as the sound approaches and lessening frequency when it passes. This is due to the "stacking up" of the wave fronts emitted from an approaching object and the stretching of the wave fronts when it recedes.

The Doppler effect when applied to echocardiography allows the determination of blood flow direction and speed. As blood cells flow to or away from an ultrasound signal, reflected waves are either compressed or expanded. This change in frequency allows calculation of blood velocity:

$$V = \frac{\Delta f}{\cos\theta} \times \frac{c}{2f_t}$$

where velocity of blood is **v,** Δ**f** is the difference in transmitted frequency and received frequency, $\mathbf{f_t}$ is the transmitted frequency, **c** is the speed of sound in blood, and $\boldsymbol{\theta}$ is the angle of incidence between the ultrasound beam and blood. Spectral display presents Doppler ultrasound data in a time-velocity graph that allows greater assessment of hemodynamics on a beat-to-beat basis.

Electromagnetic Waves

The term *electromagnetic* succinctly expresses the dual nature of *electricity* and *magnetism*. The two are intimately intertwined. Where there is electric current, there are also magnetic waves. Where there are changing magnetic waves, there is also an electric current. Electromagnetic radiation is composed of two waves, electric and magnetic, oscillating in unison but perpendicular to one another. The whole electromagnetic wave propagation is perpendicular to these oscillating waves. Electromagnetic waves possess both electric and magnetic potential. Electromagnetic waves (electromagnetic radiation, EMR) are similar to pressure waves in that they both possess frequency and amplitude. Another similarity is that they may be reflected, refracted, diffracted, or absorbed. The unique wave properties of EMR include its composition, velocity, and independence of transport by matter. Electromagnetic radiation differs from pressure waves (sound waves) in their velocity. The speed of EMR in a vacuum is 3×10^8 m/sec (186,000 miles/sec), whereas sound cannot exist in a vacuum. The speed of

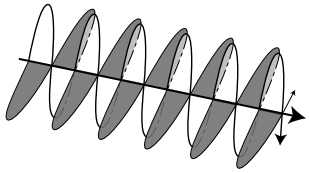

FIGURE **14-26** Electromagnetic wave showing electric wave oscillating perpendicular to magnetic wave.

TABLE 14-6 Comparisons of EMR and Sound Wave Properties

	EMR	Sound Waves
Speed	300,000,000 m/sec	344 m/sec
Wave type	Transverse	Longitudinal
Energy motion	Perpendicular to propagation	Parallel to propagation

EMR, Electromagnetic radiation.

EMR in air closely approaches 3×10^8 m/sec. The speed of sound in air is only 331 m/sec (740 miles/hr). Electromagnetic radiation and sound waves may travel through matter at varying speeds, but only electromagnetic radiation can propagate independently of matter. Sound waves only travel through matter and cannot exist in a vacuum, as shown in Figure 14-26 and Table 14-6.

Inverse Square Law

Waves represent a propagation of energy from a source. As energy moves away from its source, its strength decreases. Newton showed that the strength of the emanating energy is inversely proportional to the square of its distance from its source. Newton originally calculated this for the force of gravity; however, it has application throughout physics.[74]

$$I1 = \frac{(d2)^2}{I2\ (d1)^2}$$

where **I1** equals intensity at the original distance, **I2** is the lower intensity at a new distance, **d1** is the distance from original source, and **d2** is the new distance from the source. This is represented by the inverse square law figure (Figure 14-27), where the y plane is twice the distance from the source than is plane *x*. The energy intensity at I2 is one fourth the intensity at I1. The inverse square law applies to pressure waves, electricity, light, and radiation, with the intensity of each decreasing with increasing distance from its source.

Magnetism

Magnets are unique matter that have charges aligned in an orderly fashion. There are flows of magnetic currents, or field lines, in all magnets. To observe these invisible fields, place a magnet under a piece of paper and spread iron filings on top. The filings will line up along the magnetic fields. Magnetism is a force between electric currents. Flowing charged particles not only move energy along that current but also disrupt, or alter, the surrounding environment. This "altering" is not apparent unless one is looking for it. Hold a compass near a wire carrying an electric current. The needle will move and align itself along the flow of magnetism. Turn the wire, and the compass needle will turn. There is a force between the electric current and the compass needle (magnet). Magnetic fields are measured with a gauss meter in units of teslas; 10,000 gauss (G) equal one tesla (T). The earth's magnetic field

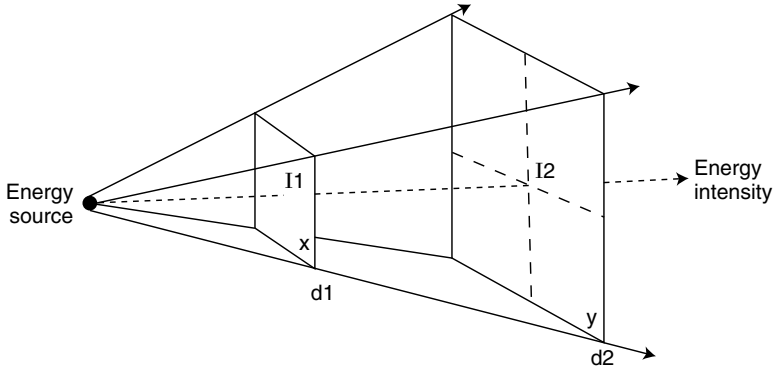

FIGURE **14-27** Inverse square law representation of decreasing intensity with increasing distance.

strength is 0.00005 T (0.5 G). A small magnet's strength is 0.01 T (100 G). The magnet's strength in a magnetic resonance imaging machine is 1 to 3 T (10,000 to 30,000 G).

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) uses a strong, continuous magnetic field to uniformly realign the spin of protons within the hydrogen atoms of water. As the axes of protons are pulled into one of two possible positions of realignment, a radiofrequency pulse is delivered at resonant frequency to energize the protons. The protons will then reemit this energy. The radiofrequency pulses are delivered in thin "slices" that may be made in the sagittal, coronal, or axial planes. Computer-generated analysis of data produces very detailed representations of internal tissues. The magnetic field used is very strong, and specific safety considerations need to be addressed when delivering anesthesia care in an MRI suite.

MRI Safety. Because of the high strength of the magnetic field in and around an MRI scanner, special precautions must be observed. Any ferrous material will interact with the magnetic field, gaining kinetic energy and thermal heat. Movable ferrous objects will also be attracted to the MRI magnet and will be pulled into the magnetic field with great force. Patients and personnel are at potential risk for both thermal injuries from implanted ferrous objects and traumatic injury from ferrous objects violently pulled into the magnetic field. The American College of Radiology has designated four safety zones that surround an MRI scanner, with zone 4 representing the immediate area around the scanner. Zone 4 poses the greatest risk of injury and has the most stringent guidelines.[75] All ferrous materials such as pagers, phones, jewelry, identification badges, and pens must be removed before entering zone 4. Patient stretchers, oxygen tanks, IV poles, and any other ferrous objects must be kept outside zone 4. Specially designed stretchers and anesthesia machines are designated for zone 4 to prevent attraction to the magnet.

Implanted ferrous materials such as ferrous foreign bodies, prosthetics, stents, and pacemakers have been studied for MRI safety. Review of current literature for acceptability for scanning is recommended.[75-78] Many implanted devices can be safely scanned in an MRI, and any knowledge or concerns of potential ferrous interaction should be brought to the attention of the designated MRI personnel.[75]

Electricity

Electricity is the change in potential energy caused by the movement of electrons from an area of high concentration (high charge density) to an area of low concentration (low charge density). The fundamental unit of charge is ***e***; it represents one electron's energy and is extremely small. Dealing with the energy of a single electron is difficult, so we use a quantized measurement called a *coulomb* (C): C = 1.6022210^{19} ***e***.

Coulomb's Law

Coulomb's law (Charles-Augustin de Coulomb, 1736-1806) states that like charges repel each other, and opposite charges attract each other inversely to the square of their distance. In short, opposite charges will attract more when closer together, and like charges will repel more when closer together. The electrical potential energy unit is the *volt*. It represents electrical "pressure" or the gradient of charges that could potentially flow. Electric current (I) is the rate of flow of an electric charge through a *conductor*. In operating room electrical equipment, the conductor is usually copper wire. Copper is a good conductor, and therefore the resistance to flow is low. Insulators, also known as *dielectrics*, do not have electrons that are easily moved and therefore resist the flow of electricity. Current is measured in amperes. An *ampere* (A) is the flow of 1 coulomb per second, 1 A = 1 C/s. A *volt* is the SI unit for a joule per coulomb.

Ohm's Law

The potential flow of electric charge is proportional to actual current, after accounting for resistance. Resistance is calculated by Ohm's law (Georg Ohm, 1789-1854):

$$E = IR$$

where **E** represents volts (V) or potential energy, **I** is current, and **R** is resistance. Resistance is measured in ohms (**Ω**). Ohm's law measures resistance to electrical flow (Figure 14-28).

Electrical Flow

The flow of electrons in electricity is from a surplus of electrons to a deficiency of electrons. Electricity must have a complete circuit for electrical flow to occur. A simple circuit is shown with a positive side (live, hot), a negative side (neutral), and a ground. The ground is a conductor that is connected to the earth (ground) and provides a low, resistive, alternate route for electricity to flow in the case of electrical surge. Electricity may be *direct current* (DC) or *alternating current* (AC). In DC circuits, the flow of electrons is always in one direction. In AC circuits, the flow of electrons reverses direction (alternates) at a set frequency, usually 60 Hz (United States) or 50 Hz (Europe) (1 *Hz* equals 1 cycle per second). Electricity is delivered by the power company as AC because its voltage can easily be maintained while traveling long distances to customers via the power grid. Operating

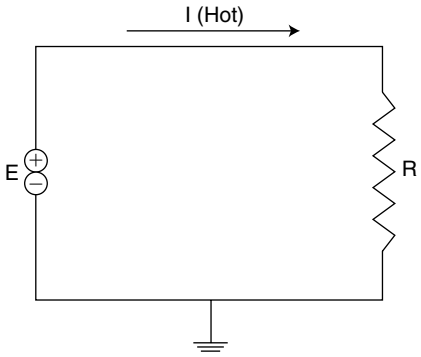

FIGURE **14-28** Basic electric circuit showing a live (hot) wire (*I = current*), a load (*R = resistance*), and a grounded neutral wire (*E = volts*).

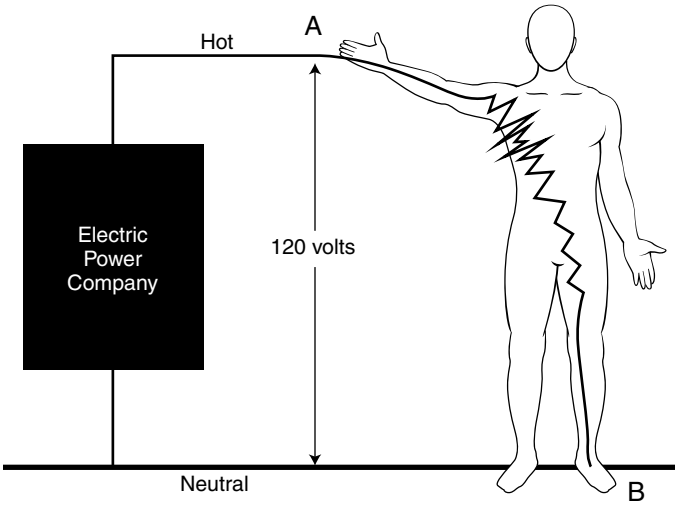

FIGURE **14-29** Electric shock. *A* is point of contact and *B* is connection to ground.

room equipment and most residential and institutional electrical equipment operate on AC. A simple AC circuit is the same as a simple DC circuit, except resistance is more complex with AC circuits, and the positive side alternates between both wires. In AC circuits, resistance is called *impedance* and is the total of all forces that impede electrical flow. In addition to the inherent characteristics of the conductive material, capacitance and inductance contribute to AC impedance. *Capacitance* is the capacity to store charge. A capacitor is composed of two parallel conductive plates separated by an insulator. When a capacitor is exposed to a voltage source in an open circuit, one plate will store a positive charge, and the other will store a negative charge. Capacitors have useful application in electronic devices but have the ability to leak *stray capacitance*. There are no absolute insulators, and stray capacitance may create an unintended charge in the casing of electrical equipment. *Electromagnetic inductance* is the transfer of an electric current between circuits without physical contact, using induced magnetic waves. Any conductors carrying an electric current will also carry a magnetic field. In AC circuits, the charge is alternating and so too will the magnetic field change. This changing magnetic field may induce a small electric current in nearby conductive materials such as equipment metal casings, despite no physical contact between the circuit and the casing.

Electric Shock. Stray capacitance and inductance may contribute a low risk of shock because they are low current flows. Direct contact of exposed electrical wiring constitutes great risk of electric shock because of higher voltages. Current leakage from wires to equipment casing exposes patients and operating room personnel to the risk of shock by three mechanisms:

1. Direct wire contact with metal casing due to insulation damage or faulty construction
2. Inductance due to the flowing alternating current's magnetic field, producing a small electrical flow in the surrounding metal casing despite no direct contact
3. Stray capacitance from the buildup of electrical potentials with an alternating current circuit despite no closed circuit electrical flow[79]

If a patient or operating room personnel make contact with both a live wire and ground they may complete an electric circuit and receive a shock. For a shock to occur, a complete circuit must be made. This can happen if a person is standing on the earth and contacts the live wire in a circuit (Figure 14-29). Shocks may be macroshock or microshock. *Macroshock* refers to large amounts of current conducted through the patient's skin and other tissues. Injuries may be minor or severe, depending on amount of current and duration of exposure. Electric current seeks the path of least resistance and is often dissipated throughout the body tissues. The amount that reaches the heart is often insufficient to cause arrhythmias.

TABLE **14-7** Effects of Macroshock and Microshock

Macroshock (mA)	Effect
1	Perception
5	Maximal harmless current
10-20	"Let-go" current
50	Loss of consciousness
100-300	Ventricular fibrillation
6000	Complete physiologic damage
Microshock (μA)	**Effect**
20	Ventricular fibrillation in dogs
100	Ventricular fibrillation in humans[53]

Conductive materials in a patient's body, though, may place that patient at greater risk by providing a low resistive path for electricity to flow to the heart. *Microshock* is the delivery of small amounts of current directly to the heart. The amount of current that may produce ventricular fibrillation has been found to be 50 microamperes or lower.[80,81] Table 14-7 gives a comparison of how different levels of microshock and macroshock affect the human body.

Electrical Safety. To decrease the risk of shock, operating room electrical systems are isolated from the main grounded electrical supply system. A *transformer* is used to isolate the electrical supply systems from one another. A transformer uses the principle of magnetic inductance to transfer electricity from one system to another system without having physical contact. This allows the operating room power supply to be ungrounded, preventing a circuit from being completed when a person contacts one live wire. However, if a person contacts both wires in a circuit, shock may occur as the path of electricity flows through the person from one line to the other. Operating room equipment casing (housing) is grounded to divert electrical flow in case of internal live wire contact with the metal housing.

If there is contact of the live wires to ground (fault), such as through touching the equipment casing, the system will become

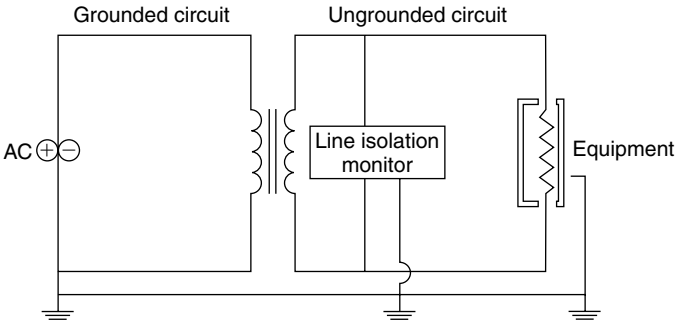

FIGURE **14-30** Ungrounded operating room electric circuit isolated from grounded hospital electrical system. Note that electrical equipment casing and line isolation monitor are connected to ground, but the electric circuit is not.

a grounded system. A second fault will enable a shock, because the newly grounded system will allow a completed circuit to pass through a person in the operating room that is grounded when a live wire is contacted. To prevent a first fault from being unnoticed, a *line isolation monitor* is placed between the live wires and ground to measure their impedance to flow (Figure 14-30).[82] If a live wire has contact or high capacitance to ground, the line isolation monitor will alarm. Line isolation monitors are usually set to alarm at 2 to 5 mA potential leak. If a line isolation monitor alarms, the last equipment plugged in should be disconnected and inspected to verify it is the offending piece of equipment. Equipment that activates a line isolation monitor may still be operational but increase the potential risk of shock should a second fault occur, because it has converted the isolated power supply system to a grounded system. Line isolation monitor alarms may also be activated because of the cumulative effect of minor leakages of many pieces of properly functioning electrical equipment. This does not mean a risk is present. Newer systems alarm at 5 mA to account for this normal leakage.

Electrocautery

Electrocautery devices use high-frequency electric currents to cauterize, cut, and destroy tissue. These devices may be unipolar or bipolar. Bipolar electrocautery devices have two tips, one to supply the electric current and the other to return the current. Bipolar devices do not require a return electrode and are less likely to cause burn or injury apart from the local area of use. Unipolar devices have only one tip to deliver an electric current, and a large-surface-area return electrode with good conductive contact must be placed on the patient. The path of current flow from the unipolar device to the return electrode should not cross the patient's heart.

The high current flows used in electrocautery units may cause electromagnetic inductance, which in turn may cause artifact in other electrical equipment such as ECG monitors. Pacemakers may also sense the electromagnetic inductance as inherent electrical activity and not initiate a paced impulse. This would put the patient at risk for asystole if there is no inherent underlying heart rhythm.[83] Electrocautery interference has also been documented as initiating paced tachycardic rhythms.[84,85] Placing a pacemaker magnet over the patient's pacemaker resets it into a continuous, asynchronous mode. Not all pacemakers are reset into a continuous, asynchronous mode, and pacemaker interrogation to understand its settings and functions should be considered prior to surgery using electrocautery.

QUANTUM PHYSICS

ELECTROMAGNETIC RADIATION

Newtonian physics is helpful in describing the wavelike properties of EMR but is incomplete in its description. Originally it was assumed that EMR, like sound waves, was propagated through a medium. A "luminiferous ether" was thought to fill the universe and was the suspected medium through which EMR traveled. The famous Michelson-Morley[86,87] experiment successfully disproved the existence of the "ether" but left open an explanation of how EMR propagates. Max Planck (1858-1947) later theorized EMR was *quantized*, meaning it was emitted only in discrete quantities of energy, and this revolutionized our perspective of the universe. Planck's constant expresses the quantized nature of EMR defined by energy, time, and frequency:

$$E = h\nu$$

where **E** represents energy, **h** is Planck's constant (6.626068×10^{-34} m^2 kg/sec), and ν is frequency.[88] Albert Einstein introduced the photon concept of Planck's discrete energy quanta and together with others ushered in the study of quantum mechanics.[89,90] Quantum mechanics is a branch of physics that explores the subatomic dynamics of pure energy and the quasi-realm of energy/mass transition.

Electromagnetic radiation is now thought to travel as photons or packets of energy and can be observed as both a particle and a wave, depending on how scientists study and measure it. The dual nature of behaving as both a particle and a wave is unique to EMR.[91] EMR is called a *photon* when it exhibits particle-like behaviors. Despite its behavior, photons have no mass. They are pure energy. The energy of EMR is directly related to its frequency. Higher frequencies correspond to higher energies, and lower frequencies correspond to lower energies. The velocity of EMR in a vacuum remains constant and does not change related to frequency. The understanding of energy as a quantized event promoted numerous advances in physics, which ultimately found application in anesthesia. The perspective of EMR as photons allows us to better explain many dynamic interactions of EMR and matter. Figure 14-31 shows the EMR spectrum.

ELECTROMAGNETIC RADIATION/MATTER INTERACTION

Electromagnetic radiation exists independently of matter. Sound (pressure) waves do not exist without matter through which their energy is transmitted. Both may be reflected, refracted (scattered), diffracted (redirected), or absorbed (interfered) by matter (Figure 14-32). An example of the interaction of EMR with matter is visible light. Visible light is composed of a narrow band of EMR frequencies between 4.3×10^{14} and 7.5×10^{14} (400 to 700 nm). These frequencies of EMR are the only frequencies our eye receptors can detect. When we "see" a color, we see the reflected frequencies that correspond to that color. Visible light is composed of the colors red, orange, yellow, green, blue, indigo, and violet and were first described by Newton. Visualizing the color blue represents the reflected EMR frequencies between 495 and 570 nanometers. The other visible light frequencies are not seen, because they have been absorbed and scattered by the material that appears blue. Materials that absorb EMR increase their vibration energy (kinetic energy), owing to their absorption of energy. We experience an example of this when wearing white or black clothing in sunlight. Black clothing absorbs many more frequencies of visible light and gains greater kinetic energy, which causes heat. White clothing appears white because of the high reflection of the visible light spectrum; it gains less kinetic energy and therefore less heat.

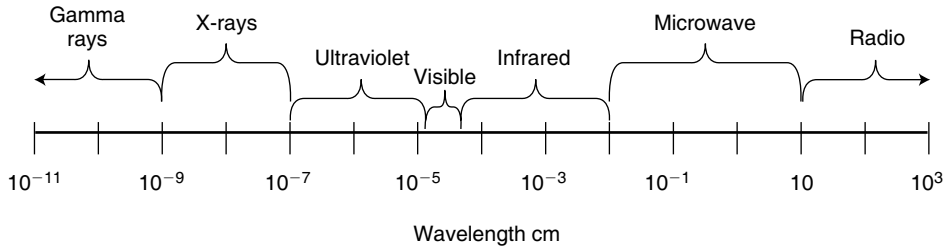

FIGURE **14-31** Electromagnetic radiation spectrum. Increasing energy associated with decreasing wavelength (increasing frequency) along the electromagnetic radiation (EMR) spectrum is shown. Example: X-rays possess shorter wavelengths, greater energy, and greater ability to permeate matter than microwaves, which have longer wavelengths and lower energy.

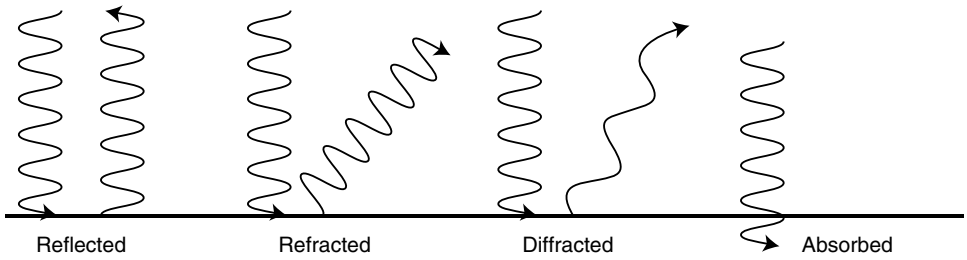

FIGURE **14-32** Electromagnetic radiation interactions with matter.

The phenomenon of matter reflecting, scattering, and absorbing specific EMR frequencies has many applications in health care, anesthesia in particular.

Electromagnetic radiation may also be converted into other forms of energy such as electricity (gas discharge), heat (incandescence), and chemical energy (photoluminescence) but must obey the law of conservation of energy. When matter is exposed to EMR, it too may change form. The analysis of EMR's interaction with matter is the underlying principle of x-ray fluoroscopy, anesthetic gas measurement, pulse oximetry, and lasers.

RADIOGRAPHY

X-Rays

X-rays are able to pass through different organic materials to varying degrees and allow the "photographic" imaging of internal structures. Though x-ray and fluoroscopic imaging offer great medical benefit, they also possess potential for great harm. X-rays are ionizing radiation and lie in the higher-energy frequencies of the electromagnetic radiation spectrum (see Figure 14-31). They possess high energy and have the ability to ionize atoms and molecules. X-rays can cause DNA damage and be mutogenic.[92] Proper protection is imperative for health care personnel when working near or with x-rays. Safety lies within the three factors of distance from source, barriers, and exposure time. The inverse square law explained how energy intensity significantly decreases with distance from its source.[93] X-rays obey this law, and the minimum recommended distance from an x-ray source is 6 feet. The greatest intensity of an x-ray is directly in front of the beam generator. Standing at least 6 feet away and behind or to the side of the beam direction lessens exposure. Although the energy intensity of x-rays decreases significantly with greater distance from the source, proper shielding is also important. Lead barriers are efficient absorbers of x-ray energy, and lead aprons and thyroid shields should be worn. X-ray technicians often wear badges that measure total exposure to x-rays over a period of time. Greater exposure to x-rays is associated with greater risks. Institutional policies establish guidelines of exposure limits. Unless practitioners are exposed to radiographic procedures frequently, the doses received usually fall well below established limits for maximal allowable exposure. Shielding and distance from the x-ray source remain the two most important factors within the control of the practitioner.

GAS ANALYSIS

Gas analysis technologies use several methods to measure organic and inorganic gases. The methods described herein focus on the technologies prevalent in the field of anesthesia. The gas analysis technologies in Box 14-1 show the most common technologies for analysis of anesthetic gases, oxygen, and carbon dioxide.

Organic and Inorganic Anesthetic Gas Analysis

Infrared Absorption Analysis

Infrared absorption analysis uses each anesthetic gas's ability to absorb specific frequencies of EMR in the infrared spectrum. A sample of a gas or mixture of gases is subjected to a known range of infrared frequencies. The frequencies lost due to absorption are measured, and identification of the gas or gases may be made by the specific frequencies each gas absorbs. Anesthetic agents' infrared absorptions are unique but close in frequency. Newer infrared absorption analysis monitors are capable of identifying specific agents without preprogramming the specific agent. Concentration is determined by the amount of infrared absorption (Figure 14-33).

Raman Scattering Analysis

The interaction of electromagnetic radiation with matter is the underlying principle used with Raman scattering analysis of gases. Raman scattering passes a monochromatic laser beam through a gas mixture, causing an increased vibration frequency of the excited gas molecules (Figure 14-34). A laser is a high-intensity beam of a known specific EMR frequency (see laser discussion in this chapter). When this laser beam interacts with an anesthetic gas molecule, it may be absorbed, as previously described with infrared absorption analysis, or it may be scattered. Scattering is a frequency change (energy change) of the initial laser beam after it interacts with gas molecules. The laser frequency interacting with

BOX **14-1**

Organic and Inorganic Anesthetic Gas Analysis Technologies

Organic and Inorganic Anesthetic Gas Analysis
- Infrared absorption analysis
- Raman scattering
- Mass spectrometry
- Piezoelectric analysis
- Interferometric refractometry
- Gas-liquid chromatography

Oxygen Analysis
- Electrogalvanic cell (fuel cell)
- Polarographic electrode (Clark electrode)
- Paramagnetic oxygen sensor
- Fluorescence quenching
- pH optode

Carbon Dioxide Analysis
- Infrared absorption analysis
- Severinghaus P_{CO_2} electrode
- Fluorescence quenching
- pH optode

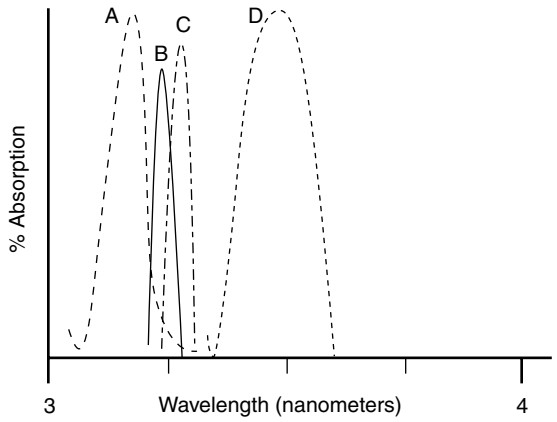

FIGURE **14-33** Individual anesthetic gas infrared absorption spectra (representation only, not actual).

the molecules may be scattered at higher or lower frequencies. Each anesthetic gas scatters laser frequencies uniquely. Analysis and identification of a gas or gas mixture may be made by comparing the gas sample scattering spectrum to that of known gas-scattering spectrums. The scattered frequencies measured in this spectral analysis are represented as Stokes lines.

Raman scattering technology requires only that a gas molecule be polyatomic for identification. Raman scattering analysis can identify oxygen, carbon dioxide, nitrogen, nitrous oxide, and all volatile anesthetics, including mixtures of volatile anesthetics.[94] Helium cannot be analyzed by Raman scattering. Raman scattering analyzers return the sample to the patient circuit and therefore do not need waste-gas scavenging. Raman scattering analyzers are small and portable but require calibration. They are less accurate with pediatric cases, which use high carrier gas flow rates and small tidal volumes.

Mass Spectrometry

Mass spectrometry historically has been the dominant technology for anesthetic gas analysis, though it has increasingly been replaced by more portable and efficient infrared absorption analysis and Raman scattering analysis technologies. Mass spectrometry ionizes gas molecules and passes them through a magnetic field. The gas molecules with the lowest mass-to-charge ratio are easily deflected by the magnetic field and collected by an ion detector (Figure 14-35). Ionized gas molecules with higher mass-to-charge ratios are deflected less by the magnetic field and detected by other ion detectors. Identification of a gas is based on the amount of deflection.

Piezoelectric Gas Analysis

Piezoelectric gas analysis incorporates both the piezoelectric effect and Henry's law.[95-97] A piezoelectric crystal will vibrate at a set frequency when an electric current is applied to it. A vibrating piezoelectric crystal coated with a liquid solution will alter its resonant frequency when exposed to a gas. As a gas dissolves into the liquid, in proportion to its concentration above the liquid gas interphase, the resonant frequency of the crystal is altered. The degree of frequency change is proportional to the concentration of gas that dissolves into the liquid. The amount of gas that dissolves into the piezoelectric crystal's liquid coating is directly related to the partial pressure of that gas. This is explained by Henry's law.

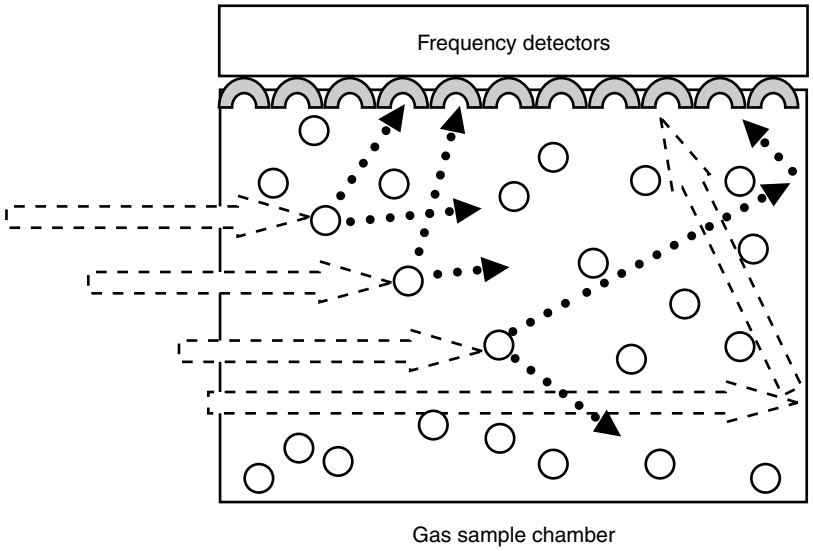

FIGURE **14-34** Raman scattering gas analysis technology.

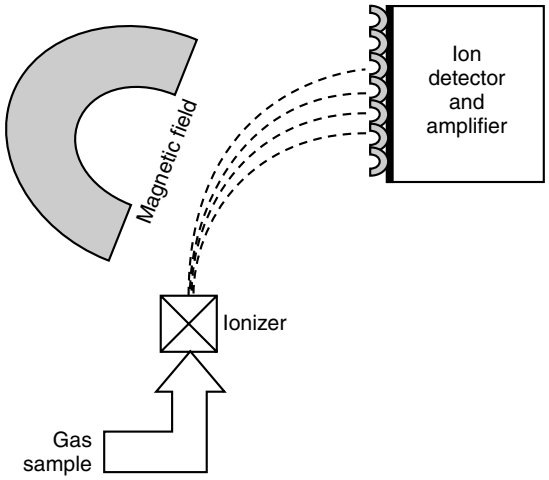

FIGURE **14-35** Mass spectrometry gas analysis technology.

A drawback of this technology is that it does not identify the specific anesthetic agent.[98]

Photoacoustic Gas Analyzer

The photoacoustic gas analyzer subjects a gas sample to a filtered, pulsating infrared light beam in a closed chamber. The pulsating beam causes the gas molecules to increase then decrease in temperature. The increase and decrease in temperature causes the chamber pressure to increase and decrease according to Gay-Lussac's law. Microphones along the chamber measure the pressure waves. A photoacoustic gas analyzer can measure anesthetic gases, mixtures of these gases, and carbon dioxide.[99] The units are small, portable, and accurate.

Oxygen Analysis

The primary role of oxygen in biological systems underscores the importance of identification and measurement of this gas when delivering anesthetics. Purposeful redundancy is used in oxygen measurement, often with more than one technology being used at a time. In the practice of anesthesia, oxygen content analysis is accomplished with several technologies. These technologies take advantage of oxygen's unique physicochemical properties and interaction with EMR. The most often used technologies pertaining to anesthesia practice are reviewed below.

Electrogalvanic Cell (Fuel Cell) Electrochemical-Oxygen Analyzer

The electrogalvanic cell (Figure 14-36) is also called a *fuel cell* because the reaction that takes place creates its own electric current by consuming its "fuel." The electrogalvanic sensor has a membrane permeable to gases but not liquids. At the anode of the sensor, electrons are liberated in an oxidative reaction. This is shown with a lead anode:

$$2Pb \rightarrow (Pb^{+2}) + 4e^{-}$$

The meter measures the current produced by the electrons consumed in the reaction at the cathode (silver or gold):

$$O_2 + 4e^{-} \rightarrow 2O_2,\ 2O_2 + 2H_2O \rightarrow 4(OH)^{-}$$

The electron flow between the anode and cathode is directly proportional to the partial pressure of oxygen in the sample gas. Current flows in proportion to oxygen concentration.

Electrogalvanic cells have a limited life related to the concentration and duration of oxygen exposures. Because of this, some nurse anesthetists remove the oxygen sensor from the circle system if an anesthesia machine is left on and not in use for extended periods of time, such as overnight. Most anesthesia machines have minimal oxygen flow at all times, so removing the electrogalvanic cell from the flow of higher oxygen concentration will extend its duration of usefulness.

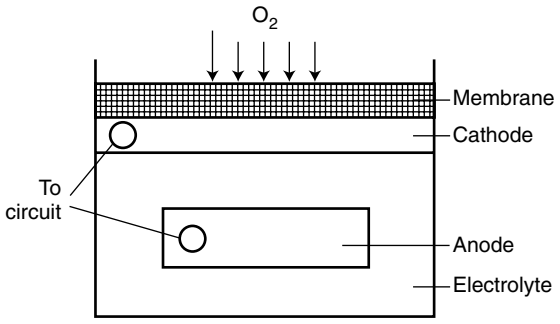

FIGURE **14-36** Electrogalvanic fuel cell.

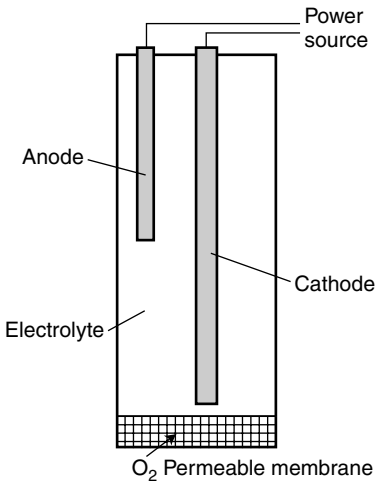

FIGURE **14-37** Polarographic electrode.

Polarographic Electrode (Clark Electrode)

The Clark polarographic oxygen electrode consists of a voltage source and a current meter connected to a platinum cathode and a silver anode (Figure 14-37). The electrodes are immersed in a potassium chloride electrolyte cell. A membrane permeable to oxygen but not electrolytes covers one surface of the cell. A polarizing voltage is applied between the electrodes. At the anode, electrons are liberated by the oxidative reaction of silver with the chloride electrolyte:

$$4Ag \rightarrow 4Ag^{+} + 4e^{-},\ 4Ag^{+} + Cl^{-} \rightarrow 4AgCl$$

The meter measures the current produced by the electrons consumed in the reaction at the cathode:

$$O_2 + 4e^{-} \rightarrow 2O_2,\ 2O_2 + 2H_2O \rightarrow 4(OH)^{-}$$

Current flows in proportion to oxygen concentration. If there is no current applied to these cells, there will be no consumption of the electrodes.[100]

Paramagnetic Oxygen Sensor: Magnetomechanical "Dumbbell Principle"

The paramagnetic oxygen sensor uses oxygen molecules' unique attraction into magnetic fields. Few other gases are attracted by

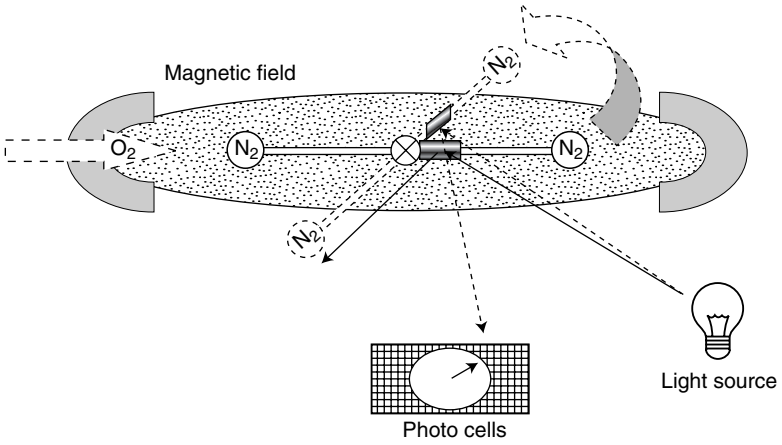

FIGURE **14-38** Paramagnetic oxygen sensor.

magnetic fields. The paramagnetic oxygen sensor is constructed with two nitrogen-filled bulbs attached together by a stem; this resembles a dumbbell. This dumbbell-shaped apparatus is suspended parallel to a magnetic field in its "at-rest" state. Nitrogen is not attracted or repelled by magnetic fields. The introduction of oxygen into this sensor causes the dumbbell apparatus to be displaced out of the magnetic field as oxygen is attracted into the field (Figure 14-38). The amount of displacement of the dumbbell apparatus is directly proportional to the concentration of oxygen. Originally these sensors measured the physical displacement of the dumbbell apparatus but were prone to artifact caused by vibration and external movement. These sensors now incorporate a small optical mirror that reflects a projected light beam. The light beam is reflected onto a photocell that generates a small voltage used to counteract the displacement of the dumbbell apparatus. Increased oxygen concentration increases the displacement of the dumbbell apparatus, which in turn directs a greater reflection of light onto the photocell. By using a generated electric current to counteract the dumbbell apparatus, displacement proportional to the oxygen concentration, external movement, and artifact are eliminated. These sensors are highly accurate, compact, and durable.

Fluorescence Quenching

Fluorescence is caused by a molecule emitting light (photons) in response to being energized. Certain molecules exhibit fluorescence in response to an electric current or exposure to EMR. These molecules are sometimes said to "glow in the dark." Neon lights are an example of noble gas fluorescence initiated by an electric current. Chemical fluorescence is seen in some sea life and in glow sticks. Both electrically and chemically initiated fluorescence is caused by energizing an electron to a higher energy level. The energized (excited) electron then returns to its lower energy level (resting state) by releasing a photon (spontaneous emission). The released photon is observed as light, with its color representing the emitted photon's frequency.[100]

Fluorescence quenching is a technology that uses oxygen's ability to suppress, or quench, certain molecules from fluorescing. When a fluorescent molecule is excited to a higher energy state, it will emit a photon. Oxygen, if present, will absorb this photon and prevent its release. The amount of fluorescence that is quenched is directly proportional to the concentration of oxygen present. By measuring the amount of emitted photons, analysis of oxygen concentration may be made (Figure 14-39).

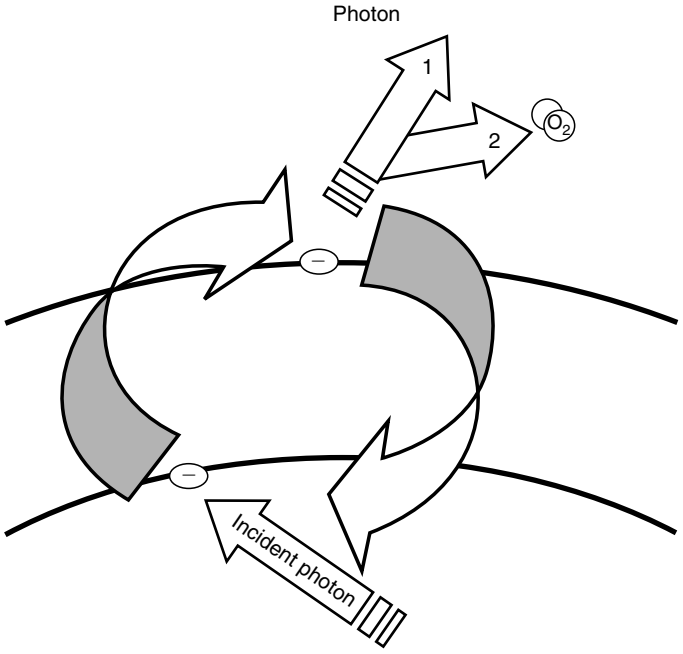

FIGURE **14-39** Fluorescence-quenching principle. *(1)* Photon release as fluorescence. *(2)* Energy absorption by oxygen, which quenches fluorescence.

Carbon Dioxide Analysis

Fluorescence Quenching

Fluorescence-quenching technology also may be used to measure carbon dioxide. Carbon dioxide is not the quencher of fluorescence; instead it causes a change in pH, liberating hydrogen ions, which react with a quenching agent or a fluorescent dye in the sensor. Fluorescence is altered by the protonation of these chemical components. The measured change in fluorescence is proportional to the concentration of carbon dioxide.

Colorimetric CO_2 Sensor

A dry-state sensor that uses a color change in the presence of carbon dioxide is often used to differentiate endotracheal intubation from esophageal intubation. These sensors use the fluorescence principle to indicate carbon dioxide in the gas phase. A paper is impregnated with a fluorescent dye that in the presence of carbon

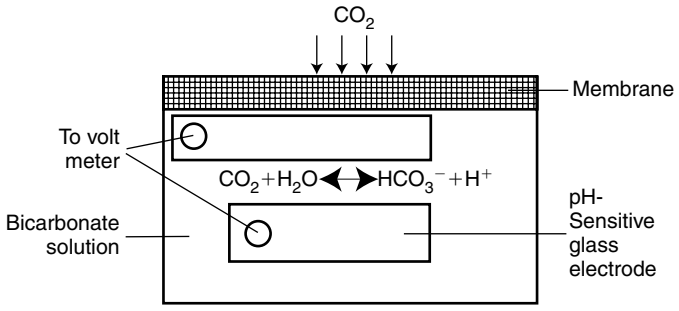

FIGURE **14-40** Severinghaus P_{CO_2} electrode.

dioxide, will fluoresce or change color. A phase-transport agent facilitates the reaction to give an immediate color change (e.g., purple), indicating carbon dioxide. Colorimetric CO_2 sensors indicate the presence, but not the amount, of carbon dioxide.

Severinghaus Pco_2 Electrode

The Severinghaus P_{CO_2} electrode (Figure 14-40) is a frequently used method for analyzing carbon dioxide in anesthesia.[101] It uses a pH-sensitive electrode immersed in a bicarbonate solution with a gas-permeable membrane. Carbon dioxide diffuses into the sensor and is converted into free hydrogen ions, generating a current of electric charge. The current is proportional to CO_2 concentration.

PULSE OXIMETRY

Pulse oximetry makes use of the property of matter that causes it to absorb certain frequencies but not other frequencies of EMR. Oxygenated and deoxygenated hemoglobin are uniquely different molecules and thus interact differently with EMR. By measuring specific frequencies that are absorbed by a pulsatile blood supply, a calculation may be made to determine the percentage of oxygenated and deoxygenated blood in that sample. The algorithm used to make these calculations is derived from the Beer-Lambert law (August Beer, 1825-1863, and Johann Heinrich Lambert, 1728-1777). This law is based primarily on the work of Lambert. Lambert's laws state the following: (1) The luminance of perpendicular light on a surface is proportional to the inverse square of the distance it travels from its source. (2) The luminance intensity of angled light is proportional to the cosine of the angle with the normal. (3) Luminance intensity decreases exponentially as the light travels through a medium. The Beer-Lambert law is as follows:

$$It = Ii \times e^{-DC\alpha}$$

where **It** is the transmitted light, **Ii** is the incident light, and e^{-DC_α} is the distance through the medium, concentration, and absorption coefficient (Figure 14-41). Pulse oximetry applies the Beer-Lambert law to the absorption of two specific frequencies, infrared and visible red, by hemoglobin. Oxygenated hemoglobin absorbs the infrared frequency that corresponds to a wavelength of 940 nanometers, and deoxygenated hemoglobin absorbs the visible red wavelength of 660 nanometers (Figure 14-42). Analysis of the wavelength that is most absorbed corresponds to that form of hemoglobin. If the wavelength of 940 is absorbed, the hemoglobin present is the oxygenated form. Pulse oximeters display a percentage measurement of saturated hemoglobin. Pulse oximeters measure the amount of absorption of these two specific wavelengths many times a second.

Pulse oximetry is inexpensive, portable, and allows early detection of hemoglobin desaturation.[102-104] Probe placement may be on the digits, ears, nose, or even the forehead to detect a pulsatile arterial blood flow. The oxyhemoglobin saturation curve displays

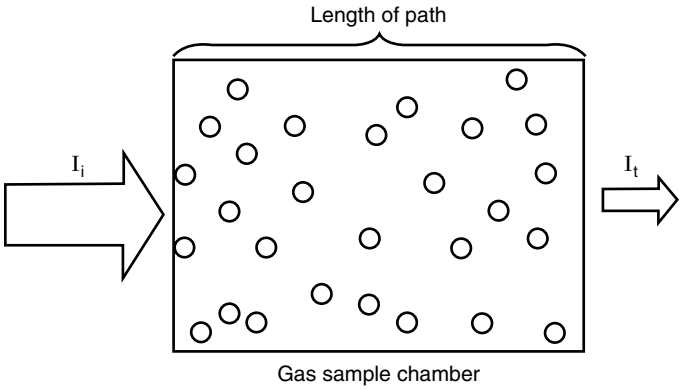

FIGURE **14-41** Incident light intensity change when transmitted through a medium.

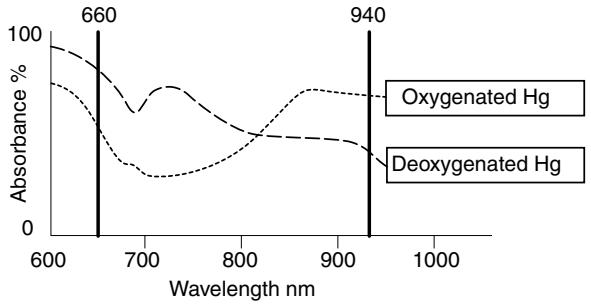

FIGURE **14-42** Oxygenated hemoglobin and deoxygenated hemoglobin wavelength absorption spectra. The intersection where oxygenated and deoxygenated hemoglobin absorb the same frequency amount is the isobestic point.

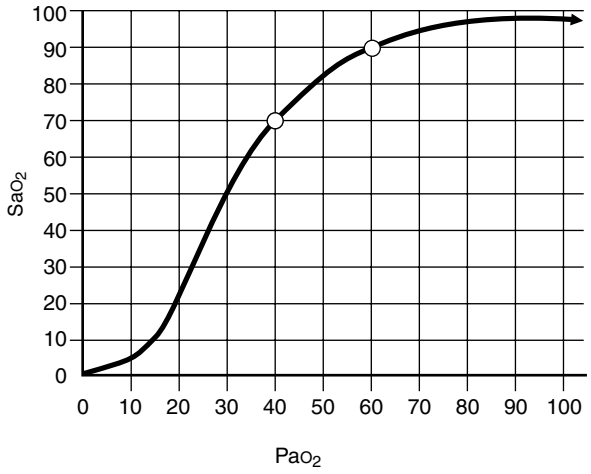

FIGURE **14-43** Oxyhemoglobin dissociation curve.

the oxygen saturation (Sao_2) relationship to Pao_2. Important points along this curve include the Sao_2 of 90%, which corresponds to the critically low Pao_2 of 60 mmHg oxygen tension. The Sao_2 of 70% corresponds to a Pao_2 of 40 mmHg oxygen tension (Figure 14-43) and is the saturation at which cyanosis becomes apparent.[105] Pulse oximetry is of great value and has become a standard of practice. Both a digital display and an auditory tone alert the nurse anesthetist to the patient's hemoglobin saturation.[106]

Disadvantages of pulse oximetry include the susceptibility of artifact from movement and ambient light sources, the risk of burns in poor perfusion states, and the limitation in detecting pulsatile

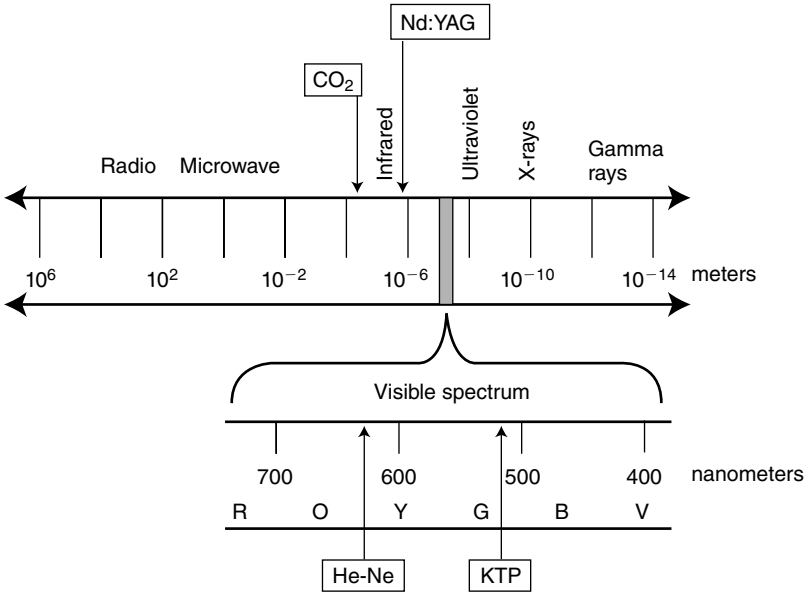

FIGURE **14-44** Common medical laser frequencies. *He-Ne*, Helium neon; *KTP*, potassium titanyl phosphate; *Nd:YAG*, neodymium-doped yttrium aluminum garnet.

TABLE **14-8** Medical Lasers and Uses

Laser	Wavelength	Tissue Penetration	Characteristics/Uses
Helium neon	633 nm	none	Aiming beam for invisible lasers
CO_2	10,600 nm	less than 0.5 mm	Highly absorbed by water Good for superficial lesions Used in airway surgeries
Argon	488 nm 514 nm	0.5-2.0 mm	Selectively absorbed by hemoglobin Good for hemangiomas, moles Used also in eye and ear surgery
KTP	1060 nm	0.5-2.0 mm	Highly absorbed by hemoglobin Multiple uses
YAG lasers	1064-2940 nm	2-6 mm	Variable intensities Used to ablate and destroy tissues Multiple uses

CO_2, Carbon dioxide; *KTP*, potassium titanyl phosphate; *YAG*, yttrium aluminum garnet.

blood flow in hypothermic or vasoconstricted patients. Additionally, some nail polish pigments interfere with accurate estimates of oxygen saturations. During high F_{IO_2} delivery, ventilation-perfusion abnormalities may be masked. A Pa_{O_2} of 100 mmHg and a Pa_{O_2} of 500 mmHg will both give the same pulse oximeter reading of 100%, regardless of the delivered oxygen. Lastly, pulse oximeters do not measure respiratory rate.[107-110]

LASERS

Lasers derive their name from the acronym **L**ight **A**mplification by **S**timulated **E**mission of **R**adiation. Certain atoms that have been energized by an incident photon may move an electron to a higher orbit, but that electron only stays there momentarily, releases a photon, and quickly returns to its resting energy level (see Fluorescence Quenching). This is called *spontaneous emission*. When many incident photons raise many electrons to higher energy levels, the *spontaneous emission* that occurs is chaotic, with photons radiating in multiple directions. However, if many atoms of a particular matter are continually energized by incident photons while their electrons are already in a higher energy state, then photons of the same frequency and direction will be emitted as the electrons are forced down to their natural resting state. This is called *stimulated emission* and is the basis of laser function. Continual energizing of certain atoms forces photons of the same frequency (monochromatic) and direction to be emitted in unison. Population inversion is the condition in which the majority of electrons in an atom are in the higher energy level rather than their natural resting state. The natural balance of resting electrons to energized electrons has been inverted. Population inversion is required to allow continual production of monochromatic, coherent, and unidirectional photons used in lasers. The intensity of lasers and the ability to direct the beam have many applications in medicine and present unique considerations for nurse anesthetists (Figure 14-44 and Table 14-8).

Laser Risks

Lasers have the ability to burn and ignite fires. The patient should have his or her eyes shielded with saline pads and laser goggles. Operating room personnel also should wear appropriate eye protection when lasers are in use.[111] The risk of fire is ever present

with lasers. Three components are needed to produce a fire: fuel, oxygen, and an ignition source. Lasers are a potent ignition source. The nurse anesthetist should be aware of this risk during laser surgeries and be prepared to take rapid action. Drapes, dressings, and linens are a few of the combustible materials that may ignite during surgery.[112] Lasers should never be kept active when not in use. Lasers are often used for otorhinolaryngologic surgeries. Endotracheal tube fires can occur during these cases. Low inspired oxygen concentrations and nonflammable or shielded endotracheal tubes should be used.[113] Some authors recommend placing saline with methylene dye in the endotracheal tube cuff to dissipate heat and signal cuff rupture.[114] A source of saline to extinguish a potential fire should be immediately available. If an airway fire occurs, stop oxygen flow, stop ventilation, extubate the patient, extinguish the fire, mask ventilate, and reintubate the patient.[115] The patient will require airway assessment and medical treatment, including bronchoscopy, lavage, and steroids.

SUMMARY

The historical view of the universe as a machine following fixed specific rules often allowed for unequivocal laws to be discovered. For a time, the actions of the universe seemed destined to be unlocked and forever understood. Unfortunately or fortunately, this is not the case. The mechanistic view of the universe in Newtonian physics loses its ability to describe certain phenomena, and this underscores a significant limitation. Advances in our knowledge of quantum events may shed light on phenomena that remain elusive.[116]

Quantum physics has brought us new insight into the subatomic world and uncovered the limitations of classical physics in fully describing the actions and reactions of the universe. What Newtonian physics has done for the physical world, quantum physics holds for the nonphysical world, the world of pure energy and the quasi-world of energy/mass transition. Events in the quantum world are not determined by fixed, describable outcomes. Quantum events are described by probabilities. Phenomena that remain only partially understood in anesthesia may be clarified by discoveries in quantum study. Consciousness, awareness, and minimum alveolar concentrations (MACs) all are described in anesthesia as probabilities. Consciousness and awareness are not "on-off" phenomena but rather fall within a spectrum. Delivery of anesthetics is sometimes measured not in fixed set doses but rather in ranges, MACs, that provide a guideline of probability for a desired outcome. Though controversial, some have suggested that consciousness is a quantum event with understanding to be found in the study of quantum mechanics.[117-120] Newtonian physics and physical chemistry will remain valued sciences that well describe many processes in the field of anesthesia, but quantum study may someday bring new advances and applications to anesthesia. Safer, more effective anesthesia techniques and technologies may evolve out of quantum understanding, or the mere search itself may stimulate new developments. Regardless, the future is exciting. Chemistry and physics have and will continue to provide a conceptual and analytical framework from which we can derive understanding, establish clinical rationales, and direct the practice of safe and effective anesthetic management of patients under our care.

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CHAPTER 15

Anesthesia Equipment

◆ *Michael P. Dosch*

"To a large extent, anesthesia machines are *inherently dangerous*. A machine that has the power to induce anesthesia necessarily has the power to cause death and serious injury. An anesthesia department may want to institute periodic training to make sure that everyone in the department is familiar with *all* of the machines in the hospital."[1] It would disturb any of us to read in the news about an adult, without driver's training, who attempted to drive a car and caused injury or death as a result. Shouldn't it be equally disturbing to learn that only a minority of anesthetists report that they check their gas machines before use?[2,3] Because anesthesia equipment malfunction is so rare, misuse and human error are much more of a threat to patient safety than outright malfunction.[4-7] However, when errors in the use of gas delivery equipment occur, the outcome is often mortality or serious morbidity.[4] Human error can be most effectively combated by a strong individual, department, and industry commitment "to ensure that no patient is harmed by anesthesia" (the mission of the Anesthesia Patient Safety Foundation).[8] The means of accomplishing this goal are educational and motivational. We anesthetize patients with many different kinds of problems, for many different kinds of surgical and diagnostic procedures. But there is one thing that is present in every anesthetic: the anesthesia gas machine. It is the purpose of this chapter to provide timely, accurate, and patient-safety-focused information about this important and ubiquitous patient-safety technology.

As the previous generation of equipment passes out of use (e.g., Excel, Modulus, Narkomed 3), it is deemphasized in this edition to allow more focus on current anesthesia equipment systems. The main additions to this chapter are the new pre-use checklist for the anesthesia gas machine and its impact on patient safety; and new adaptive modes of ventilation (pressure control with volume guarantee, and autoflow). Differences between gas machines are presented here if understanding these differences is important to using the machine safely. Brief descriptions of new gas machines are presented (Aisys, ADU, Aespire, Avance, and Aestiva [GE Healthcare, Madison, Wisconsin]; Fabius GS and Apollo [Dräger Medical, Telford, Pennsylvania]).

A major objective of this chapter is that readers will gain skill and safety in the use of the anesthesia gas machine. Therefore throughout the chapter, explicit directions on how to use the machine safely are presented; these directions are based on manufacturers' guidelines and on reports of mishaps from the anesthesia literature. Because of the variety of machines currently in use, no direction in this chapter can be considered universally applicable. The directions given here must be adapted to individual practice settings only after study of the operator's manuals and appropriate local peer review.

Several factors make learning about gas machines difficult. Each model has unique aspects—even those from the same manufacturer. It is not always possible for the anesthetist to be available when department in-service education is conducted. Also, continuing education content may be too limited, or an opportunity to use new equipment soon after an educational session may not occur. New equipment constantly appears in the anesthesia work area. Although anesthesia equipment is designed to meet all legal and technical requirements, the designers of the equipment are not users. Some designs may be recognized as flawed only when they are used clinically. Instructional materials accompanying equipment often are inadequate. For example, no matter how well written, supplying one instruction manual per *machine* is inferior to supplying one instruction manual per *user*. The potential lack in equipment competency caused by these factors can be a safety problem.[9-11] Users may be legally obligated to know and follow manufacturers' instructions (checklists, operating manuals) and warnings, because these may contribute to the standard of care. Some courts have defined deviation from manufacturers' instructions as *prima facie* negligence.[12]

To make learning the content easier, this chapter views the machine from a systems approach. For example, all machines have systems to provide (and measure) gas composition, including life-sustaining gases (oxygen), anesthetizing gases, and metabolic by-products (carbon dioxide). When this capability of every gas machine is understood, one need only determine how a particular machine accomplishes this, and how this function is checked before use to operate the machine safely (in this respect). Once all the systems—and their interplay—are understood, learning new equipment is easier. High-fidelity patient simulation is a novel approach that holds promise for both learning anesthesia equipment more efficiently, and studying gas-machine hazards. Simulation has allowed exploration of questions that could not be studied in the past because of risks to patients.[13,14]

ORGANIZATION OF THE ANESTHESIA GAS MACHINE

Presenting the anesthesia gas machine as a litany of components does not promote retention, much less aid in the development of a solid concept of the overall organization of the machine. An accurate concept of the overall organization should help one to understand the role of the individual components better, which should in turn promote correct use and thus patient safety. This section presents the *supply, processing, delivery, and disposal (SPDD) model.*

Supply, Processing, Delivery, and Disposal Model

The SPDD model is depicted in Figure 15-1 and Box 15-1. This model is comprehensive in that the path of gases can be followed from their arrival in the operating room to their disposal from it. Most anesthesia gas-machine components can be located easily within the overall scheme. Gas flows in the diagram proceed generally from left to right. The vertical bar separates components within the machine and proximal to the common gas outlet (left side), from external components downstream from the common gas outlet (right). The fact that nitrous

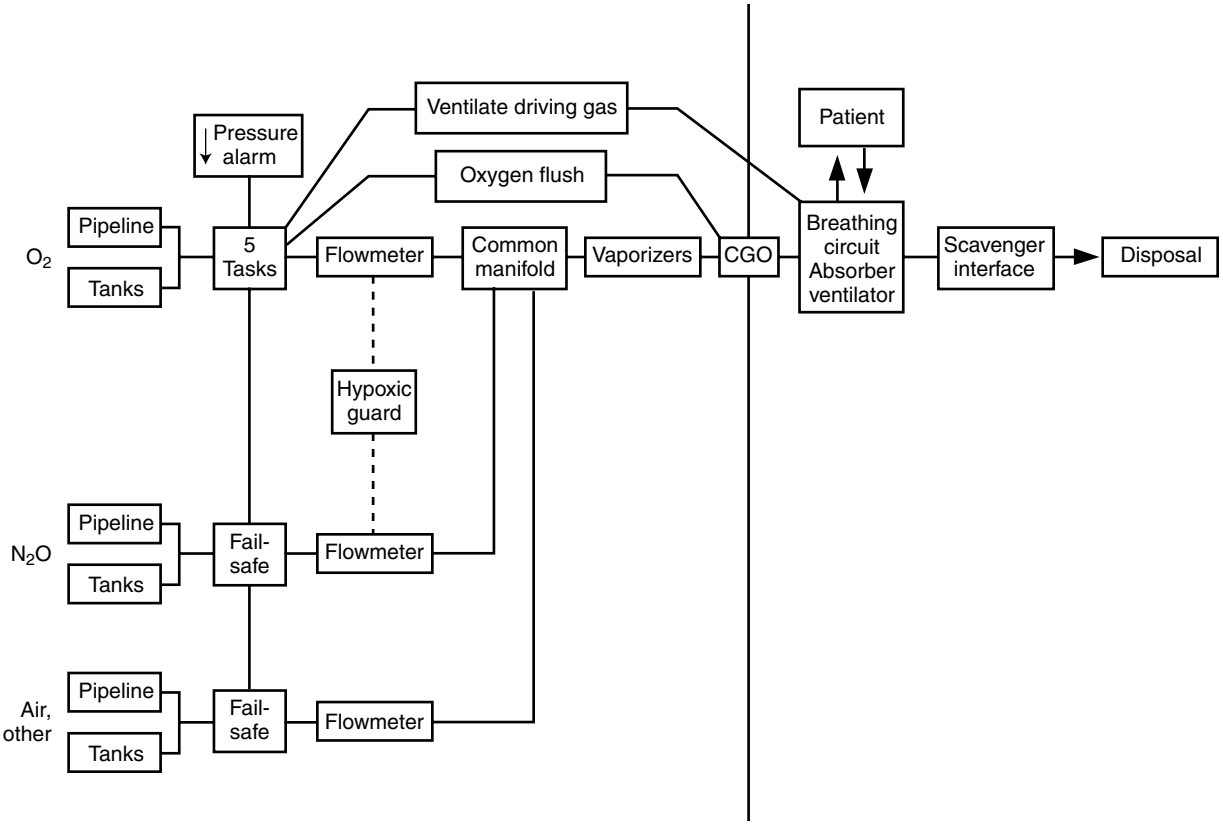

FIGURE **15-1** Supply, processing, delivery, and disposal (SPDD) model. CGO, Common gas outlet. (Courtesy Michael P. Dosch.)

BOX **15-1**

Components in Supply, Processing, Delivery, and Disposal (SPDD) Model

Supply

How do gases come to the anesthesia gas machine? (Site: back of the machine)

- Pipeline
  - Wall outlets
  - Connecting valves and hoses
  - Filters and check valves
  - Pressure gauges
- Cylinders
  - Hanger yokes (yoke block)
  - Filters and check valves
  - Pressure gauge
  - Pressure regulators

Processing

How does the anesthesia gas machine prepare gases before their delivery to the patient? (Site: within the machine, proximal to common gas outlet)

- Fail-safe (oxygen pressure-failure devices)
- Flowmeters (main, auxiliary, common gas outlet, scavenging)
- Oxygen flush
- Low oxygen pressure alarms
- Ventilator-driving gas
- Proportioning systems (hypoxic guard)
- Oxygen second-stage regulator (if present)
- Vaporizers
- Check valves distal to vaporizers (if present)
- Common gas outlet

Delivery

How is the interaction of gases with the patient controlled and monitored? (Site: breathing circuit)

- Gas delivery hose connecting common gas outlet and breathing circuit
- Breathing circuits
- Nonrebreathing
- Circle
- Carbon dioxide absorption
- Ventilators
- Integral monitors
- Oxygen analysis
- Disconnect
- Spirometry (volumes and flows), capnography, airway pressure
- Ventilator alarms
- Addition of positive end-expiratory pressure
- Means of humidification

Disposal

How are gases disposed of? (Site: scavenger)

- Scavenger systems
  - Interface—closed (active and passive) or open
  - Scavenger flowmeter

BOX **15-2**

Components in the High-, Intermediate-, and Low-Pressure Pneumatic Systems

High-Pressure System (Exposed to Cylinder Pressure)
- Hanger yoke
- Yoke block with check valves
- Cylinder pressure gauge
- Cylinder pressure regulators

Intermediate-Pressure System (Exposed to Pipeline Pressure—About 50 psi)
- Pipeline inlets, check valves, and pressure gauges
- Ventilator power inlet
- Oxygen pressure-failure devices
- Flowmeter valve
- Oxygen second-stage regulator (if present)
- Flush valve

Low-Pressure System (Distal to Flowmeter Needle Valve)
- Flowmeter tubes
- Vaporizers
- Check valves (if present)
- Common gas outlet

oxide and air, unlike oxygen, have only one task in the machine is easy to appreciate. The five tasks of oxygen are easy to follow. Understanding the similarities and differences between the fail-safe and hypoxic guard systems is facilitated. The model makes clear that the scavenging system, rather than the patient, is the ultimate destination of gases. Oxygen is central to the figure, because it is the most essential gas delivered. The reader should note that not every component of the SPDD model in Box 15-1 is depicted graphically in Figure 15-1. The reader should make frequent reference to the model while reading this chapter.

The model organizes the information on the basis of how components are used, rather than on the pressures to which they are exposed. From the viewpoint of pressure that components are exposed to, components are classified as part of the high-, intermediate-, or low-pressure systems within (proximal to the common gas outlet) the gas machine (Box 15-2).

Introduction of new gas machines raises questions about the adequacy and safety of older equipment.[1,15] One can determine whether current equipment is obsolete by considering how closely it meets current safety standards and practice needs, by the availability of service, and by the presence of essential safety features.[16,17] Certain systems or components are required by the anesthesia workstation standard, which is a voluntary industry-group consensus standard (Box 15-3).[18]

BOX **15-3**

Required Components of an Anesthesia Workstation

The current anesthesia gas machine (workstation) standard is **ASTM F1850** (a standard promulgated by the American Society for Testing and Materials). F1850 specifies what is needed for an anesthesia workstation. The components are typically built into new gas machines, or they may be added to older machines. Required components include the following:

Battery backup for 30 minutes

Alarms
- Grouped into high, medium, and low priority.
- High-priority alarms may not be silenced for more than 2 minutes.
- Certain alarms and monitors must be automatically enabled and functioning prior to use, either through turning the machine on or by following the pre-use checklist: breathing circuit pressure, oxygen concentration, exhaled volume, or carbon dioxide (or both).
- A high-priority pressure alarm must sound if user-adjustable limits are exceeded, if continuing high pressure is sensed, or for negative pressure.
- Disconnect alarms may be based on low pressure, exhaled volume, or carbon dioxide.

Required monitors
- Exhaled volume
- Inspired oxygen, with a high-priority alarm within 30 seconds of oxygen falling below 18% (or a user-adjustable limit)
- Oxygen supply failure alarm
- A hypoxic guard system must protect against less than 21% inspired oxygen if nitrous oxide is in use.
- Anesthetic vapor concentration must be monitored.
- Pulse oximetry, blood pressure monitoring, and electrocardiogram (ECG) are required.

Pressure in the breathing circuit is limited to 12.5 kPa (125 cm water).

The electrical supply cord must be nondetachable or resistant to detachment.

Cylinder supplies
- The machine must have at least one oxygen cylinder attached.
- The hanger yoke must be pin-indexed, have a clamping device that resists leaks, and contain a filter. It must have a check valve to prevent transfilling and a cylinder pressure gauge.
- There must be cylinder pressure regulators. The machine must use pipeline gas as long as pipeline pressure is greater than 345 kPa (50 psi).

Flowmeters
- Single control for each gas
- Each flow control next to a flow indicator
- Uniquely shaped oxygen flow control knob
- Valve stops (or some other mechanism) are required such that excessive rotation will not damage the flowmeter.
- Oxygen flow indicator is to the right side of a flowmeter bank.
- Oxygen enters the common manifold downstream of other gases.
- An auxiliary oxygen flowmeter is strongly recommended.

An oxygen flush is present, capable of 35 to 75 L/min flow that does not proceed through any vaporizers.

Vaporizers
- Concentration-calibrated
- An interlock must be present.
- Liquid level indicated, designed to prevent overfilling
- "Should" use keyed-filler devices
- No discharge of liquid anesthetic occurs from the vaporizer, even at maximum fresh gas flow.

Only one common gas outlet at 22-mm outer diameter, 15-mm inner diameter, which is designed to prevent accidental disconnection.

Pipeline gas supply
- Pipeline pressure gauge
- Inlets for at least oxygen and nitrous oxide
- Diameter index safety system (DISS) protected
- In-line filter
- Check valve

Checklist must be provided (it may be electronic or performed manually by the user).

A digital data interface must be provided.

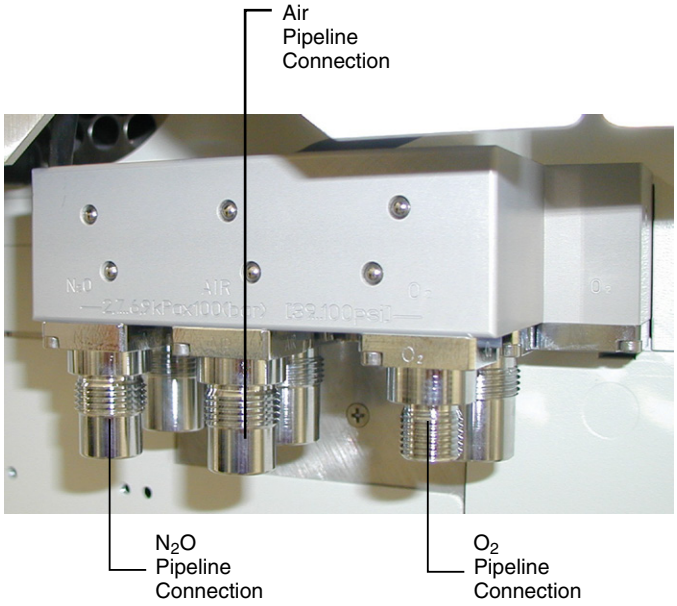

FIGURE **15-2** Pipeline connections using the diameter index safety system (DISS) ensure that only the correct gas hose can be connected to each inlet on the back of the anesthesia gas machine. (From *Apollo Operator's Instruction Manual,* Document No. 90 38 237, Rev. 01. Telford, Penn: Dräeger Medical Inc; 2005. © Drägerwerk AG & Co. KGaA, Lubeck. All rights reserved.)

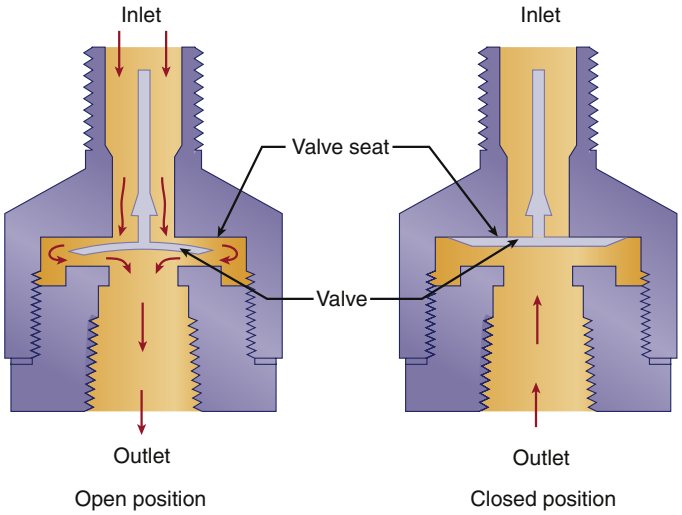

FIGURE **15-3** Check valve in the pipeline gas supply inlet at the back of the anesthesia gas machine. Gas enters from the supply hose at "Inlet" and proceeds (*downwards in the illustration*) into the machine (*left*). The right panel shows that gas cannot leak out of the machine if the supply hose is disconnected. (From Bowie E, Huffman LM. *The Anesthesia Machine: Essentials for Understanding.* Madison, Wis: Ohmeda, a Division of BOC Health Care, Ind; 1985. In Miller RD, et al, eds. *Miller's Anesthesia.* 7th ed. Philadelphia: Churchill Livingstone; 2010.)

SUPPLY

The concept of supply is concerned with these questions. How do gases (and electrical power) come to the anesthesia gas machine? What are the likely faults and hazards?

Pipeline Supply

Configuration

Oxygen is produced by the fractional distillation of liquid air. It is delivered to facilities and stored as a liquid at a temperature of minus 184° C.[19] The liquid oxygen is converted to a gas and supplied to hospital pipelines at a pressure of 50 psi (344 kPa). In the operating room suite, main and partial-area shutoff valves are present to isolate sections with leaks, interrupt supply in case of fire, and allow repair work on subsections. Wall outlets or hoses dropped from the operating room ceiling are finished with quick-connect couplers. These couplers are used so that the connection of gas machine supply hoses to wall outlets does not require tools. However, the springs and rubber gaskets (O-rings) these couplers contain provide a connection that is less secure than a wrench-tightened connection; thus they are a common source of leaks.[20-22]

Systems processing nitrous oxide are similar. Nitrous oxide is delivered to the hospital in large (size H) cylinders, which are connected to a manifold. Regulators reduce the pressure so that nitrous oxide, like oxygen, is supplied to the pipelines at 50 psi.[19] Consequently, 50 psi is the normal working pressure of the anesthesia gas machine. Shutoff valves and wall outlets with quick-connect couplers are similar for nitrous oxide and oxygen. Delivery piping for both nitrous oxide and oxygen uses the diameter index safety system (DISS) to prevent misconnections. In this system, gas-piping connections are sized and threaded differently so that cross-connection is difficult, though not impossible (Figure 15-2).[20,23]

Supply hoses connect the pipeline inlets on the back of the machine to the wall outlets. At the pipeline inlet, a filter, check valve, and pressure gauge are present. The check valve ensures unidirectional forward flow, so that a machine running on cylinder supplies, with the hoses disconnected at the wall outlet, does not leak (Figure 15-3). The filter is required by the current anesthesia workstation standard (ASTM-F1850) because it may help prevent damage to the anesthesia gas machine from particulate matter present in the pipeline gas supply.[18,24]

Problems with Pipeline Supply

Some of the problems associated with pipeline use can be particularly dangerous because they are occult. Pressure loss, excess pressure, cross-connection of gas delivery pipelines, contamination, leaks, and theft of nitrous oxide (for recreational use) have been reported.[25] These problems continue to be reported, and they have consequences for patient safety. There were 45 deaths related to pipeline problems in the United States from 1972 to 1993, and this number is probably an underestimate.[19] Two patients became hypoxemic during anesthesia due to delivery to a hospital of nitrogen tanks with oxygen fittings in 1996.[23] Seven deaths related to piped medical gases were reported from 1997 to 2001.[26] Two patients became hypoxemic due to purging of oxygen lines with nitrogen in 2000.[27] A serious failure of the bulk liquid oxygen supply was noted in 2004, but no patients were harmed.[28] Complications can arise if oxygen analyzers fail or are misused.[2,11,29] Always trust an oxygen analyzer reporting a low inspired oxygen, until you can prove it wrong.

Pipeline supplies of gas have been reported to contain particulate, gaseous, and bacterial matter; other contaminants; and water.[24,25,30,31] In 1993 the National Fire Protection Association (NFPA) adopted more stringent testing standards. The Joint Commission has established standards that allow site visitors to randomly approach and question operating room staff to ensure they are aware of the location and function of shutoff valves, and alarms related to gas supplies in their area.[30]

Loss of Oxygen Pipeline Pressure

Loss of oxygen pipeline pressure is indicated by the pipeline pressure gauge. In addition, if pressure loss is profound, the oxygen low-pressure alarm sounds, and the fail-safe valves halt the delivery of all other gases. Some newer machines are designed to switch to air to drive the ventilator bellows with loss of oxygen pipeline pressure. With the new electronic alarms, operator response may be delayed because the electronic alarms lack the distinctive and familiar "whistle" of a pneumatic oxygen low-pressure alarm.[32]

Two recent simulation studies point to the need for change in the way we teach and respond to loss of oxygen pipeline pressure.[33,34] In a simulated loss of pipeline oxygen, most residents recognized the oxygen-loss alarms. But less than half knew how to change an empty oxygen cylinder, attempted to change it (even after prompting), or recognized that bag-valve-mask (Ambu) ventilation would lead to patient awakening.[33] A group of volunteer specialist anesthetists (completed residency and in practice) managed a simulated oxygen pipeline failure equally poorly.[34] In their pre-use check, 70% failed to identify an empty oxygen cylinder, and only 25% checked for backup ventilation equipment (a bag-valve-mask) before induction. Most failed to conserve cylinder oxygen (by using low fresh gas flows, and turning off the mechanical ventilator), and all used untested pipeline supplies of oxygen when informed that pressure had been restored.[34] These responses could be categorized as unwise at least, or unsafe at worst. In a third recent report, more than 700 anesthetics were given over a 3-week period without any checks that the emergency oxygen cylinder was full.[35]

Optimal management of loss of oxygen pipeline pressure has the following goals: maintenance of oxygenation, ventilation, and depth of anesthesia; and ensuring the safety of the oxygen supply.[34] Box 15-4 gives a suggested guideline for management.[28,33,34,36-39] With complete loss of oxygen pipeline pressure, the anesthetist should fully open the E cylinder of oxygen, disconnect the pipeline, and consider the use of low fresh gas flows and manual ventilation to conserve the emergency cylinder supply of oxygen. If the E cylinder of oxygen is not opened fully, flow from it may end before the cylinder is empty. The author recommends disconnecting the hose at the quick-connect fitting at the wall during an oxygen pressure-loss event, when doing so is not strictly necessary, for two reasons. First, it *must* be disconnected in the case of a cross-connection (which is more fully described later in the chapter), otherwise the contents of the oxygen cylinder will not flow. Remembering one strategy that is effective for two reasonably similar problems is easier than remembering two different strategies. Second, if the loss of pipeline pressure is followed by the flow of contaminated contents from the oxygen pipeline, disconnecting when pipeline pressure is lost protects the patient from exposure to these contaminants.

Although excessive pipeline pressure will not trigger alarms in the machine, it should do so in the hospital physical plant or engineering department. Excessive pressure can damage respiratory apparatus or machinery of various types connected to the pipeline, including the anesthesia gas machine.

Cross-Connection of Gases

Cross-connection of gases can occur anywhere from the liquid oxygen supply and piping, to the wall outlets, hoses, and internal circuitry of the anesthesia gas machine. Incidents of cross-connection continue to be reported. Mishaps in which cross-connection was a factor have been reported as recently as 2009.[40-43] Fatalities (as recently as 2002) have been associated with the shipment in error to the hospital of liquid nitrogen instead of oxygen, liquid carbon dioxide rather than nitrous oxide, the unintentional cross-connection of oxygen and nitrous oxide pipelines during renovation of an operating room, and alteration of an oxygen flowmeter so that it would fit a nitrous oxide outlet in a cardiac catheterization laboratory. A common factor associated with patient injury has been failure to use an oxygen analyzer.

Although not all of the above incidents involved patients connected to anesthesia gas machines, cross-connections also continue to be reported in anesthetized patients. In 1997 a case was described in which the nitrogen hose from the gas machine was discovered to be fitted with a quick-connect coupler for air (at the end that would be plugged into the wall outlet).[23] This did not result in patient injury, but would have allowed the delivery of 100% nitrogen had the machine been set to deliver air only. The consequences of this type of error in the oxygen wall-outlet hose could be disastrous. In 1995 it was reported in the United States that two patients became hypoxemic as a result of delivery of liquid nitrogen to the hospital in a tank with oxygen fittings.[44] In 2009 a wall fitting for carbon dioxide in a lithotripsy area allowed connection of a nitrous oxide hose from the gas machine, resulting in end-tidal carbon dioxide over 105 mmHg.[40] These incidents underscore our susceptibility to errors of ancillary personnel who install and test gas delivery apparatus. But they also highlight many patient-safety aspects, which anesthetists do control: properly checked oxygen analysis monitors, correctly checking the gas machine before use, and proper response to oxygen-analyzer alarms.

In the event of a suspected crossover, one would see declining inspired oxygen concentration. The anesthetist must open the emergency cylinder oxygen supply, disconnect the pipeline, and use low fresh gas flows and manual ventilation. If the pipeline is not disconnected, the pipeline gas will continue to flow, rather

BOX 15-4

Guideline for Oxygen Pipeline Supply Failure

Always check for the presence of a full E cylinder and an alternative means of ventilation (bag-valve-mask [Ambu] device) before using an anesthesia machine. If pipeline pressure fails or fraction of inspired oxygen drops, follow these steps:

1. Do not attempt to fix the oxygen analyzer—it must be trusted until it can be proved wrong.
2. Turn on backup oxygen cylinder on machine fully, and disconnect pipeline. Ensure that measured fraction of inspired oxygen begins to rise. If the fraction of inspired O_2 does not increase (with fresh gas flow adequate to wash in the O_2 quickly), ventilate the patient by Ambu bag with room air.
3. Use low flows of oxygen. Maintain anesthesia with a volatile agent. Ensure that F_{IO_2} and agent concentration are appropriate.
4. Turn off the ventilator and ventilate manually through the circle system.
5. Call for help if needed; calculate the time remaining for the current cylinder; call for additional oxygen cylinders, and install them on the machine if needed.
6. Find out how long the problem is expected to last; participate in the hospital disaster plan, which may require prioritizing oxygen for those patients who need it most.
7. Do not reconnect patient to pipeline gas until the gas supply is tested.
8. If unable to use the circle, ventilate with an oxygen source (freestanding cylinder) or with room air via a bag-valve-mask device, and institute total intravenous anesthesia.

TABLE 15-1 E Cylinder Characteristics*

Gas	Color, United States (International)	Service Pressure psi (kPa × 10^{-2})	Capacity (L)	Pin Position
Oxygen	Green (white)	1900 (131)	660	2-5
Nitrous oxide	Blue (blue)	745 (51)	1590	3-5
Air	Yellow (black and white)	1900 (131)	625	1-5

Data from Dorsch JA, Dorsch SE. *A Practical Approach to Anesthesia Equipment*. Philadelphia: Lippincott Williams & Wilkins; 2011; *Standard Specification for Particular Requirements for Anesthesia Workstations and Their Components* [F1850-00]. Philadelphia: American Society for Testing and Materials; 2005; NFPA 99: *Health Care Facilities* [Table 5.1.11]. Quincy, Mass: National Fire Protection Association; 2012:49.
*Note that slightly different values may be found in different sources.

than the cylinder oxygen supply. This is because the pressure distal to the cylinder regulator is set at 45 psi (310 kPa), compared with the typical pipeline pressure of 50 psi (344 kPa). Lower pressure is intentionally set on the cylinder regulator so that flow proceeds from the higher-pressure pipeline source if a cylinder is inadvertently left open after the machine has been checked.[45] This is analogous to the situation with an intravenous main line and a piggyback line: whichever is held higher is the one that will flow (greater hydrostatic pressure). In the case of cross-connection between oxygen and nitrous oxide pipelines, the contents of the oxygen pipeline (now nitrous oxide) continue to flow (because the pipeline pressure is 50 psi), whether or not the oxygen cylinder is open. Thus, regardless of the problem with the pipeline supply (lack of pressure or cross-connection), the cylinder *must* be opened; the author advocates disconnecting the pipeline in any instance of problems with the pipeline. If the pipeline is not disconnected and has pressure within it, the emergency supply of oxygen may not flow from the cylinder.

Cylinder Supply

Cylinders are present on the anesthesia machine as reserves for emergency use. Thus they should be open *only* when they are checked, or when the pipeline supply is unavailable.[46] A fresh oxygen cylinder need not be obtained if the cylinder on the machine has an adequate pressure, the amount of which would depend on the availability of pipeline supplies and additional backup oxygen cylinders (see later in chapter under PreAnesthesia Checklist). Cylinders are labeled, marked, and color coded (Table 15-1).[18,47] Anesthetists who practice outside the United States must be aware that the color scheme may differ from country to country. Service pressure and cylinder contents are reported slightly differently in various sources.[48]

Pin position refers to the pin index safety system (PISS) illustrated in Figures 15-4 and 15-5. In this system, each cylinder valve has a unique arrangement of holes that corresponds to its intended contents. The holes mate with pins in the yoke, which is the point where cylinders are attached to the gas machine. The PISS is thus another means of preventing misconnections. The system can be defeated if the pins are missing, are removed, or if more than one washer is used. Anesthetists should check both pins and washers whenever cylinders are replaced. Furthermore, they should be aware that not all E cylinders are of precisely the right size to fit properly on the

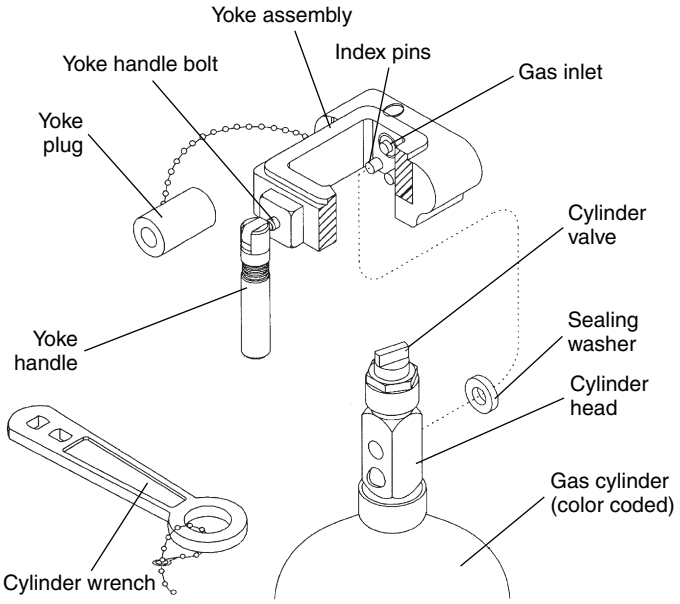

FIGURE 15-4 Pin index safety system, cylinder valve, and yoke. (From Dräger Medical Inc. Apollo Operator's Instruction Manual, Document No. 90 38 237, Rev. 01. Telford, Pennsylvania: Drägerwerk AG & Co. KGaA, Lubeck; 2005.)

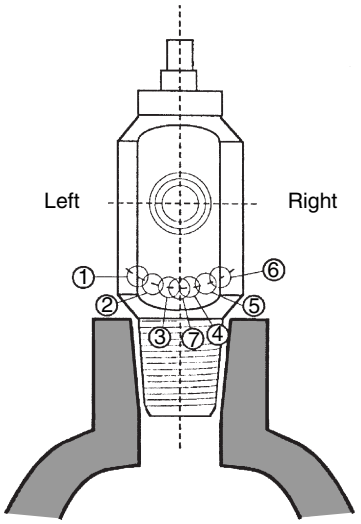

FIGURE 15-5 Pin index safety system: pin positions. (Modified from Eichhorn JH, Ehrenwerth J. Medical Gases: Storage and Supply. In Ehrenwerth J, Eisenkraft JB, eds. *Anesthesia Equipment: Principles and Applications*. St. Louis: Mosby; 1993:1-26.)

machine. Installation of a longer aluminum cylinder has interfered with the casters and prevented an anesthesia gas machine from being moved.[49]

The cylinder valve is the most fragile part of the cylinder, so it must be protected during transport. The cylinder valve consists of a body, the port where gas exits, a conical depression (opposite the port) for the securing screw, the holes where the pins on the yoke fit, and safety relief devices. If a fire causes the temperature and pressure within the cylinder to increase, safety relief devices release cylinder contents in a controlled fashion, rather than explosively. Manufacturers use one or more of the following on cylinder valves: a frangible disk that bursts under pressure, a valve that opens at extreme pressure, or a fusible plug made of Wood's metal (which melts at elevated temperatures).

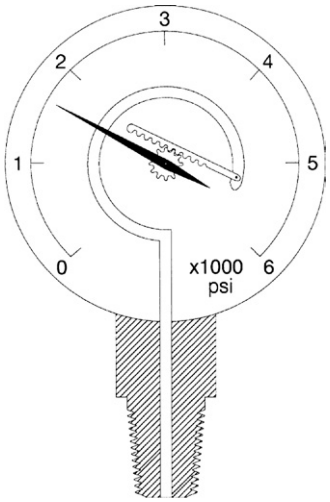

FIGURE **15-6** Bourdon-type pressure gauges are aneroid gauges used for measuring cylinder (and pipeline) pressure. (From Cicman J, et al. *Operating Principles of Narkomed Anesthesia Systems*. Telford, Penn: Dräger Medical Inc; 1993.)

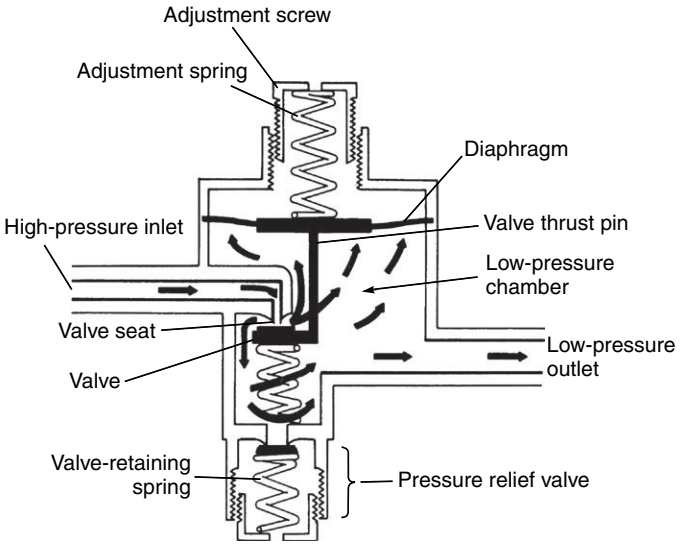

FIGURE **15-7** A schematic view of a cylinder regulator. (From Bowie E, Huffman LM. *The Anesthesia Machine: Essentials for Understanding*. Madison, Wis: Datex-Ohmeda; 1985.)

The hanger yoke serves three functions: it orients cylinders, provides a gas-tight seal, and ensures unidirectional flow into the machine. It also contains a filter that is required by standard.[18] The unidirectional valve within the hanger yoke minimizes the likelihood of transfilling, or of leakage to the atmosphere (if a yoke is empty). It also allows cylinders to be replaced during use. If two cylinders are open, transfilling occurs when gas flows from the cylinder with higher pressure into the cylinder with lower pressure, rather than proceeding toward the flowmeters. Transfilling is a potential fire hazard because filling a cylinder generates heat. The cylinder pressure gauge is a Bourdon-type gauge (Figure 15-6).

Immediately distal to the hanger yoke for each gas is a regulator (Figure 15-7). Two diaphragms move together, connected by a rod. The smaller of the two diaphragms opens or closes the high-pressure inlet (from the cylinder). Gas entering the regulator exerts pressure on the larger diaphragm, whose movement tends to close the inlet. Thus gas can enter the regulator only at a rate controlled by a feedback loop. The outlet pressure is adjustable by a screw and spring that bear on the inlet diaphragm. Thus the regulator converts the high (but variable) cylinder pressure to a constant downstream pressure (45 psi [310 kPa]), which is intentionally slightly less than pipeline pressure in order to prevent silent depletion of cylinder contents.[18,30,32] Pipeline pressure varies, depending on the load that is placed on it throughout the facility. If a cylinder is left open, and pipeline pressure drops below 45 psi, gas will flow from the cylinder. No alarm will sound to warn the user of this condition.[25] Further, if the cylinder is left open after checking and the pipeline fails, the operator will not be alerted to the failure at the time it occurs, because gas will simply begin to flow from the cylinder, without alarms. If the mechanical ventilator is in use, a full E cylinder of oxygen may be depleted in as little as 1 hour, because the ventilator-driving gas in a bellows ventilator is usually oxygen.[36,50] The low oxygen supply failure alarm that rings subsequently announces the *end* of the emergency supply, instead of its beginning. This is the rationale for keeping cylinders closed after their pressure has been checked.

The U.S. Department of Transportation issues regulations for the manufacture, handling, transport, storage, and disposal of cylinders. These regulations have binding legal force. Industry advisory groups such as the Compressed Gas Association (CGA) and the National Fire Protection Association also have a role in setting cylinder standards. Cylinders are constructed of steel approximately ¼ inch in thickness. Only nonferrous (aluminum) cylinders may be used in the magnetic resonance imaging (MRI) environment.[48] Fatalities have occurred when steel cylinders have impacted patients in the MRI scanner.[51]

BOX 15-5

Rules for Safe Handling of Cylinders

Always
- Protect the cylinder valve when carrying a cylinder; it is the most fragile part.

Never
- Stand a cylinder upright without support; instead, lay it on its side.
- Leave empty cylinders on the machine.
- Leave the plastic cover on the port while installing the cylinder.
- Use more than one washer between a cylinder port and the yoke.
- Rely only on a cylinder's color for identification of its contents; read its labeling.
- Oil valves.
- Remove a cylinder from a yoke without filling the space with a yoke plug if available (see Figure 15-4), which is a backup strategy for guarding against check valve failure.

Anesthetists must be aware of the rules for the safe handling and use of cylinders.[25,52] Gas under pressure in cylinders has an enormous potential energy, which may be lethal if it is released in a rapid, uncontrolled fashion following damage to the cylinder valve. Selected rules for safe handling of cylinders are presented in Box 15-5.

When installing a cylinder, check the labels, crack the valve, check that both PISS pins are present, check that only one washer is present, place the cylinder in the hanger yoke, observe for the absence of an audible leak, and check for proper gauge pressure. The valve is "cracked" to remove dirt from the port. This is done by opening the valve briefly and carefully before the cylinder is

placed on the machine. While cracking the valve, hold the cylinder securely, and do not point the port toward oneself or other personnel.

When relying on cylinder supplies in an emergency, one must be able to calculate how long an oxygen cylinder will last. The following relationship should be used:

$$\frac{\text{Capacity L}}{\text{Service Pressure psi}} = \frac{\text{Contents Remaining L}}{\text{Gauge Pressure psi}}$$

Remember to consider the oxygen flow rate set on the flowmeter when deciding how long the available liters will last. As an example, if the oxygen flow is 2 L/min, and the cylinder's oxygen gauge pressure is 500 psi, how long will the cylinder last? From Table 15-1, we know that the service pressure is 1900 psi and that the capacity is 660 L. Substituting these values into the previous relationship, we obtain the following:

$$\frac{660\text{ L}}{1900\text{ psi}} = \frac{x\text{L}}{500\text{ psi}}$$
$$\text{and } x = 174\text{ L}.$$

Because 2 L of oxygen flow each minute, the cylinder will last approximately 87 minutes (174 L ÷ 2 L/min). This type of calculation is not applicable to compressed gases stored as liquids (nitrous oxide or carbon dioxide). It should be remembered that this calculation refers only to requirements at the flowmeters, and assumes manual ventilation. Use of a mechanical ventilator consumes approximately a minute volume of driving gas each minute, and thus should be avoided in situations in which oxygen supply is limited to cylinders only.[50]

The contents of cylinders must meet the purity requirements for medical gases established by the United States Pharmacopeia (USP). The contents are also regulated in the United States by the U.S. Food and Drug Administration (FDA). Oxygen is used to power ventilators throughout the hospital because it is dry, readily available, and relatively inexpensive.

Nitrous oxide is stored as a liquid; therefore the cylinder pressure of 745 psi (5136 kPa) represents the vapor pressure of liquid nitrous oxide at room temperature. The nitrous oxide cylinder pressure gauge remains at 745 psi until the liquid is gone; at this point, the cylinder is more than three-quarters empty. After this point, the nitrous oxide cylinder pressure swiftly declines with further use. Thus nitrous oxide cylinders should be changed if their pressure is less than 745 psi. Rapid removal (more than 4 L/min) from a cylinder may cause the formation of frost on its wall or freezing of the valve, owing to the loss of the latent heat of vaporization from the liquid nitrous oxide. Nitrous oxide is nonflammable, but it does support combustion.[25,48] Anesthesia personnel must be alert to the possibility of nitrous oxide abuse.[53]

Compressed air is not entirely dry. Its composition varies from sample to sample, but its major constituents are nitrogen (78%), oxygen (21%), and argon (nearly 1%). Carbon dioxide (0.03%) and other gases are present in trace amounts.

Electrical Power Supply

Electrical power is supplied to the gas machine through a single power cord, which can become dislodged. Because of this possibility, as well as the possibility of loss of main electrical power, new gas machines must be equipped with battery backup sufficient for at least 30 minutes of limited operation.[18] Which systems remain powered during this period is specific to each model, thus users must read the operator's manuals. For example, if you disconnect electrical power from the ADU (anesthesia delivery unit [GE Healthcare]) it loses patient monitors (electrocardiogram, noninvasive blood pressure, gas analysis, pulse oximetry, and other monitors displayed on the right screen), but fresh gas flow, volatile-agent delivery, and ventilation continue during the period that battery backup is used. Once battery power is lost, nitrous oxide and agent delivery are cut off.[54]

Convenience receptacles are usually found on the back of the machine so that monitors or other equipment can be plugged in. These convenience receptacles are protected by circuit breakers or fuses. It is a mistake to plug devices that convert electrical power into heat into these receptacles (air or water warming blankets, intravenous fluid warmers) for two reasons.[55] First, these devices draw a lot of amperage (relative to other electrical devices), so they are more likely to cause a circuit breaker to open. Second, the circuit breakers are in nonstandard locations (so check for their location before your first case). If a circuit breaker opens, all devices that receive power there (such as monitors and, in some configurations, the mechanical ventilator) may cease to function. If one is not familiar with the circuit-breaker location, valuable time may be lost while a search is conducted.

Loss of Main Electrical Power

Devices that typically *require* wall-outlet electrical power include mechanical ventilators, physiologic monitors, room and surgical-field illumination, digital flowmeter displays for electronic flowmeters, cardiopulmonary bypass pump/oxygenators, air warming blankets, gas/vapor blenders (Suprane Tec 6 [GE Healthcare]), and vaporizers with electronic controls (Aladin cassettes in the ADU).

Devices (or techniques) that typically *do not* rely on wall-outlet electrical power include spontaneous or manually assisted ventilation, mechanical flowmeters, scavenging, laryngoscope, flashlights, manual intravenous bolus or gravity-controlled infusions, battery-operated peripheral nerve stimulators or intravenous infusion pumps, monitoring by the anesthetist using the five senses, and variable bypass vaporizers (Tec 7 [GE Healthcare]; Vapor 2000 [Dräger Medical]).

Generally, hospitals have emergency generators that will supply operating-room electrical outlets in the event power is lost. But these backup generators are not completely reliable. A 90-minute interruption in power during cardiopulmonary bypass, complicated by almost immediate failure of the hospital generators, has been described.[56] Injury to personnel as they hurried in the dark to fetch lights and equipment was an unanticipated hazard.

With power failure in older gas machines, the principal problems were loss of room illumination and failure of mechanical ventilators and electronic patient monitoring. In general, new gas machines have battery backup sufficient for 30 minutes of operation—however, typically without patient monitors (e.g., electrocardiogram, pulse oximetry, gas analysis). Mechanical ventilation may or may not be powered by the backup battery (depending on the model). New flowmeters that are entirely electronic (Aisys and Avance [GE Healthcare]) require a backup pneumatic/mechanical (needle-valve and flowtube) flowmeter.[15,57-59] Mechanical flowmeters with digital display of flows have a backup glass flow tube that indicates total fresh gas flow (ADU[54] [GE Healthcare]; Fabius GS[60] and Apollo [Dräger Medical]).

New gas machines with mechanical needle valve flowmeters and variable bypass vaporizers (e.g., Fabius GS, Apollo, or Aestiva [GE Healthcare]) have an advantage during electrical power failure in that delivery of gases and agent can continue indefinitely.[46,60] However, in the event of generator failure, anesthesia would be limited to flashlight illumination and monitoring by the five senses. The Apollo (Dräger Medical) provides gas and vapor delivery, mechanical ventilation, and integrated monitoring

(e.g., oxygen, breathing circuit volume and pressure, gas analysis) for 30 minutes or more if main electrical power is lost.[61,62] Patient monitors will not function on battery power. Pneumatic functions remain even after the battery is exhausted: vaporizers, S-ORC (fail-safe and hypoxic guard), adjustable pressure-limiting (APL) valve, flowmeters, breathing pressure gauge, cylinder and pipeline pressure gauges, and total fresh gas flowmeter.

Because of the differences between models, it remains important to understand and anticipate how each particular anesthesia gas machine type responds when main electrical power is lost. This information must be reviewed in the operator's manual.

PROCESSING

In this section, the various aspects of the anesthesia gas machine's preparation of gases before their delivery to the patient are discussed.

Manufacturers and Models

Manufacturers of anesthesia gas machines in the United States include Dräger Medical and GE Healthcare. There are some imported models in the market as well (e.g., Paragon, Mindray). Dräger Medical Inc. (Telford, Pennsylvania) is the manufacturer of the Narkomed series (6000 and 6400, GS, MRI, Mobile models), the Apollo, and the Fabius GS. GE Healthcare (Madison, Wisconsin) is the manufacturer of the Aestiva, Aestiva MRI, Avance, Aisys, Aespire, and ADU.

Gas machines that are not currently produced remain in widespread use, because the service life is long—10 to 15 or more years. Currently produced models meet or exceed the specifications of the anesthesia workstation standard F1850. The differences among new gas machines are significant; thus what one learns on one may not transfer very well to a different model. This is particularly true of preanesthesia checkout (see below in a later section). The differences are pointed out in this chapter when they are relevant to clinical practice or to demonstrate by comparison how systems function. This section continues with an overview of several current gas machines.

Fabius GS

The Dräger Fabius GS (Figure 15-8) includes volume, pressure, flow, and inspired oxygen monitoring; but not physiologic monitors or gas analysis. The thermal anemometry ("hot wire") flow sensor in the breathing circuit is unique to this machine and a few others.[60] The screen displays tidal and minute volume, respiratory rate, and a respiratory pressure waveform.

The ventilator is piston driven; corrects tidal volume for compliance and leaks; and features manual, spontaneous, volume-controlled ventilation (VCV); pressure-controlled ventilation (PCV); pressure-support ventilation (PSV); and synchronized intermittent mandatory ventilation (SIMV) with PSV.[60] Like the Apollo, the mechanical ventilator is activated in two steps (the mode is chosen, and then confirmed by a second key press). The machine uses a manual checklist with several electronic self-tests (e.g., system, leaks and compliance, flow sensor, oxygen sensor). With the Fabius GS (as with all the new models), users must review the operator's manual to check the machine correctly. Sample preanesthesia checkout procedures are available.[63] The flowmeters are needle valves with electronic capture and display, with a common gas outlet glass flowmeter as backup. Variable-bypass vaporizers are used, and these may be removed without tools.

The Fabius GS breathing circuit is lower volume than older gas machines (2.8 L plus bag; of which 1.2 L is absorbent volume).[64,65] The absorber head is not warmed. Loose carbon dioxide absorbent granules or prefilled canisters may be used. There is an

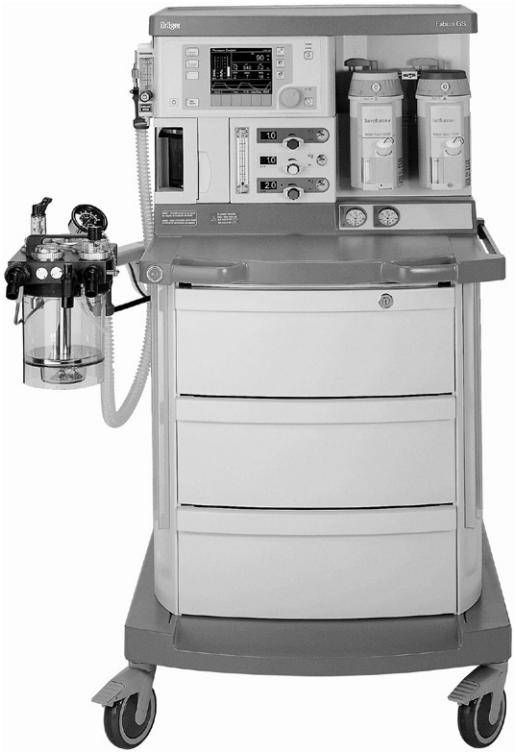

FIGURE **15-8** Fabius GS. (Courtesy Dräger Medical Inc, Telford, Penn.)

open scavenger interface. Fresh gas decoupling causes the manual breathing bag to fluctuate during the mechanical ventilator cycle, which serves as a further disconnect alarm.

In case of electrical power failure, there is a 45-minute battery reserve with fresh gas, vaporizers, integrated monitors, and ventilator operational. Because they are not part of the gas machine, patient monitors will not function. Several pneumatic functions remain after the battery is exhausted: vaporizers, hypoxic guard, adjustable pressure-limiting (APL or "popoff") valve, flowmeters, breathing pressure gauge, cylinder and pipeline pressure gauges, and common gas outlet flowmeter.

Narkomed 6000/6400

The Dräger Narkomed 6000 (Figure 15-9) includes volume, pressure, flow, and inspired oxygen monitoring. It also includes gas monitoring (infrared agent and carbon dioxide) and an ultrasonic flow sensor in the breathing circuit (unique to this machine). An integrated patient monitoring module is available as an option, so all parameters are displayed on the single-touch screen.[66]

The 6000 includes a piston ventilator (Divan) with tidal volume corrected for leaks, patient and breathing circuit compliance, and fresh gas flow (by fresh gas decoupling). The ventilator is capable of manual, spontaneous, VCV, PCV, and SIMV modes. Like the Fabius GS, there is no "bag/vent" switch, because changing ventilator mode is controlled electronically. Like most new model ventilators, it is accurate to very low tidal volume (range 10 to 1400 mL), which lessens the need for nonrebreathing circuits.

From a cold startup, there is a 1-minute power-on self-test, then a 5-minute ventilator self-test.[66] One can bypass the ventilator test for 10 days (or 10 times) only, after which the ventilator is unavailable until its self-test is performed. The machine checkout, as with most newer machines, is unique is some respects. For example, the manufacturer recommends breathing through each

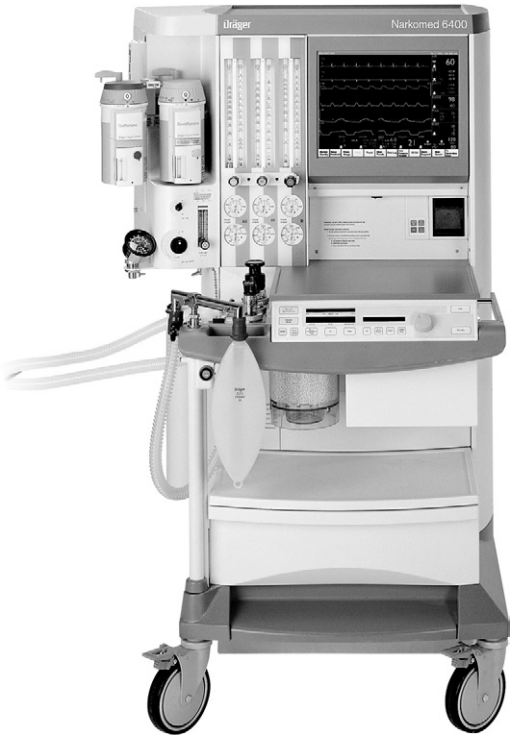

FIGURE **15-9** Dräger Narkomed 6000/6400. (Courtesy Dräger Medical Inc, Telford, Penn.)

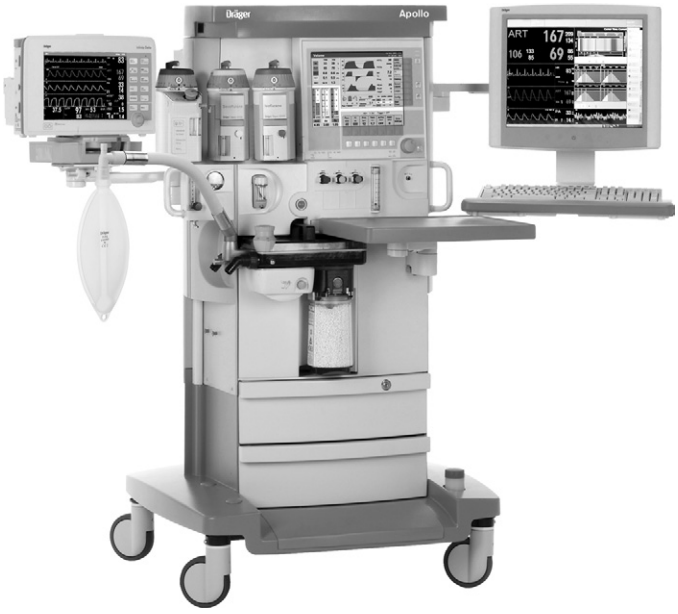

FIGURE **15-10** Dräger Apollo. (Courtesy Dräger Medical Inc, Telford, Penn.)

FIGURE **15-11** GE Healthcare Aestiva. (Courtesy GE Healthcare, Madison, Wis.)

circuit limb to test unidirectional valves and disconnecting the oxygen wall hose to check the oxygen pipeline pressure-failure device. Sample checkout protocols are available.[63]

Flowmeters are composed of needle valves and glass flowtubes, but electronic capture of fresh gas flows has been added in the 6400. Variable-bypass vaporizers are used, and these may be removed without tools. The breathing circuit is lower volume (1.5 L absorbent volume), and the absorber head is warmed.[66] Only loose carbon dioxide–absorbent granules may be used. An open scavenger interface or passive evacuation may be used. In case of power failure, there is a 30-minute battery reserve with fresh gas, vaporizers, monitors, and ventilator operational.

Apollo

The Dräger Apollo (Figure 15-10) includes volume, pressure, flow, and inspired oxygen monitoring. It also includes gas monitoring (agent and carbon dioxide). Spirometry is optional.[15,61,62] The piston ventilator corrects tidal volume for leaks, compliance, and fresh gas flow (by fresh gas decoupling). Like the Fabius, the mechanical ventilator is activated in two steps (the mode is chosen, and then confirmed by a second key press). The ventilator is capable of manual, spontaneous, VCV, PCV, PSV, and SIMV modes. SIMV may be used in either volume or pressure modes. It is accurate to very low tidal volume (range 20 to 1400 mL).[62,67] Mechanical needle valves govern fresh gas flow, which is electronically measured and displayed on screen. A backup total fresh gas flowmeter tube is present. An electronic checklist assists the user in pre-use checkout.[61] The scavenger interface is open.

Aestiva

The Aestiva (GE Healthcare; Figure 15-11) has many traditional (i.e., mechanical/pneumatic) systems, but with a modern and capable 7900 ventilator. It includes volume, pressure, flow, and inspired oxygen monitoring. Gas analysis and patient physiologic monitors must be added (like most current machines except ADU, Aisys, Avance, and 6400).[15,68] The 7900 ventilator uses an oxygen-driven standing bellows capable of manual, spontaneous, VCV, PCV, PSV-Pro (which includes apnea backup[69]), and SIMV.

The flow sensors compensate tidal volume for compliance losses and leaks in the absorber head and bellows, so the ventilator is accurate to very low tidal volume (range 20-1500 mL).[67] These variable orifice flow sensors have shown some sensitivity to moisture in the breathing circuit in the past.[70] The "bag/vent" switch activates the mechanical ventilator in one step. The absorber

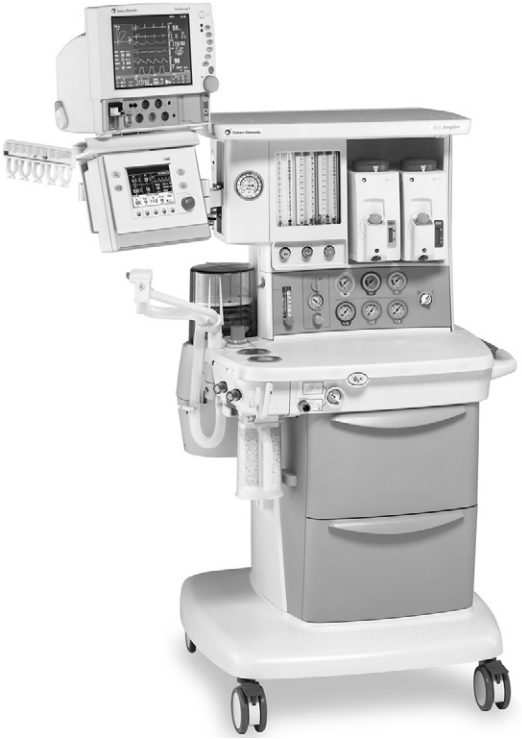

FIGURE **15-12** GE Healthcare Aespire. (Courtesy GE Healthcare, Madison, Wis.)

FIGURE **15-13** GE Healthcare Aisys. (Courtesy GE Healthcare, Madison, Wis.)

head design allows for easier disassembly and cleaning than older models. The Aestiva uses a pre-use checklist that relies on the user to perform more manual procedures than the checklist for the Apollo, Fabius, Aisys, or ADU.

Flowmeters are traditional mechanical needle valves with glass flowmeter tubes. Thus there is no electronic capture of fresh gas flows, as in machines with digital flow display. The oxygen sensor is the galvanic fuel cell type, and the hypoxic guard is mechanical (Link-25).[68] Variable-bypass vaporizers are used, and these may be removed without tools. The breathing circuit is relatively high volume (5.5 L, including dual canisters of 1.35 kg absorbent each).[64,71] Loose fill granules or prepackaged absorbent may be used. The machine is compatible with circle or nonrebreathing circuits. The scavenger is available as a closed scavenger interface. There is a 30-minute battery reserve with fresh gas, vaporizers, and ventilator operational. The Aestiva is also available in a version compatible with the magnetic resonance imaging (MRI) suite.

Aespire

The Aespire (GE Healthcare; Figure 15-12) is like the Aestiva in most of its systems, but is more compact. The standing bellows, oxygen-driven ventilator offers tidal volume compensation. Volume control and pressure control are the two modes of ventilation available.[72]

Aisys

The Aisys (GE Healthcare), along with Avance, ADU, and 6400, is a complete workstation, in that physiologic monitors are included (e.g., electrocardiography, blood pressure, pulse oximetry).[59] The Aisys (Figure 15-13), introduced in 2005, uses the oxygen-driven, standing bellows 7900 Smartvent (like Aestiva) but offers more modes. Modes available include manual, spontaneous, VCV, PCV, pressure control with volume guarantee (PCV-VG, which is unique to Aisys and Avance), PSV-Pro with apnea backup, and SIMV with pressure support of the patient's spontaneous breaths (SIMV-PS) in either volume or pressure mode. Spirometry is included to help monitor and control ventilation. The ventilator can support a very wide range of tidal volumes (20-1500 mL[67]), so there is no need for nonrebreathing circuits for children. Like most modern ventilators, the low circuit volume, freedom from leaks, and microprocessor control support the use of low-flow anesthesia. The fresh gas inlet enters the circle system distal to the inspiratory valve (like Avance and ADU), supporting fast response to changes in desired gas concentrations, even at low flows.[73]

Aisys is similar to the ADU in that it uses Aladin cassette vaporizers, which are electronically controlled. Aisys is similar to Avance—and unique in the North American market—in that it uses electronic control, measurement, and display of fresh gases (Figure 15-14). The user does not control the flow of each gas directly, as is usual, but instead selects the desired carrier gas (nitrous oxide or air), total fresh gas flow, and inspired oxygen concentration. There are no needle valves or glass flowmeter tubes to control individual flows of oxygen, nitrous oxide, or air. In case of electronic failure, there is a backup needle valve and glass flowmeter tube for control and display of total fresh gas flow.[15,58,59]

Avance

The Avance (GE Healthcare; Figure 15-15) is similar to the Aisys in most respects: electronic fresh gas flow controls with backup pneumatic control, modern and capable multimode 7900 ventilator, spirometry, and integrated physiologic monitoring. The pneumatic/mechanical Tec 6 and Tec 7 vaporizers included in the Avance are the primary difference between it and the Aisys.

ADU

The ADU (GE Healthcare; Figure 15-16) includes all monitoring: volume, pressure, flow, inspired oxygen, gas analysis (agent and carbon dioxide), patient physiologic monitoring, and spirometry (flow-volume and pressure-volume respiratory loops). The ventilator is an oxygen-driven standing bellows, with tidal volume

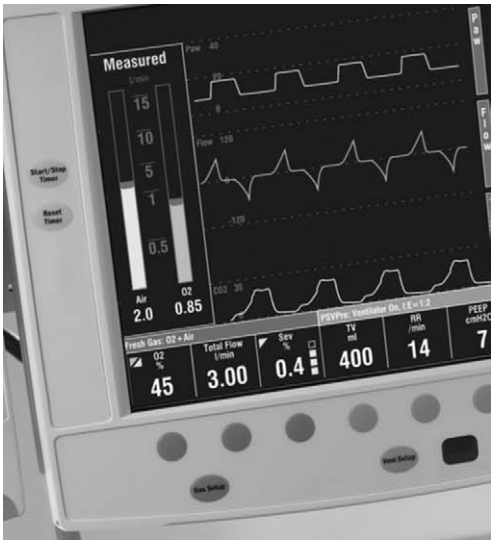

FIGURE **15-14** Electronic control of inspired oxygen, carrier gas, and total fresh gas flow, Aisys. (Courtesy GE Healthcare, Madison, Wis.)

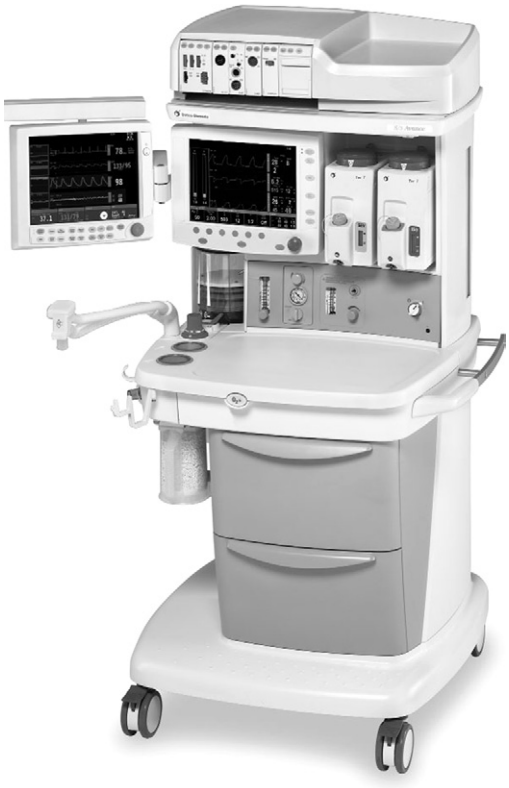

FIGURE **15-15** GE Healthcare Avance. (Courtesy GE Healthcare, Madison, Wis.)

corrected for leaks, compliance, and fresh gas flow (via the D-Lite sensor at the Y-piece). It is accurate to very low tidal volumes (20-1400 mL[74]) and capable of manual, spontaneous, VCV, PCV, SIMV, and PSV. The "bag/vent" switch activates the mechanical ventilator in one step.[54,74]

The ADU (like Aisys, Fabius, and Apollo) uses an almost completely automated checklist routine. Because the D-Lite sensor is removed from the breathing circuit during checkout, one must perform a high-pressure check of the breathing circuit after reassembly.

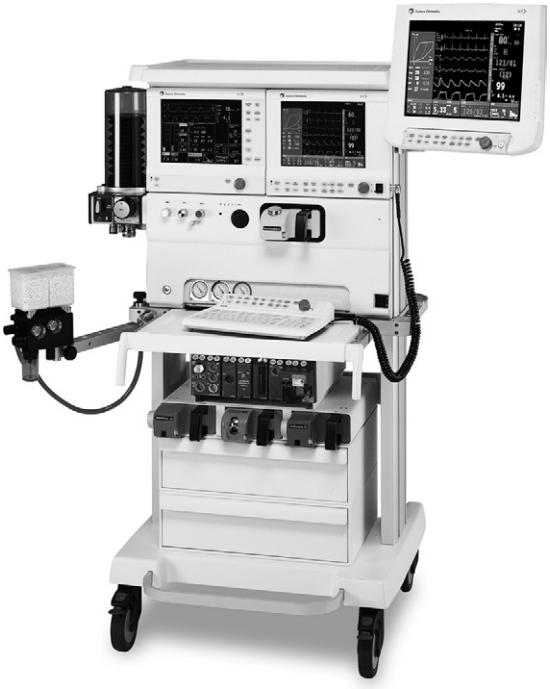

FIGURE **15-16** GE Healthcare Anesthesia Delivery Unit (ADU). Machine monitors are on the left screen (including video screen display of fresh gas flow); patient monitors are on the right (including electrocardiograph and blood pressure). (Courtesy GE Healthcare, Madison, Wis.)

Fresh gas flow control is accomplished by mechanical needle valves. Flow is captured and displayed electronically, with a glass common gas outlet flowmeter as an optional backup. The Aladin vaporizer cassettes may be tipped from the vertical during transport without any risk, because they are merely repositories for liquid anesthetic. The vaporizer's electronic mechanisms, which are within the gas machine, control the delivery of any agent chosen.

The breathing circuit is very low volume, about 2 L (with 600 mL absorbent volume).[74] Only the manufacturer's carbon dioxide absorbent canisters may be used, which are single-use or refillable with loose granules. Certain disposables are only available from the manufacturer (e.g., spirometry tubing, D-Lite sensor, absorbent granule canisters). The machine is technically compatible with nonrebreathing circuits, but the need for them is questionable because the machine can ventilate patients who weigh as little as 3 kg.

The scavenger interface is open. Scavenger suction adequacy is indicated on an optional glass flowmeter below the bellows. There is a 30-minute battery reserve with fresh gas, vaporizers, and ventilator operational. Patient monitoring (right screen) is lost unless main electrical power (or generator backup) is available. In this respect most gas machines, new or old, function similarly.

Path of Gases Through the Machine

Oxygen, nitrous oxide, and air follow similar paths through the anesthesia gas machine (see Figure 15-1). Each passes from its supply point to a flowmeter. All gases (except oxygen and in newer models, air) pass through a fail-safe valve before proceeding to their flowmeters. This valve is held open by pressure in the oxygen circuitry within the anesthesia gas machine. After passing through their respective flowmeters, the gases are joined for the first time in a common manifold. Oxygen is always added to the common manifold downstream of other gases so that the chance of hypoxic

BOX 15-6

Components of Flowmeters

- Knob
- Needle valve
- Valve stops (not present on all machines)
- Flowtube
- Indicator float

breathing mixtures is lessened (e.g., in the event that a flowmeter tube has cracked).[75] The combined gases enter any vaporizer that is turned on, and then pass through the common gas outlet. A delivery hose with a locking connection conducts gases from the common gas outlet to the breathing circuit.

The breathing circuit and ventilator (if used) transport gases to and from the patient. An amount equal to the fresh gas flow per minute (minus patient uptake, plus gases excreted), leaves the breathing circuit and is conducted to the scavenger interface. From there, it is disposed of in the hospital ventilation or suction systems.

Five Tasks of Oxygen

Oxygen has five tasks in the anesthesia gas machine: (1) it proceeds to the fresh gas flowmeter, (2) powers the oxygen flush, (3) activates fail-safe mechanisms, (4) activates oxygen low-pressure alarms, and (5) compresses the bellows of mechanical ventilators (see Figure 15-1). The other gases supplied by the machine have only one pathway; they are transported via flowmeter and breathing circuit to anesthetize the patient (nitrous oxide) or sustain life (oxygen, and the oxygen fraction from the air flowmeter). Newer machines can switch to air as a driving gas for the ventilator bellows if oxygen pressure is lost.

Flowmeter

The first task of oxygen is proceeding through the flowmeter and on to the patient as a life-sustaining gas. Flowmeters have several components (Box 15-6). Control knobs are color and touch coded; thus the oxygen flow control knob is distinct, in visual appearance and tactile form, from the control knobs for the other gases (Figure 15-17).[76,77]

It is not necessary to use more than moderate force to shut off gas flow. The needle valve, which controls gas flow through the flowmeter, can be damaged if excessive force is used. Valve stops (Figure 15-18) are usually incorporated to prevent damage. Note that there are no valve stops in the ADU needle valves. Flow increases when the knob is turned counterclockwise. All current gas machines use mechanical needle valves except Avance and Aisys, which use electronic controls for flow. On these machines, backup oxygen controls using mechanical/pneumatic needle valves are present, in case of electronic or electric failure.

Display of Fresh Gas Flow. An indicator float in a glass tube (Thorpe tube) is the classic way to capture and display fresh gas flow. Oxygen flow and concentration is calibrated to ±5% (or ±20 mL/min) accuracy at room temperature and sea level.[57] Flowmeter tubes are specific for each gas and cannot be interchanged. The flowtube is tapered to be narrower at its bottom. Thus it may be referred to as a *variable orifice flowmeter* because the annular opening around the float is larger at higher flows. If a gas has two tubes, they are connected in series with a single control valve (Figure 15-19). It is standard in the United States (but not in the United Kingdom) for the oxygen flowtube to be placed to the right of other

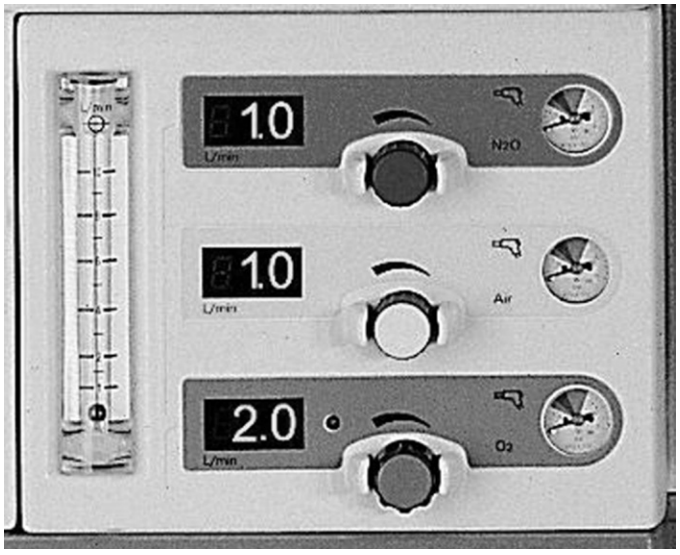

FIGURE **15-17** Flowmeters on the Fabius GS are arranged vertically. The oxygen knob (*at the bottom*) is different visually, and to touch, from control knobs for air and nitrous oxide. To the left of each flow-control knob is a digital display of flow; to the right is the pipeline pressure gauge for each gas. The common gas outlet flowmeter is to the left. (Copyright Drägerwerk AG & Co. KGaA, Lubeck. All rights reserved.)

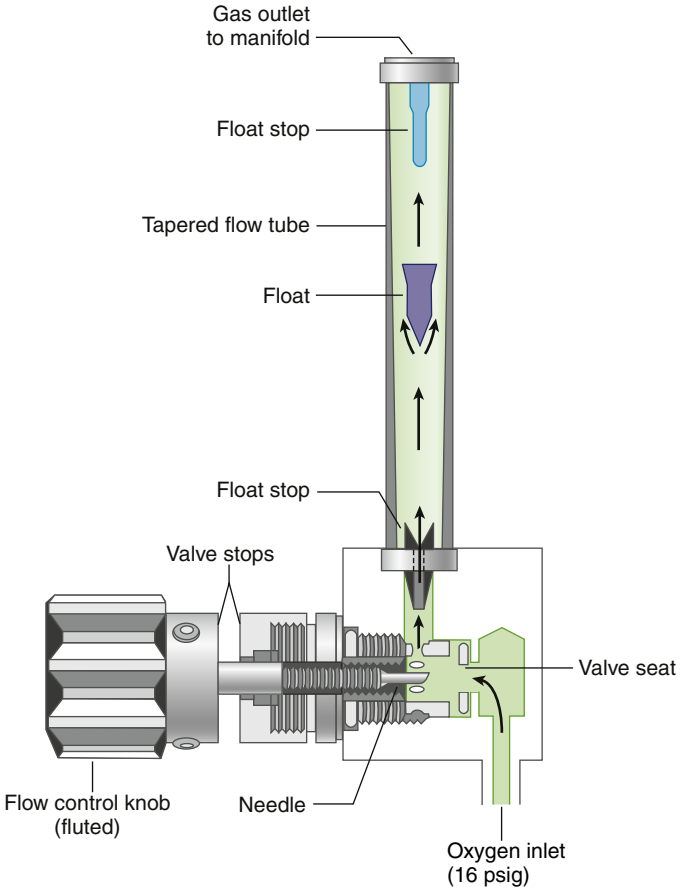

FIGURE **15-18** Flowmeter components. (From Bowie E, Huffman LM. *The Anesthesia Machine: Essentials for Understanding*. Madison, Wis: Datex-Ohmeda; 1985.)

flowtubes. Flowmeters on the Fabius GS are unique in that they are arranged vertically, rather than side by side (Figure 15-17).[60,65] The flowtubes are the most fragile part of the machine. They are susceptible to breakage, leaks at their seals, and inaccuracy due to the presence of dirt or static electricity.[25]

Rather than using glass flowtube displays, many newer gas machines capture and display flows electronically by means of an anemometer, or by a transducer and chamber of known volume. The chamber fills to a set pressure, and then the gas is allowed to proceed. The number of times this cycle occurs per minute can be converted to gas flow, which can be saved and sent to the automated medical record. These newer machines dispense with glass flowtubes, instead displaying fresh gas flows as colored bar graphs, with numeric data, on a computer screen (e.g., ADU, Fabius GS, Aisys, Apollo). At the common gas outlet, machines with electronic flow displays have a backup glass flowmeter, to measure total fresh gas flow continuously, and in the event of screen or electrical power failure. The Narkomed 6400 uses regular glass flowtubes for display of flows, but can capture flows electronically.[66]

Setting fresh gas flow on the Aisys and Avance is quite different. The flowmeter controls and display are all electronic. The display is numeric, with an optional bar-graph display. The user sets the inspired oxygen concentration desired, the total fresh gas flow, and what carrier gas is desired (nitrous oxide or air) (see Figure 15-14).[57-59,73]

Care of Flowmeters. Flowmeters with conventional needle valves and glass flowtubes should be turned off before pipelines are connected, cylinders are opened, or the machine is turned on. If a flowtube is left open, the float will shoot to the top of a glass tube and may damage it. Flowmeters should be included in visual monitoring sweeps. Never adjust a flowmeter without looking at it. Read ball-type indicator floats in their center (Dräger) and plumb bob–type floats at the top (older Datex-Ohmeda). Remember to turn off flowmeters after each case, and particularly at the end of the day. Failure to do so may contribute to premature drying of the carbon dioxide absorbent, which not only hastens its exhaustion, but has been implicated in an increased degradation of volatile agent, the generation of carbon monoxide in canisters, and canister fires.[78-86]

Other Flowmeters

Auxiliary Oxygen Flowmeters. Auxiliary oxygen flowmeters are an accessory currently offered on most models of gas machines. They are useful for attaching a nasal cannula or simple face mask. In the past, it was common to attach a nasal cannula to an adapter at the common gas outlet. The auxiliary oxygen flowmeter is advantageous, because the breathing circuit and gas delivery hose (between the common gas outlet and breathing circuit) remain intact while supplemental oxygen is delivered to a spontaneously breathing patient. Thus if the anesthetist needs to switch from a nasal cannula to the circle breathing system during a case, he or she can accomplish this instantaneously and without the possibility of forgetting to reconfigure the breathing circuit properly. Another advantage is that an oxygen source is readily available for the Ambu bag if the patient needs to be ventilated manually for any reason during a case (e.g., breathing circuit failure). One disadvantage is that the auxiliary flowmeter is unusable if the pipeline supply has lost pressure or been contaminated; this is because the auxiliary flowmeter is supplied by the same wall outlet and hose connection that supplies the main oxygen flowmeter. If users do not realize this, time could be wasted while they attempt to use this potential oxygen source.[87] Another disadvantage is that the fraction of inspired oxygen supplied cannot be varied with the auxiliary flowmeter. The chance of fire in sedated patients undergoing head and neck surgery can be lessened with reduced F_{IO_2}, scavenging the oxygen, and tenting the drapes.[88]

Common Gas Outlet Flowmeters. Common gas outlet flowmeters (Figure 15-20; also, to the left in Figure 15-17) are used as a backup on gas machines that electronically capture and display flows on a computer screen. If offered as an option, they are strongly recommended; they are the only indication of oxygen flow if the computer display fails, or in a power-failure situation after battery backup is exhausted.

Scavenging Flowmeters. Scavenging flowmeters are used on most new machines that use scavenging interfaces. An indication that suction is adequate is mandatory with these systems, in order to avoid exposure to waste anesthesia gases (see Disposal section). Unfortunately, the suction indicator is usually not visible from the operator's normal position.[89] On the Fabius GS, for example, it is on the back of the machine near the E cylinders.[60] On the ADU, the scavenger suction flowmeter is behind and beneath the bellows block on the left side of the machine (Figure 15-21).[54] On the Aisys, the adjustment is beneath the bellows block.[90] Even

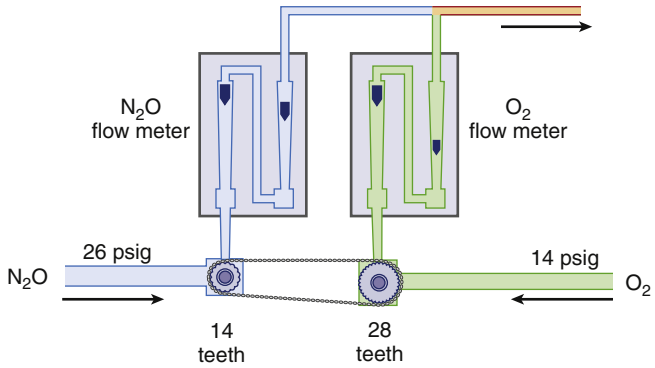

FIGURE **15-19** When two flowmeters are present for one gas, they are arranged in series (gas flows first through fine [calibrated in mL] then coarse [calibrated in liters] flow tubes). The figure also depicts the Link-25 proportioning system. (From Miller RD, et al, eds. *Miller's Anesthesia*. 7th ed. Philadelphia: Churchill Livingstone; 2010.)

FIGURE **15-20** The common gas outlet flowmeter on the ADU is located to the left of the writing surface. (From *S/5 Anesthesia Delivery Unit User's Reference Manual,* Catalog No. 8502304. Madison, Wis: Datex-Ohmeda; 2000.)

though scavenging flowmeters are desirable, they may not be included with the basic package but only as an optional accessory (e.g., the ADU).

Oxygen Flush

The second task of oxygen in the processing area of the machine is to supply the oxygen flush valve. The flush valve is required by standard to deliver from 35 to 75 L/min.[18,91] The purpose of the flush valve is to quickly fill the breathing circuit with oxygen. The flush valve is often protected by a rim that lessens the chance of accidental activation of the flush. Should this occur, barotrauma can result. Users should avoid activating the flush while the mechanical ventilator is in the inspiratory phase; during this phase, the ventilator relief valve closes, preventing gas from exiting to the scavenger.[92] If flushing is necessary for filling the ventilator bellows, it should be done in short pulses, during the expiratory phase.

The oxygen flush line proceeds directly from the gas supply source to the common gas outlet (see Figure 15-1). Activating the flush bypasses the vaporizers, and adds 100% oxygen to the breathing circuit. If partial pressures of nitrous oxide or volatile agent have already been established in the breathing circuit (during maintenance), excessive use of the oxygen flush tends to dilute these inhaled agents and may lessen the depth of anesthesia.

FIGURE **15-21** The scavenger suction flowmeter on the ADU is located behind and beneath the bellows block on the left side of the machine.

Fail-Safe Systems

If pipeline oxygen pressure fails, and other gases such as nitrous oxide keep flowing, the patient might receive a hypoxic gas mixture (less than 21% oxygen). Therefore gas machines incorporate devices that halt the supply of all other gases in the event of oxygen supply pressure failure. These are called *fail-safe systems*. It is required by standard that the set concentration of oxygen at the common gas outlet does not decline if the pipeline pressure decreases.[18] This requirement is satisfied by the presence of gate-like valves in the internal supply line for nonoxygen gases. The "gate" in each is held open by pressure in the oxygen line (Figure 15-22). Flow of nitrous oxide may be shut off with oxygen pressure below a set limit (e.g., Avance, Fabius GS) or proportionally decreased (e.g., Aestiva, ADU).[54,57,68,71,74] It is important to note that fail-safe systems do not analyze oxygen pipeline contents, so they are activated only if oxygen pipeline pressure falls. They do not protect the patient from a crossover, in which oxygen pipeline pressure is intact, but the line does not contain oxygen.

Fail-safe devices were once placed in air lines as well, with the rationale of leaving oxygen (however briefly) as the last gas flowing, even if oxygen pipeline pressure is lost. However, it is not possible to deliver a hypoxic mixture of air, and leaving air flowing is useful to drive the ventilator bellows in case of oxygen pipeline pressure failure. So the trend in newer equipment is to place fail-safe valves in the nitrous oxide line only, and rely on electronic proportioning systems to prevent hypoxic gas mixtures if oxygen pipeline pressure fails. This is accomplished by shutting off nitrous oxide, and leaving agent and air flowing, with air available to drive the ventilator bellows.

Low-Pressure Alarms

The fourth task of oxygen is powering the low-pressure alarms, which signal the operator when pressure is lost in the oxygen circuitry. The older oxygen supply failure alarm was a container with a whistle at its outlet that was pressurized by oxygen when the anesthesia gas machine was turned on. When pipeline pressure decreased to 28 psi, or when the machine was shut off, a characteristic loud whistle was heard as the container released its contents. Newer models lack this distinctive alarm, substituting a variety of visual and auditory alarms.[20,29,32] The proper response to loss of

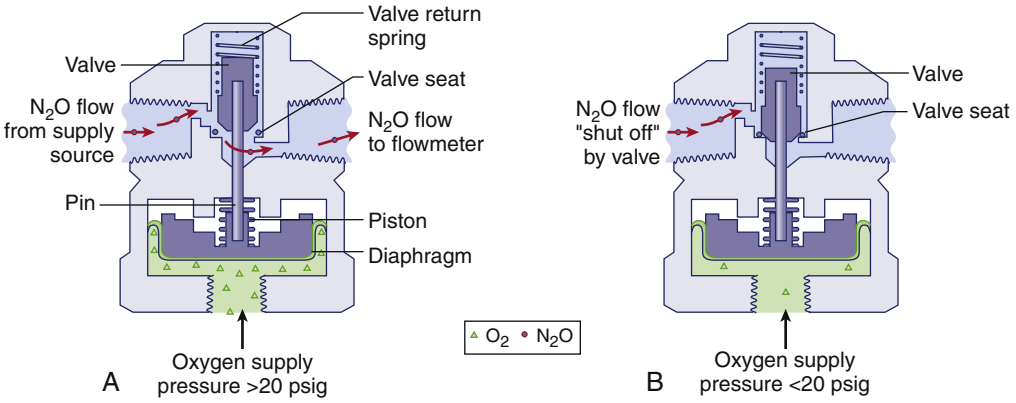

FIGURE **15-22** Fail-safe valve in the nitrous oxide line. (Redrawn from Bowie E, Huffman LM: The Anesthesia machine: Essentials for Understanding. Madison, WI, Ohmeda, A Division of BOC Health Care, Inc., 1985. In RD Miller et al., Eds: *Miller's Anesthesia*, 7th ed, Philadelphia, 2010, Churchill Livingstone.)

pipeline pressure is discussed earlier in this chapter (see Supply section).

Ventilator Driving Gas

The fifth task of oxygen in many anesthesia gas machines is compression of the ventilator bellows. All GE Healthcare anesthesia ventilators use 100% oxygen as their driving gas.[71,74] The ADU may use either air or oxygen, and will switch automatically from oxygen to the secondary drive gas (air) if oxygen pressure is lost.[54,74]

Older Dräger ventilators (e.g., AV-E, AV-2) used oxygen to drive a Venturi device, which augmented the driving gas with entrained room air.[93] Room air enters through a shiny (chrome or stainless steel) cylindrical muffler, which may be seen at the back of some Narkomed models. If this muffler becomes dirty, insufficient gas may enter; the lack can interfere with the ability of the ventilator to compress the bellows. If driving gas is prevented from exiting via the muffler, the bellows may remain compressed and barotrauma results.

Newer model piston ventilators use electric motors to compress the bellows and deliver tidal volume (e.g., Narkomed 6000/6400, Fabius GS, Apollo).[60-62,66] Thus ventilator delivery of tidal volume is unaffected by variation in, or even the absence of, oxygen pipeline pressure. Piston ventilators may operate for prolonged periods with only cylinder supplies of gases because they do not consume oxygen to drive the bellows. This is an advantage in office-based anesthesia, in other settings where pipelines are not available, and in emergency loss of pipeline pressure.[94]

Proportioning Systems (Hypoxic Guard)

All current anesthesia gas machines incorporate nitrous oxide–oxygen proportioning ("hypoxic guard") systems designed to prevent the delivery of hypoxic breathing mixtures. All link oxygen and nitrous oxide flows, so that final breathing mixtures at the common gas outlet are at least 23% to 25% oxygen.* The ratio of nitrous oxide to oxygen is thus kept at not more than 3 to 1.

An example of a pneumatic-mechanical proportioning system is the Link-25 (used on Aestiva and Aespire). In this system, the flowmeter control knobs for nitrous oxide and oxygen are linked by a chain; oxygen flow is increased automatically when nitrous oxide flow is increased. The Link-25 system (Figures 15-19 and 15-23) also incorporates secondary regulators, so it has both pneumatic and mechanical components.

On contemporary machines, these hypoxic guard system controls are primarily electronic. Dräger Medical calls their system a "sensitive oxygen ratio controller" (S-ORC), and uses it in the Apollo, Fabius, and Narkomed 6000.[62] This system also maintains at least 23% oxygen, but does so by limiting nitrous oxide flow. Electronic alarms are incorporated, and the system includes a nitrous shutoff (so a fail-safe system is incorporated as well).

Hypoxic guard systems are not foolproof. Box 15-7 lists four situations in which a hypoxic breathing mixture can be delivered despite the use of these systems. Lack of oxygen in the oxygen pipeline may be detected with an oxygen analyzer. A system that is broken or defective[95] should be detected in the pre-use checklist, as should leaks downstream of the flowmeters. The most dangerous of these circumstances is the last, the administration of a third gas, especially that of an inert gas such as helium. It is not widely appreciated that the hypoxic guard systems link *only* nitrous oxide and oxygen. Perhaps because of the name, the faulty assumption is made that *all* hypoxic breathing mixtures are prevented. These systems would *not* prevent the administration of a hypoxic mixture if a third inert gas (such as helium) is present on the gas machine. The proper use of a calibrated oxygen analyzer in each general anesthetic will always be of vital importance.

Many older Narkomed machines have a switch with two positions: "Nitrous Oxide–Oxygen" and "All Gases." In the Nitrous Oxide–Oxygen position, the hypoxic guard is active, and only these two gases may flow. In the All Gases position, the hypoxic guard and alarms are inactivated, and all gases (except nitrous oxide) may flow.[93] The ADU has a similar switch.

Oxygen Analysis

Systems that warn of trouble with oxygen supply (low pressure alarms) or lessen the chances of hypoxemia (hypoxic guard system, fail-safe system) are based on *pressure* within the oxygen circuitry of the gas machine. They do *not* sample the oxygen lines to determine that *oxygen* is present. There is only one system that ensures that oxygen is present in the oxygen pipeline or cylinder (and ultimately in the breathing circuit and the patient): inspired oxygen analysis. Monitoring inspired oxygen is mandatory in every general anesthetic, and the function of the oxygen monitor must be checked before giving any kind of anesthesia care, because general anesthesia may need to be induced as a backup plan in any anesthetic.[96-99]

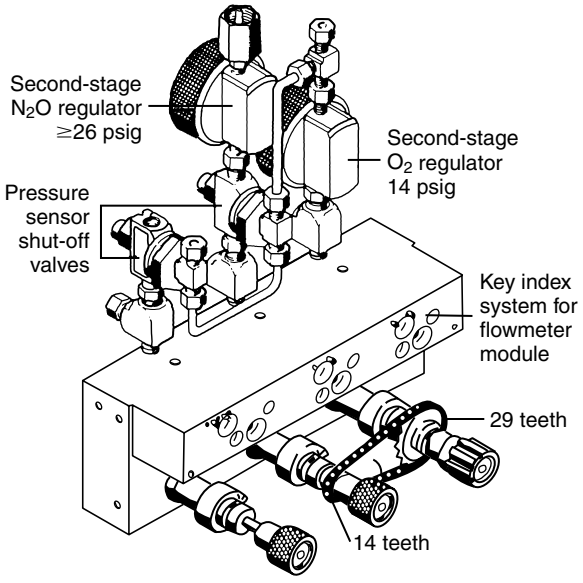

FIGURE **15-23** A chain connects oxygen and nitrous oxide flow controls in the Link-25 proportioning system. Either may be adjusted separately, but the chain enforces at most a 3:1 ratio of nitrous oxide to oxygen. The chain is not normally visible. (Courtesy Datex-Ohmeda, Madison, Wis.)

BOX **15-7**

Circumstances Under Which Hypoxic Guard Systems Can Permit Formation of a Hypoxic Mixture

- Wrong supply of gas in oxygen pipeline or cylinder
- Defective pneumatics or mechanics
- Leaks downstream of flow control valves
- Inert gas administration (e.g., a third gas such as helium)

*References 54, 57, 60, 62, 66, 73, 90.

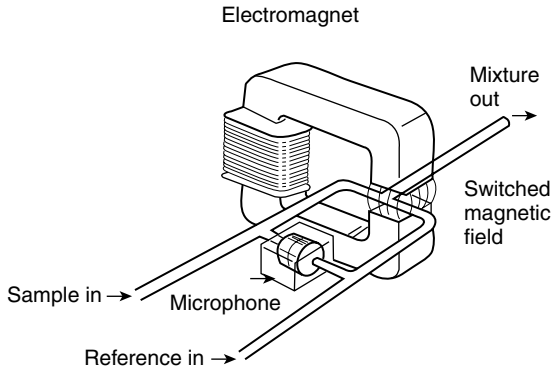

FIGURE **15-24** Paramagnetic oxygen analyzer. (Courtesy Datex-Ohmeda, Madison, Wis.)

Two types of sensors are in current use: electrochemical (galvanic fuel-cell; found in Aestiva, Aespire), and the paramagnetic analyzer (most others). The paramagnetic analyzer (Figure 15-24) is widely used because of its fast response, low cost, and extremely low maintenance requirements.[100] A paramagnetic analyzer is often found in gas analysis monitors (which detect anesthetic agent and carbon dioxide).

Vaporizers

Underlying Physical Principles

A vapor is composed of molecules (in the gaseous phase) of a substance that is a liquid at room temperature and 1 atmosphere of pressure. Vaporization proceeds at a rate that depends on the physical characteristics of the vaporizing liquid and the temperature. Different liquids evaporate at different rates. Elevated temperature increases the rate of evaporation of any liquid, whereas decreased temperature slows the rate. As evaporation proceeds, the remaining liquid and its container cool because heat energy is carried from the liquid with the energetic, mobile, evaporating molecules. An example would be the cooling effect of stepping out of the shower, or the chilling effect of evaporating gasoline or ether on the hand. In both cases, the evaporating molecules acquire the latent heat of vaporization from their surroundings. Thus one would expect an anesthetic vaporizer to cool as vaporization proceeds. This cooling slows the rate of further vaporization. To prevent this, materials such as copper are chosen for containing liquid anesthetics in current vaporizers. Copper has high thermal conductivity (transferring environmental heat easily to the liquid anesthetic) and high thermal capacity (acting as a thermal reservoir to help stabilize liquid anesthetic temperature).[25,77,101]

The rate of vaporization depends only on the temperature, the vapor pressure of the liquid, and the partial pressure of the vapor above the evaporating liquid—not on the ambient pressure of the remaining gases present. For example, water at constant temperature evaporates at the same rate into completely dry air, regardless of whether it is at sea level, in a hyperbaric chamber, or at elevations far above sea level.

Classification and Design

Variable-Bypass. Table 15-2 compares current variable-bypass vaporizers with heated-vapor (Tec 6) types.[25,102-106] All vaporizers blend the combined flow of fresh gases from the flowmeters with sufficient vapor to form clinically useful concentrations. The problem is ensuring that the vapor concentration is appropriately limited. For example, a fully saturated isoflurane vapor consists of nearly 31% isoflurane (238 mmHg [31 kPa], the saturated vapor pressure of isoflurane at 20° C divided by the barometric pressure of 760 mmHg [101 kPa]).[77] To limit vapor output to a clinically useful concentration, only a small portion of the fresh gas flow is allowed to come into contact with the liquid and pick up anesthetic vapor.

TABLE 15-2 Classification of Vaporizers

Characteristic	Variable Bypass	Injector
Example	Datex-Ohmeda Tec 4, 5, 7 ADU Aladin Dräger Vapor 19, 2000	Datex-Ohmeda Tec 6 (Desflurane)
Splitting ratio (carrier gas flow)	Variable-bypass (vaporizer determines carrier gas split)	Dual-circuit (carrier gas is not split)
Method of vaporization	Flow-over	Gas/vapor blender (heat produces vapor, which is injected into fresh gas flow)
Temperature compensation	Automatic temperature compensation mechanism	Electrically heated to a constant temperature (39° C, thermostatically controlled)
Calibration	Calibrated, agent specific	Calibrated, agent specific
Position	Out of circuit	Out of circuit
Capacity	Tec 5, 300 mL; Tec 7, 225 mL; Vapor 19, 200 mL; Aladin, 250 mL	390 mL

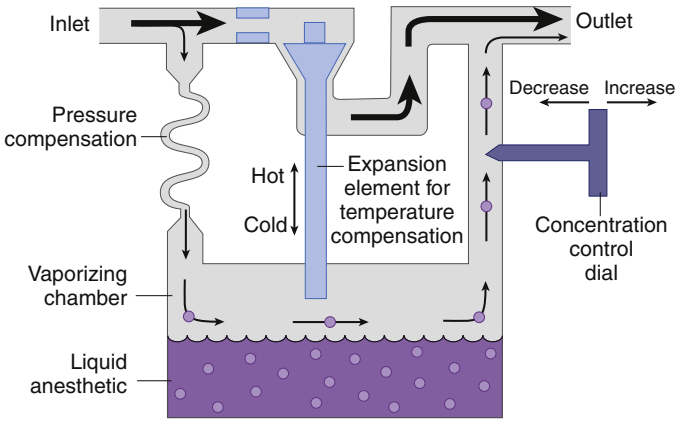

FIGURE **15-25** The Dräger Vapor 19 vaporizer. (Copyright Drägerwerk AG & Co. KGaA, Lubeck. All rights reserved.)

The *splitting ratio* (gas entering the vaporizing chamber, divided by total fresh gas flow) is automatically determined in a variable-bypass vaporizer by the internal resistance to flow; the operator merely has to set the control dial to the desired concentration (Figure 15-25). Setting the dial to a higher percentage increases the amount of flow sent through the vaporizing chamber. The small portion of the gas flow entering the vaporizing chamber ("carrier gas" or "chamber flow") flows over the liquid and picks up anesthetic vapor. Full saturation of the carrier gas is ensured

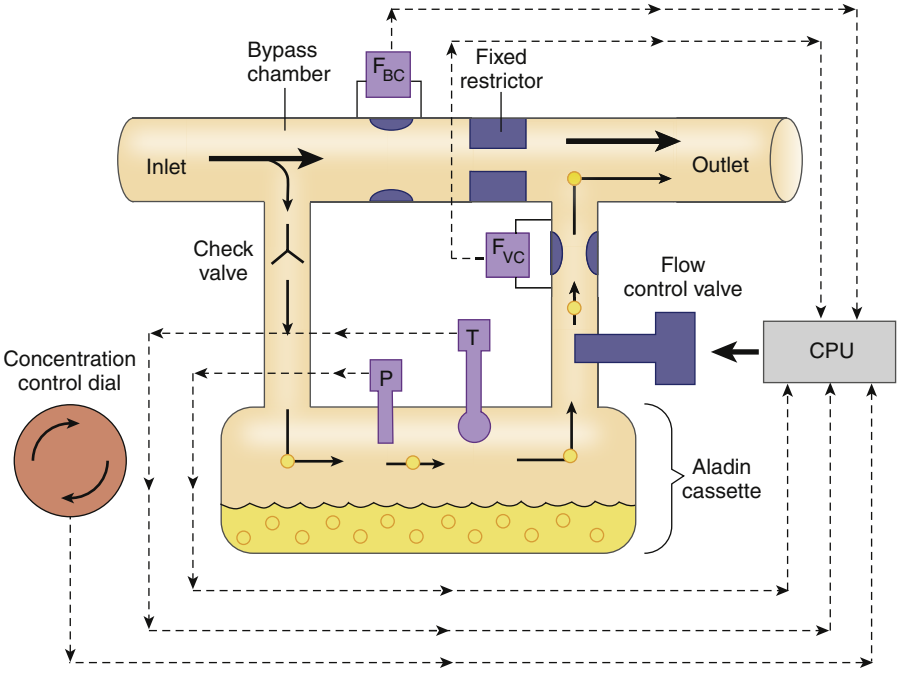

FIGURE **15-26** The ADU vaporizer. A microprocessor controls output by monitoring F_{BC} (bypass chamber flow), F_{VC} (vaporizing chamber flow), P (pressure), and T (temperature) in the vaporizing chamber. (From Miller RD, et al, eds. *Miller's Anesthesia*. 7th ed. Philadelphia: Churchill Livingstone; 2010.)

by means of a series of wicks and baffles. This fully saturated (and thus known) concentration of carrier gas at the vaporizing chamber outlet is then diluted with the balance of the fresh gas that bypassed the vaporizing chamber ("bypass flow") to produce the desired final concentration at the vaporizer outlet.

A temperature-compensation device is built into variable-bypass vaporizers, so that more gas is directed into the vaporizing chamber as the vaporizer cools. Variable-bypass vaporizers are calibrated for concentration and are agent specific. Like the Tec 6, variable-bypass vaporizers are *out of circuit*, meaning out of the breathing circuit. Their capacities for liquid agent are listed in Table 15-2. Variable-bypass vaporizers in the ADU and Aisys are electronically controlled, based on inputs from pressure, flow, and temperature sensors at various sites in the vaporizer (Figure 15-26).

Measured-Flow (Vernitrol). Anesthetists who practice in the military, or who use older equipment on mission trips outside of North America, may encounter *measured-flow* vaporizers. In a measured-flow vaporizer, the operator determines how much gas should be bubbled through the anesthetic liquid by means of a formula; this amount is then set on a second oxygen flowmeter, marked "Oxygen for Vernitrol." If the vaporizer cools, the operator must recalculate and set a new chamber gas flow; this is called *manual temperature compensation*. These devices can be used with multiple agents and are out of the breathing circuit. It is possible to use them safely, but their design is not as inherently safe as that of more modern types.[107] Measured-flow vaporizers are no longer manufactured in the United States, and factory service for them is no longer available. The military still trains anesthetists on the use of these vaporizers, and they may be seen overseas. They are not addressed in the current anesthesia gas machine standard.[18]

Tec 6 Injector. The Tec 6 vaporizer uses a completely different principle of operation as compared with variable-bypass types (Figure 15-27): it is a heated, dual-circuit vaporizer.[103,108-113] Fresh gas flow from the common manifold passes through the vaporizer in one circuit. This fresh gas never flows over, or comes into contact with the liquid agent as it would in a variable bypass vaporizer. Instead, an appropriate amount of vapor is added to the fresh gas as it flows through the vaporizer. The vapor output has two control points. One is the setting on the concentration control dial, and the other is linked to a transducer that is responsive to the amount of fresh gas flow. Thus more vapor is delivered from the vapor circuit if either the desired volume-percent setting, or the fresh gas flow, is increased. To maintain a known vapor pressure in the second circuit, the Tec 6 is heated to 39° C; this produces a vapor pressure of approximately 1500 mmHg (200 kPa). Desflurane is near boiling at room temperature; if it were placed in a variable-bypass vaporizer, it would constitute nearly 100% of the output at first, and a hypoxic breathing mixture would result.[110,114]

The output of any modern vaporizer may be influenced by extremes of fresh gas flow, extremes of temperature, or back pressure from the breathing circuit and ventilator. Current vaporizers function accurately over a wide range of settings, at various ambient temperatures and fresh gas flows (Table 15-3).[102-104,106,115] Furthermore, they are more resistant than previous models to the effects of intermittent back pressure (the so-called "pumping effect") that increases vaporizer output. This can be accomplished by incorporating unidirectional valves at the vaporizing chamber inlet or outlet, or distal to the vaporizer.

Using Vaporizers

Contemporary vaporizers are secured to the anesthesia machine in manifolds that hold two or three units. The operator is prevented from delivering more than one agent simultaneously by an interlock system. The interlock ensures that only one vaporizer is on, that gas enters only the one that is on, that all vaporizers are

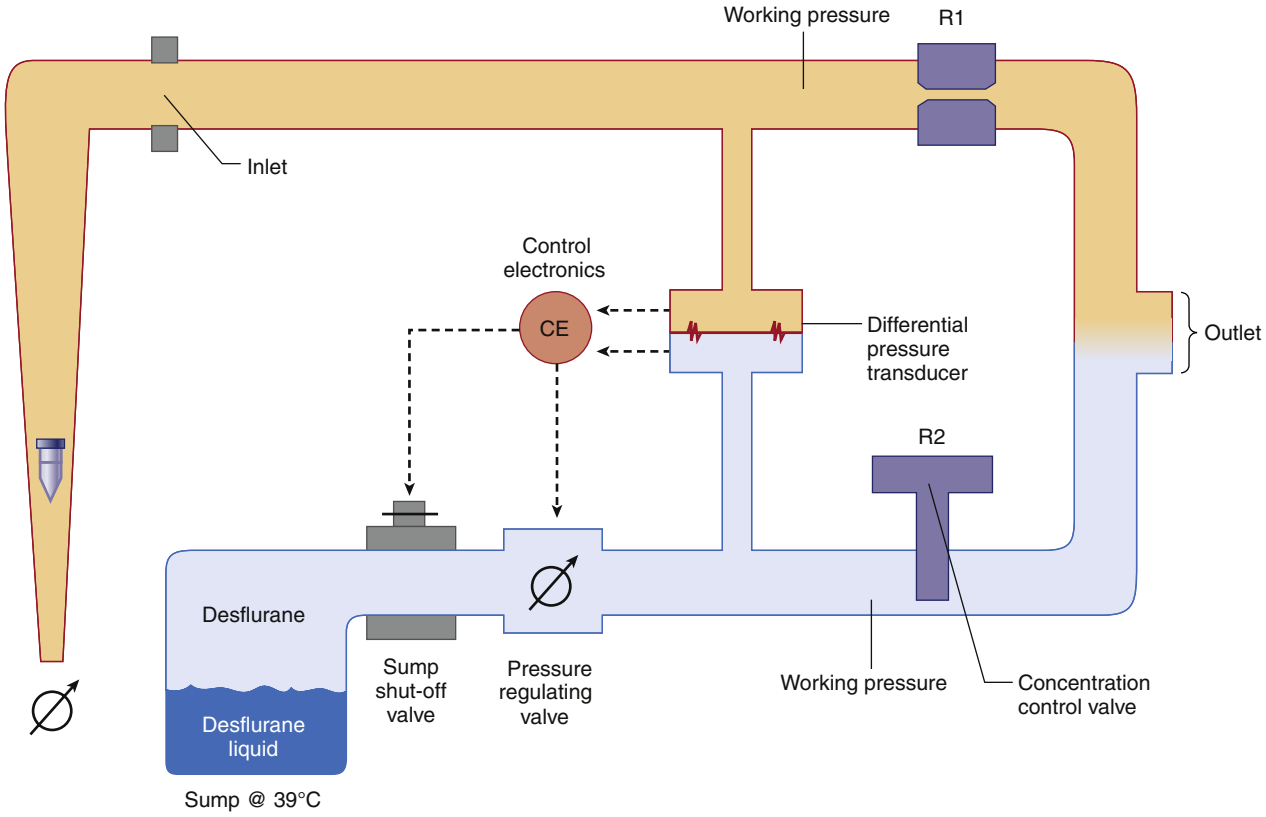

FIGURE **15-27** Principle of operation of the Datex-Ohmeda Tec 6 vaporizer. (From Miller RD, et al, eds. *Miller's Anesthesia*. 7th ed. Philadelphia: Churchill Livingstone; 2010.)

TABLE **15-3** Accuracy of Current Vaporizers*

Characteristic	Datex-Ohmeda Tec 4	Datex-Ohmeda Tec 5	Datex-Ohmeda Tec 6	Datex-Ohmeda Tec 7	Dräger Vapor 19.3	Datex-Ohmeda Aladin (ADU)
Fresh gas flow (L/min)	0.2-10	0.2-15	0.2-10	0.2-15	0.25-15	0.2-8
Temperature (° C)	20-35	17-35	18-30	18-35	15-35	18-25

*The vaporizers listed function accurately within the ranges specified.

locked in so that leaks are decreased, and that trace vapor output is minimal when a vaporizer is off.[77,116]

Variable-bypass and Tec 6 vaporizers are all filled in a similar fashion. Funnel-type (Figure 15-28) and keyed-filler–type (Figure 15-29) systems are permitted by standard.[18] Keyed-filler types are preferred because their use lessens the chance that filling with the wrong agent will occur (although it is still possible).[109,117-122] The standard requires that overfilling be prevented in the normal operating position, and that liquid level indicators be visible to the operator.[18] These indicators usually take the form of a sight glass with two etched lines, corresponding to low and maximum liquid levels within the vaporizer. To fill either the funnel type or keyed-filler vaporizers, the anesthetist should turn the vaporizer off, check the anesthetic liquid (to ensure that the agent and the vaporizer match) and then pour it in. The vaporizer is full when the liquid level reaches the maximum line on the sight glass.[115,123] It is a misconception that while using the keyed-filler vaporizer, one should hold the bottle up until it stops bubbling. If the vaporizer is turned on, is not horizontal, or the keyed-filler device is not perfectly tight on the bottle, this method results in overfilling.[124] Overfilling may result in discharge of liquid anesthetic from the vaporizer outlet, which has caused patient injuries.[25] The Tec 6 uses a similar system, but the desflurane bottle has a permanently attached, noninterchangeable spout. The sight glass on the Tec 6 is a liquid crystal display that indicates when the level of liquid is low enough to allow the addition of a full bottle, and it shows when the sump is full. Although the Tec 6 vaporizer is unique in that it can be filled while in operation,[103] it is safer to turn it off momentarily to do so. All variable-bypass vaporizers *must* be shut off while they are being filled.*

Models

The Dräger Vapor 19 fits in a manifold with an interlock system. If a vaporizer is removed from the machine, a short-circuit block must be added for leaks to be prevented. The interlock protects against simultaneous inhaled agent administration, regardless of

*References 60, 66, 102, 104, 115, 124.

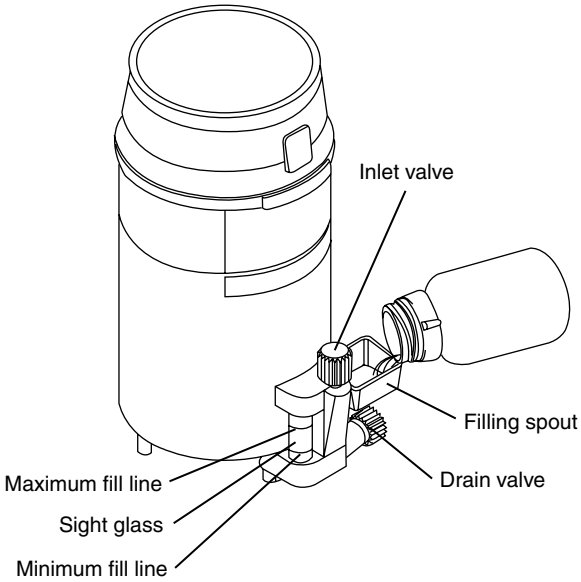

FIGURE **15-28** Filling a vaporizer with a funnel-type filling system. (From Dräger Medical Inc. *Narkomed 2C Anesthesia System—Setup and Installation Manual*. Telford, PA, 1994, Drägerwerk AG & Co. KGaA, Lubeck.)

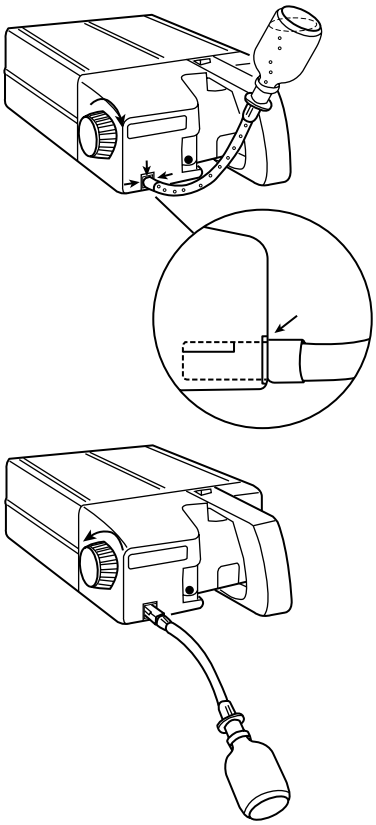

FIGURE **15-29** Filling a vaporizer with a keyed-filler system. (From *S/5 Anesthesia Delivery Unit User's Reference Manual*, Catalog No. 8502304. Madison, Wis: Datex-Ohmeda; 2000.)

which vaporizer is removed. There is no check valve between the vaporizer outlets and the common gas outlet in Dräger gas machines. The Vapor 19 has a button that must be depressed before the control dial can be turned on. All contemporary vaporizers are designed to increase agent concentration as the dial is turned counterclockwise (as viewed from above).

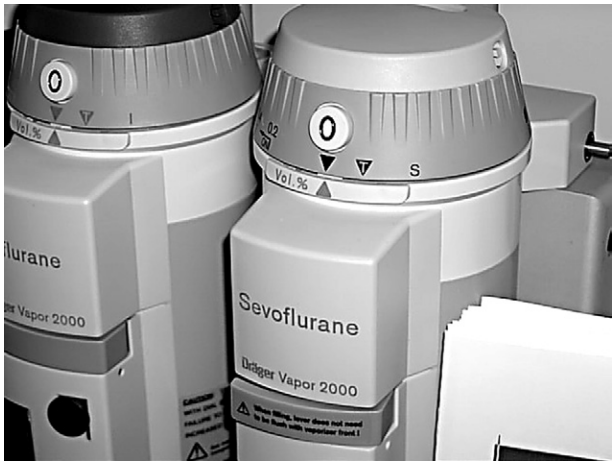

FIGURE **15-30** The Dräger Vapor 2000. Note the "T" (transport) setting to the right of "0."

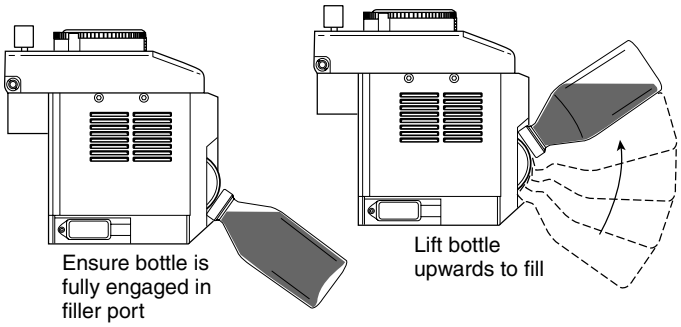

FIGURE **15-31** Filling the Datex-Ohmeda Tec 6 vaporizer. (From *Tec 6 Vaporizer: Operation and Maintenance Manual*. Madison, Wis: Datex-Ohmeda; 1993.)

The Dräger Vapor 2000 (Figure 15-30) is similar to the Vapor 19, except that it is removable by hand. It has a unique "T" (transport) setting that allows the vaporizer to be tipped or transported without liquid anesthetic fouling the control mechanisms.

The Datex-Ohmeda Tec 7 is a variable-bypass vaporizer similar to the older Tec 4 and Tec 5 models. It is designed to require less frequent service.

Use of the Datex-Ohmeda Tec 6 vaporizer is unique, as could be suspected from its unique principle of operation. However, it is not difficult to use. Filling the Tec 6 has been described in general terms. The operator must check the desflurane bottle to ensure that it is the right agent, push it into the vaporizer firmly, and rotate it upward until the display indicates that the vaporizer is full. The operator then rotates the bottle downward and holds it for an instant (to allow any drops to drain back into it). Finally, he or she supports the bottle while withdrawing it from the vaporizer (Figure 15-31).[103] If the Tec 6 leaks as it is being filled, check for the lack of an "O" ring on the bottle spout.[121]

The operator turns the Tec 6 vaporizer on by turning the concentration control dial to the "On" position while depressing the dial release (on the back of the dial, opposite the zero indicator). The vaporizer requires electric power and a warm-up period of approximately 10 minutes before it can be used from a cold start.[103]

The Tec 6 has several visual indicators that are grouped in a status display (Figure 15-32).[103] These include a light that indicates "Operational" status, a "No Output" indicator light (and audible alarm), a "Low Agent" light (and audible alarm), a "Warm-Up" status light, and an "Alarm Battery Low" light. The No Output

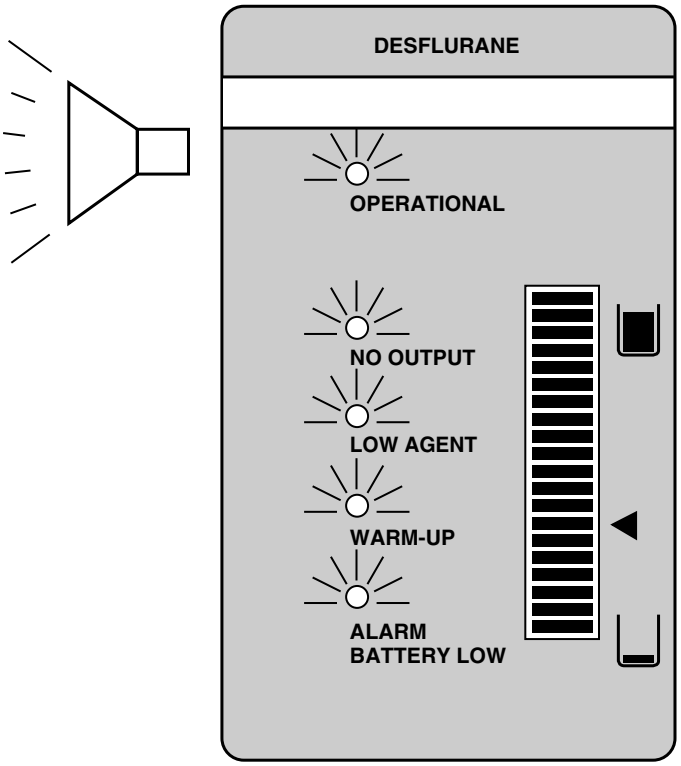

FIGURE **15-32** Display panel of the Datex-Ohmeda Tec 6 vaporizer. (From *Tec 6 Vaporizer: Operation and Maintenance Manual*. Madison, Wis: Datex-Ohmeda; 1993.)

FIGURE **15-33** Datex-Ohmeda ADU vaporizer cassettes. The isoflurane cassette is plugged into the vaporizer port, and controls may be adjusted with the control wheel to the left of the port. (Courtesy Datex-Ohmeda, Tewksbury, Mass.)

BOX 15-8

Hazards of Modern Vaporizers

- Incorrect (unintended) agent administration
- Tipping
- Overfilling with agent
- Reliance on breath-by-breath gas analysis rather than preventive maintenance
- Leaks
- Electronic failures

alarms are activated if the agent level is less than 20 mL, if the vaporizer is tilted more than 10 degrees from the vertical, if there is a power failure lasting longer than 10 seconds, or if an internal malfunction occurs. The cause of a No Output alarm may be sought if it occurs during a case; however, considering the rapid emergence that is characteristic with the use of desflurane, the operator should ensure continued depth of anesthesia by switching to a different agent without undue delay.

Preoperative checkout for variable-bypass vaporizers is relatively straightforward. They are checked to determine whether they are turned off, whether they are full, whether the filling cap is tightly closed, and whether the interlock is functioning. Depending on the machine, they may need to be checked for leaks as well.[46] The Tec 6 requires a more extensive checkout. After performing the appropriate leak test of the machine low-pressure system, the operator checks the amber Alarm Battery Low indicator and replaces the battery if necessary. Next, he or she turns the Tec 6 on to at least 1%, and disconnects its electrical plug. Within 15 seconds of disconnection, the No Output light and alarm should activate. If they do not, the battery must be replaced and the vaporizer retested before use. If everything is functioning correctly, the operator reconnects the power and turns the dial to the "Off" position; he or she then presses the mute button for 4 seconds to test all alarms and the display. When the mute button is pressed, all lights and the alarm should activate.[103]

The Aladin (ADU) vaporizer uses one central electronic control mechanism for all agents.[54,105] Cassettes containing the liquid anesthetic are inserted into a port connected to these control mechanisms, which recognizes the contents of the cassette and dispenses agent into the stream of fresh gas flow (Figure 15-33). The cassettes and control mechanisms are checked as part of the electronic equipment checklist daily. The ADU will not deliver volatile agent or nitrous oxide without main power or battery backup, and adequate oxygen pressure.

Hazards of Contemporary Vaporizers

Many of the hazards historically associated with the use of vaporizers have been corrected by advances in design, but a few hazards remain (Box 15-8). Vaporizer contamination with incorrect agents continues to be noted.[114,117,118] Diligence during filling is not enough to prevent contamination. Departments should strongly consider replacing funnel-type with keyed-filler vaporizers in equipment purchases.

Aladin vaporizers found on ADU and Aisys are not sensitive to tipping. If any other vaporizer tips by more than 45 degrees from the vertical, the operator's manual or a field service technician must be consulted. Tipping is hazardous, because the entry of liquid agent into the control assembly at the top of the vaporizer can have unpredictable effects on its function, including potential overdose to the patient. The vaporizer sump can be drained and gas run through it for a specified time and at a specified concentration before the vaporizer is returned to use. For the recommended corrective action for a particular make and model, the operator's manual must be consulted.

Overfilling may be prevented by following the manufacturer's guidelines for filling (e.g., fill only to the top etched line on the liquid level indicator glass, fill only when the vaporizer is off).[123] Managers should not conclude, in this era of cost constraints, that breath-by-breath agent analysis can substitute for regular preventive maintenance of vaporizers. Vaporizers go out of calibration, and may then deliver too-high or too-low concentrations of agent.[125] Leaks are relatively common, often due to malposition of vaporizers on the back bar, accidental dislodgement, loss of gaskets,

or mechanical damage.[119,126-128] These leaks may not be detected with the standard checklist, unless the negative pressure check is performed. Tec 6 vaporizers can also leak liquid while being filled if the desflurane bottle is missing the rubber O-ring near its tip.[121] This can be mistaken for a defective vaporizer. As vaporizers incorporate electronics, they are susceptible to electronic failure or unanticipated interactions of new designs with each other.[109,119,120] Recent case reports detail ADU vaporizers failing due to fresh gas unit failure, and from copious emesis soaking the machine.[129,130]

New Agents and Low Flows

Low fresh gas flows should not be instituted too early when desflurane or sevoflurane is used. Induction at low flows would be extremely prolonged, creating the risk of awareness in the time interval between offset of inductions, and onset of action of the volatile agent. Overpressure can be combined with low flows, but 18% of 2 L contains far fewer desflurane molecules than 18% of 6 L, and it is the number of molecules presented to the brain per unit time that causes an increase in anesthetic tension within the brain.

Imagine a 1000-mL sink filled with water, with 100 mL/min inflow (of which 1 mL is methylene blue) and 100 mL/min outflow. The goal is turning the initially colorless water in the sink as blue as the inflow solution. Now, imagine the effect of increasing the inflow to 500 mL/min (of which 5 mL is methylene blue) and increasing the outflow to 500 mL/min. Would the 1000 mL in the sink turn blue any faster in the second case? Of course, but not because the concentrations are different (both inflows are 1% methylene blue), but rather because the rate of inflow in the second example is a greater proportion of the capacity of the sink.

Wash-in is based on the concept of a time constant. One time constant (equal to capacity divided by flow) brings a system 63% of the way to equilibrium; two time constants to 86%; and three time constants to 95%. Thus the first sink will reach 63% of equilibrium in 10 minutes (1000 mL ÷ 100-mL flow), whereas the second sink reaches this same state of equilibrium in only 2 minutes (1000 mL ÷ 500-mL flow). In the same way, the volume (capacity) of the functional residual capacity, hoses, and breathing circuit can be brought to equilibrium with the inflow more quickly by using a higher rate of inflow (fresh gas flow). A rational approach for ensuring anesthesia that conserves volatile agents would include a nonrebreathing (semi-open) induction (fresh gas flow, 5 to 8 L/min), followed by low fresh gas flow during maintenance (fresh gas flow, 1 to 2 L/min). This approach helps conserve tracheal heat and humidity, gases, and agent. Emergence, like induction, must occur at higher, nonrebreathing flows; otherwise, it will be unacceptably prolonged.

DELIVERY

This section discusses how the flow of gases to and from the patient is controlled and monitored.

Breathing Circuits

Fundamental Considerations

The purpose of all types of anesthesia breathing circuits is the delivery of oxygen and anesthetic and the elimination of carbon dioxide. Carbon dioxide is eliminated from the breathing circuit by washout with adequate fresh gas flow; or by absorption in carbon dioxide absorbent granules.

Any breathing circuit creates some resistance to gas flow. Resistance in a circuit may be minimized by reducing the circuit's length and increasing its diameter, by avoiding the use of sharp bends, by eliminating valves, and by maintaining laminar flow. It is important to decrease resistance to flow, because added airway resistance is uncomfortable for the conscious patient. Furthermore, the unconscious or anesthetized patient, challenged by increased work of breathing, may not be able to increase respiratory effort, and may hypoventilate. The resistance of the anesthesia breathing circuit is low—typically less than that of an endotracheal tube.

Rebreathing of exhaled gases occurs with the use of anesthesia breathing circuits (as it does in space or submarine environments). In other breathing circuits, such as those in the ventilators used in intensive care units, it is not found. Rebreathing may be useful. Its advantages include cost reduction, an increase in tracheal warmth and humidity, and a decrease in the potential for exposure of operating room personnel to trace and waste gases (because of decreased rate of release of anesthetic gases into the environment). The degree of rebreathing in an anesthesia breathing circuit is increased as the fresh gas flow is decreased, because there is relatively less fresh gas added to the circuit, and more of the next inhalation will be exhaled gas. Higher fresh gas flow is associated with less rebreathing in any type of circuit. The higher the fresh gas flow, the more quickly the composition of gas in the breathing circuit will resemble that at the common gas outlet (the dialed-in concentrations of agent, nitrous oxide, and oxygen).

Patients under anesthesia may re-breathe any component of their exhalations—nitrogen, O_2, CO_2, N_2O, and volatile agent. The effects of rebreathing each of these components differ. Rebreathing of exhaled oxygen has no ill effects. Rebreathing of exhaled nitrogen slows induction. Nitrogen that is not eliminated from the breathing circuit delays the establishment of the desired agent concentration; thus high fresh gas flows are appropriate during induction. In contrast, rebreathing of exhaled agent during maintenance is highly desirable for cost and environmental considerations. Rebreathing of CO_2 has the undesirable effect of producing respiratory acidosis, so it is best avoided. Because higher flows reduce the discrepancy between desired concentrations and the concentrations actually inspired, they are appropriate during emergence as well. At the end of an anesthetic, as the flow of volatile agent and N_2O is turned off, it would be undesirable for exhaled agent and N_2O to be rebreathed, because this would delay emergence. So gas that is free of agent (and nitrous oxide) is supplied at high flow, to create a favorable concentration gradient that speeds elimination of agents from the body.

Dead space is increased to some degree with the use of any respiratory apparatus. The effect of an increase in mechanical (apparatus) dead space is that rebreathing of exhaled CO_2 is more likely. This is one reason that ventilator tidal volumes are set much larger than the volume of a spontaneous breath. To avoid hypercarbia in the face of an acute increase in dead space, a patient must increase minute ventilation (V_E). Conversely, because alveolar ventilation is the minute ventilation minus dead space ventilation ($V_A = V_E - V_D$), if the patient's minute ventilation is fixed (such as by respiratory depression), increasing dead space decreases alveolar ventilation, and increases arterial CO_2 tension.[131] Dead space ends where the inspiratory and expiratory gas streams diverge. In a circle system, dead space ends at the Y-piece. It is not increased by longer inspiratory and expiratory plastic hoses (although, with longer limbs in the breathing circuit, there may be compliance losses than decrease tidal volume). Use of a face mask is associated with greater dead space than is the use of an endotracheal tube.

The anesthesia gas machine uses dry gases so that the problems of internal corrosion and bacterial colonization are avoided. However, provision of completely dry gases to the patient's airway can cause various problems. It is common for anesthesia providers to use various means of passively humidifying and heating

TABLE 15-4 Classification of Breathing Circuits

Type	Reservoir	Rebreathing	Example
Open	No	No	Open drop Insufflation Nasal cannula or simple face mask
Semi-open	Yes	No	Circle at high fresh gas flow (more than minute ventilation); or a nonrebreathing circuit
Semi-closed	Yes	Yes (partial)	Circle at low fresh gas flow (less than minute ventilation)
Closed	Yes	Yes (complete)	Circle at extremely low fresh gas flow, with adjustable pressure-limiting valve closed

inspired gases (with a heat and moisture exchanger, or by using low fresh gas flows). Active humidification has become less common, because it is less effective at preventing hypothermia than heated-air surface warming blankets, and because the added moisture can clog gas-analysis lines and soda lime granules, or obstruct unidirectional valves.[132]

Anesthesia breathing circuits are unique among respiratory equipment in the degree to which they allow manipulation of the inspired concentration of a variety of components for therapeutic benefit. Each component of the breathing mixture follows its own concentration gradient because it is made to wash in to the breathing system, and then to wash in from the breathing system into the patient's lungs. In the lungs, gases flow down their concentration gradients, interchanging with pulmonary and blood gases. Understanding the pharmacokinetics of inhaled agent administration involves not only knowledge of respiratory physiology, but also familiarity with the "physiology" of the patient-machine system. For example, the concentration set on the dial differs from the concentrations in the breathing circuit, in the lungs, in the blood, and in the brain. Furthermore, these concentration differences are not constant but vary over time, depending on a number of patient- and machine-related factors. The concentration inspired most closely resembles that delivered from the common gas outlet when rebreathing is minimal or absent (this is typical at high fresh gas flow). Of course, it is desirable that the alveolar concentration differ from the inspired concentration at times. At the start of the emergence phase, the inspired concentration of anesthetic is decreased so that anesthetic gas is washed out while ventilation is continued. Thus emergence is very different from passively "waking up," and is as much an active process as induction.

Classification of Breathing Circuits

Table 15-4 gives a classification of breathing circuits that is based on whether a reservoir (breathing bag) is present, and on the degree to which rebreathing occurs.[133] Patients have access to the atmosphere only in open systems; this is not true in semi-open, semi-closed, or closed systems. A reservoir is present in these three types to provide for the moments during the inspiratory phase when flow in the trachea is greater than fresh gas flow. Both nonrebreathing (Mapleson, Bain) systems and the circle system, at fresh gas flows greater than minute ventilation, are semi-open.[134] If the fresh gas flow to the circle system is less than V_E, some rebreathing must be occurring. In a closed system, rebreathing is total. The adjustable

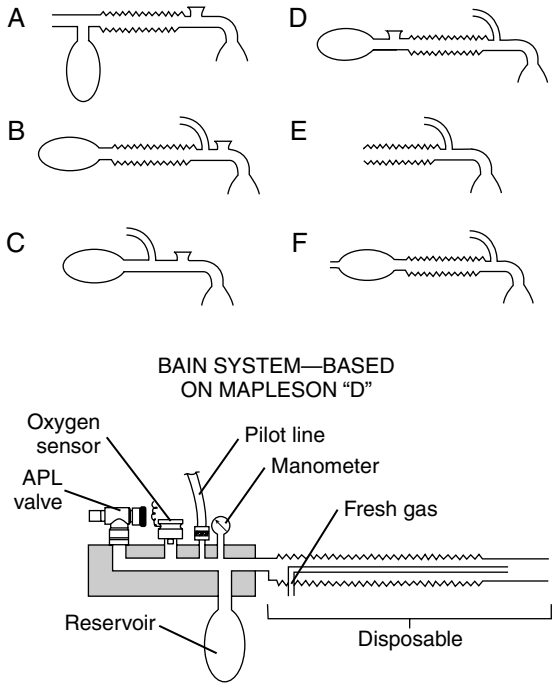

FIGURE 15-34 Mapleson's classification of breathing systems. (From Cicman J, et al. *Operating Principles of Narkomed Anesthesia Systems*. Telford, Penn: Dräger Medical; 1993.)

BOX 15-9

Common Features of Nonrebreathing Systems

- All lack unidirectional valves.
- All lack soda lime carbon dioxide absorption.
- Fresh gas flow determines the amount of rebreathing in all.
- Resistance and work of breathing are low in all (no unidirectional valves; no absorbent granules).

pressure-limiting (APL or "popoff") valve is closed, and the supply of O_2, N_2O, and agent just matches the patient's uptake.[135]

Nonrebreathing Circuits. Mapleson published a classification of nonrebreathing circuits in 1954; this classification is still used today (Figure 15-34).[136] Rebreathing is prevented in systems like the Mapleson D because during the expiratory pause, fresh gas fills the corrugated limb, forcing the previously exhaled gas distally (toward the reservoir). If fresh gas flow is sufficient, no alveolar gas is rebreathed. The Mapleson F circuit is also referred to as the *Jackson-Rees modification of Ayre's T-piece*. The common features of nonrebreathing systems are listed in Box 15-9. These circuits offer very low resistance to breathing, and can be used for patients of almost any age, from premature infants to adults. The fresh gas flow required to prevent rebreathing is two to three times minute ventilation.[77] This number can be calculated; however, in practice, many use a minimum fresh gas flow of 5 L/min.

The Bain system, shown at the bottom of the figure, is often referred to as a *modified Mapleson D circuit*, because the arrangement of its components (entry point of fresh gas, reservoir bag, and APL valve) is similar to that of the Mapleson D. However, in the Bain system the fresh gas hose is directed coaxially within the corrugated limb, and this configuration gives the inhaled gases greater heat and humidity. Unfortunately, unrecognized kinking or disconnection of this relatively hidden fresh gas hose converts the

entire corrugated limb into dead space.[137-139] The resulting respiratory acidosis has been severe enough to cause arrhythmias.[139] Users of Bain systems must test the circuit for these problems before they use the system. Pethick's test and a similar test are available and should be used.[77]

The use of the nonrebreathing circuit has declined for several reasons. Many modern gas machines are not designed to accommodate them (e.g., Fabius GS or Narkomed 6000). It is more common to see a pediatric circle system used, which is characterized by smaller and less compliant corrugated limbs, as compared with the adult circle system. The minimum weight of a child for which a pediatric circle would be suitable has been stated as 10 to 20 kg. However, when infants of mean weight as low as 6 kg were studied, the pediatric circle was equal to a nonrebreathing circuit in preserving blood gas values and end-tidal CO_2, whether assisted or spontaneous breathing was employed.[140] No one guideline applies to all situations, because the decision on whether to use a pediatric circle system in any given child depends on familiarity, clinical judgment, and the anticipated duration of unassisted respiration.

Pediatric circle systems do not place undue burdens (in terms of work of breathing) on spontaneously ventilating patients.[141] The pediatric circle system is low compliance; the work of breathing associated with it is reasonable; it requires less reconfiguration to set up; and it allows the use of lower fresh gas flows (the high fresh gas flow required in nonrebreathing circuits cools children and is more costly).[142] Modern ventilators are accurate to very low tidal volumes (10 to 20 mL), and modern monitoring such as capnography and spirometry allows a high degree of confidence that a child is being ventilated adequately with the pediatric circle.

If a nonrebreathing circuit is used in the middle of a number of adult cases using the circle system, some disassembly and reassembly is required, accompanied by the possibility of error or misconnection. The small amount of resistance offered by the soda lime canisters and unidirectional valves of the circle system is deleterious only during spontaneous respiration, which is limited in duration in most general anesthesia for children. The advantages and disadvantages of nonrebreathing circuits are summarized in Box 15-10. Although they are useful, nonrebreathing circuits are associated with loss of heat from the patient and with greater use of volatile agents, owing to their requirement for relatively high fresh gas flow.

Circle System. The circle system is the breathing circuit most commonly used in the United States, because it prevents rebreathing of carbon dioxide while allowing rebreathing of all other gases. Gas flow during mechanical ventilation is shown in Figure 15-35. The circle system has separate inspiratory and expiratory limbs. Gas in the inspiratory limb only goes towards the patient; gas in the expiratory limb only proceeds away from the patient. The inspiratory and expiratory unidirectional valves enforce this flow pattern, which ensures that all exhaled gas is directed through the absorbent granules, and is thus cleansed of carbon dioxide. Even when rebreathing takes place at low fresh gas flows, if the valves are functioning, and the granules are unexpired, no rebreathing of carbon dioxide can occur.

A single-limb, coaxial circle system is also available in which, like the Bain, the inspiratory limb is contained within the expiratory (Figure 15-36). It is checked and used like any circle system. Like the Bain, the coaxial circle is less bulky, and is thought to provide greater heat and humidity to inhaled gases. Disadvantages include the potential for obstruction or lack of patency of either limb, which may cause respiratory acidosis or even mimic esophageal intubation.[137,138] This respiratory acidosis does not respond to increased minute ventilation—if exhaled gases are not forced through the absorbent granules, no amount of ventilation will cleanse carbon dioxide from the exhaled gases. The tests for inner tube patency that can be used for a Bain circuit are not readily adaptable to the coaxial circle system.

BOX 15-10

Nonrebreathing Systems: Advantages and Disadvantages

Advantages
- Lightweight
- Convenient
- Easily sterilized and scavenged
- Exhaled gases in corrugated limb may give heat and humidity to inhaled gas (Bain)

Disadvantages
- Unrecognized disconnection or kinking of fresh gas hose in the Bain circuit (use Pethick's test)
- Pollution and increased costs of agents and gases, owing to need for higher flows
- Loss of heat from patient
- May require disconnection of circle fresh gas supply hose and scavenger connections for assembly; can be reassembled improperly

Gas enters the circle system from the common gas outlet by way of the fresh gas delivery hose, and it exits the circle to the scavenger via the APL valve (or the ventilator relief valve if mechanical ventilation is used). The APL valve creates an adjustable leak during manual ventilation. If it is completely open and the bag is squeezed, all gas exits to the scavenger, because this is the path of least resistance. If the valve is completely closed, all gas ventilates the lungs, and the volume of the circle increases, because the fresh gas flowing in has no means of escape. The setting of the APL is constantly adjusted during manual ventilation of the lungs so that a variable resistance sufficient to force gas to inflate the lungs is maintained. If gas cannot exit through the APL or ventilator relief valve, pressure will build within the system.[143]

Unidirectional valves enforce a pattern of gas flow that forces exhaled gases through the CO_2 absorbent granules (Figure 15-37). The valve leaflet (disk) is subject to damage, occlusion, foreign body contamination, and sticking with collected moisture or absorbent dust, particularly on the expiratory valve disk.[144-147] Daily performance of a preanesthesia checklist, and regular maintenance, should enable the operator to detect or prevent most of these problems. Thus there are only two common reasons for an increase in inspired CO_2: the absorbent granules have been exhausted, or the unidirectional valves are faulty. Figure 15-38 shows that incompetence of an inspiratory or expiratory valve turns the entire corrugated limb into dead space.[45,148] This usually results in an increase in inspired and expired CO_2.

If inspired CO_2 of more than 1 to 3 mmHg is detected on the capnograph (Figures 15-39 and 15-40), the fresh gas flow should be increased to 5 to 8 L/min; this converts the system to a semi-open configuration, in which rebreathing of exhaled gases is minimized. Similar to the mechanism in the Mapleson nonrebreathing circuits, a high fresh gas flow in the circle dilutes exhalations and sends them to the scavenger. If increasing the fresh gas flow substantially causes the inspired CO_2 to decrease, the absorbent granules are exhausted and should be replaced at the end of the case. Some gas machines (e.g., ADU) with prepackaged granules or canisters allow granules to be changed during the case, although they are not meant to function for more than very brief periods without

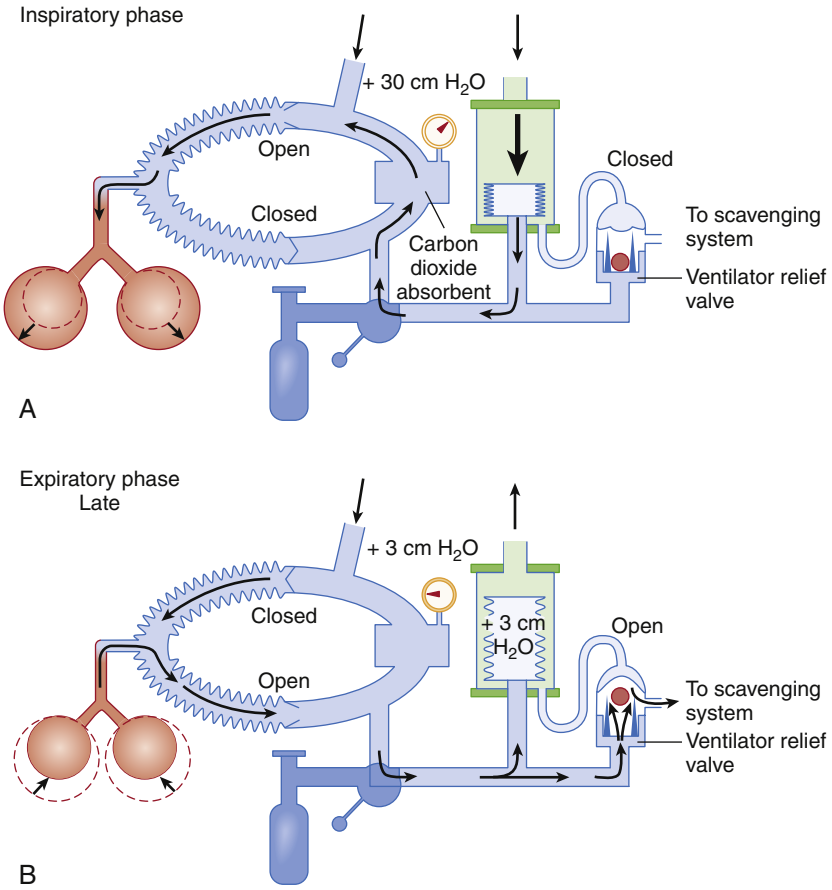

FIGURE **15-35** Gas flow in a circle system during mechanical ventilator inspiration. **(A)** Shows inspiration. As driving gas compresses the bellows, it propels gas into the inspiratory limb past the inspiratory unidirectional valve, inflating the lungs. Driving gas pressure also closes the ventilator relief valve, which is the route to the scavenger. **(B)** Shows expiration. Lung deflation propels gas into the expiratory limb past the expiratory unidirectional valve. The exhaled gases fill the bellows to a small pressure first, then excess gas proceeds to the scavenger via the ventilator relief valve. A small weight within the ventilator relief valve makes filling the bellows the path of least resistance, until a small positive end-expiratory pressure (PEEP) builds up, lifting the weight, and opening the valve. Note (1) Fresh gas flows into the circle continuously and (2) flow in the circle is unidirectional, which forces all exhaled gas through the carbon dioxide absorbent granules. (From Miller RD, et al, eds. *Miller's Anesthesia*. 7th ed. Philadelphia: Churchill Livingstone; 2010.)

a canister attached. If elevated inspired CO_2 persists in spite of the higher fresh gas flow, the unidirectional valves are likely to be incompetent. The operator should remove the expiratory valve, inspect and dry it, and then reassemble it (while ventilating the patient with an Ambu bag).[25,146] Note that this may be more difficult in newer absorber heads (e.g., the ADU), and will always be more difficult when the user has never performed it before. This argues for reading the operator's manual and practicing without a patient attached before the maneuver is attempted, because failure to reassemble the valve quickly will result in hypoventilation and interruption in volatile anesthetic delivery. Perhaps the best recommendation is to bring a new gas machine into the room; any valve adjustment can take place outside the pressure of the clinical situation and will not distract the anesthetist from patient care.

It is mandatory to check unidirectional valves before use. There are a multitude of means proposed to check the unidirectional valves, which vary in ease of performance and complexity.* One suggested method with applicability to a variety of gas machines follows. The daily check of the unidirectional valves is done during the ventilator checkout. A spare breathing bag is placed on the elbow fitting at the patient's end of the Y-piece, and mechanical ventilation of this "artificial lung" is begun. The user carefully observes that the valves lift and fall, and that gas flows back and forth in a tidal fashion between the mechanical ventilator bellows and the artificial lung expected during inspiration and expiration.[54] The test should be repeated using the manual/spontaneous limb of the circuit, simulating assisted ventilation of the artificial lung. Breathing through the elbow or mask of a clean circuit (with a paper mask on) is an alternative method, but presents problems of cross-contamination.

Simulating manual breathing and ventilator breathing checks not just for unidirectional valve function; it checks for obstruction to expiration secondary to mold flash or plastic wrap emboli, problems that have resulted in mortality.[146,150-153] Dräger suggests a similar test, but also breathing through each limb individually as follows.[60,66] If the inspiratory limb is detached and occluded with one's palm, the operator should be able to exhale, but *not* inhale, through the expiratory limb. Similarly, if the inspiratory

*References 60, 66, 93, 144, 146, 149.

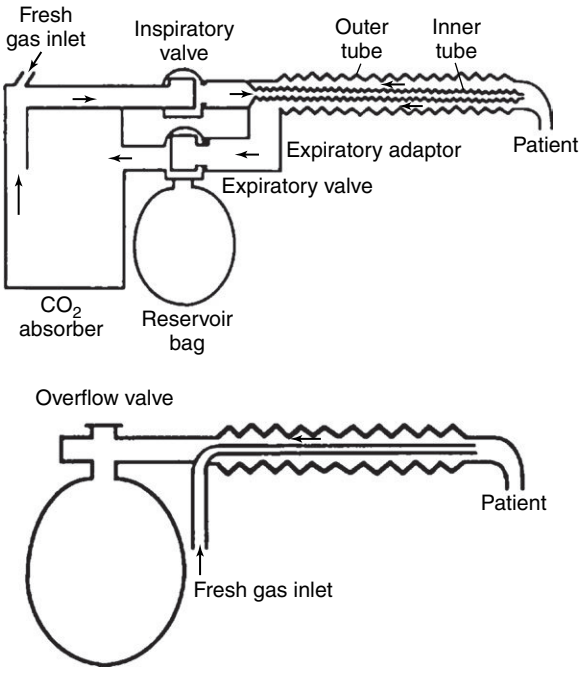

FIGURE **15-36** In the coaxial circle system *(top)*, the inspiratory limb is contained within the expiratory limb, like the Bain *(bottom)*.

limb is replaced and the expiratory limb detached and occluded, the operator should be able to inspire, but *not* expire, through the inspiratory limb. This test may be more sensitive than the first test mentioned. If a preanesthesia check is performed daily, the capnograph is used properly, and the operator is aware of the steps that should be taken in the event of an increase in inspired CO_2, perhaps this more rigorous test need be performed only if unidirectional valve function is in doubt, particularly because it is problematic to perform this more rigorous test in a hygienic fashion.[25]

Newer machines have electronic routines to check for leaks and compliance. This helps the ventilator accurately deliver the set tidal volume. These checks must be repeated when the type of circuit is changed, for example, from adult to pediatric. Dräger does not recommend expandable breathing circuit hoses with the Narkomed 6000, because their volume and compliance may change after the leak and compliance testing is performed, which will degrade the accuracy of the delivered tidal volume.[66] With any newer gas machine, these hoses should be expanded before the leak and compliance test is initiated.

The advantages and disadvantages of the circle system are listed in Box 15-11. One advantage of at least partial rebreathing is relative constancy of inspired concentrations. In a completely nonrebreathing circuit, each breath is fresh gas, so depth can vary much more quickly. The use of lower flows also reduces the rate of release of anesthetic agents into the environment. The circle conserves respiratory tract humidity. Misconnections, although a potential disadvantage, occur much less frequently now than in the past, because the diameter of breathing hoses (22 mm) has been standardized to be different from the diameter of scavenger hoses (19 or 30 mm).[18] Nevertheless, misconnections continue to be reported.[154,155] Maintenance of the circle system is detailed in the operator's manuals, and these must be consulted before one disassembles and cleans the absorber head.

Several design changes in newer circle systems facilitate low-flow anesthesia. Low fresh gas flow is desirable to reduce pollution and the cost of using volatile agents and nitrous oxide, preserve tracheal heat and moisture, delay the drying of carbon dioxide–absorbent

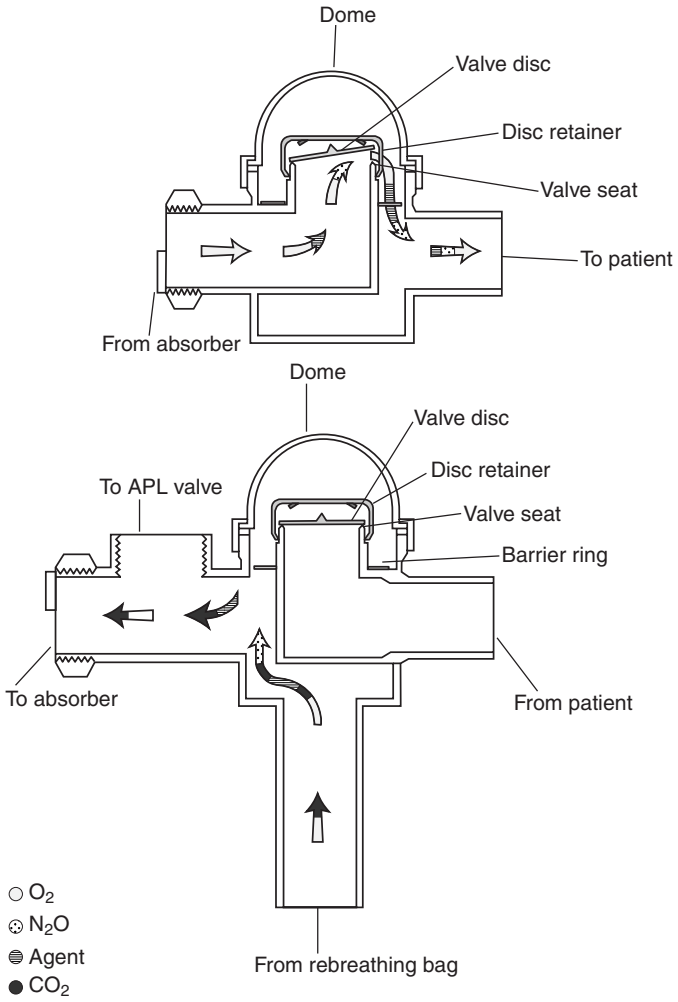

FIGURE **15-37** Gas flows in inspiratory (*top*) and expiratory (*bottom*) unidirectional valves during inspiration. (From Bowie E, Huffman LM. *The Anesthesia Machine: Essentials for Understanding*. Madison, Wis: Datex-Ohmeda; 1985.)

granules, and preserve patient body temperature. Factors that enhance the safety and efficiency of low flows in modern circle breathing systems and ventilators are shown in Box 15-12.

A traditional-sized absorber head like the Aestiva is larger than the volume of many of the newer designs.[64,68,74] Circles with smaller volume will have shorter time constants. The time constant equals capacity divided by flow, and measures how quickly a breathing system reaches equilibrium with a change in the inflow. In a circle system with lower volume, changes in dialed concentration of agent will be reflected more quickly in the inspired concentration, at any flow rate, as compared to a higher volume circle system. In a nonrebreathing circuit, or a circle system at flows substantially higher than minute ventilation, each breath reflects the dialed concentration of agent because there is no rebreathing of exhaled gases in either. Thus a circle system with higher flows is suitable when rapid changes are desired, such as at induction and emergence.

There are, however, circumstances in which to avoid low flows (fresh gas flow 1 L/min). Absolute contraindications include patients with smoke inhalation injury, malignant hyperthermia, or other conditions in which washout of potentially dangerous gases or a high oxygen uptake is expected. If equipment breakdown occurs mid-case that would affect the safety of low flows (i.e., failure of inspired oxygen or anesthetic agent monitors, or failure of soda lime granules), higher flows should be used. Relative

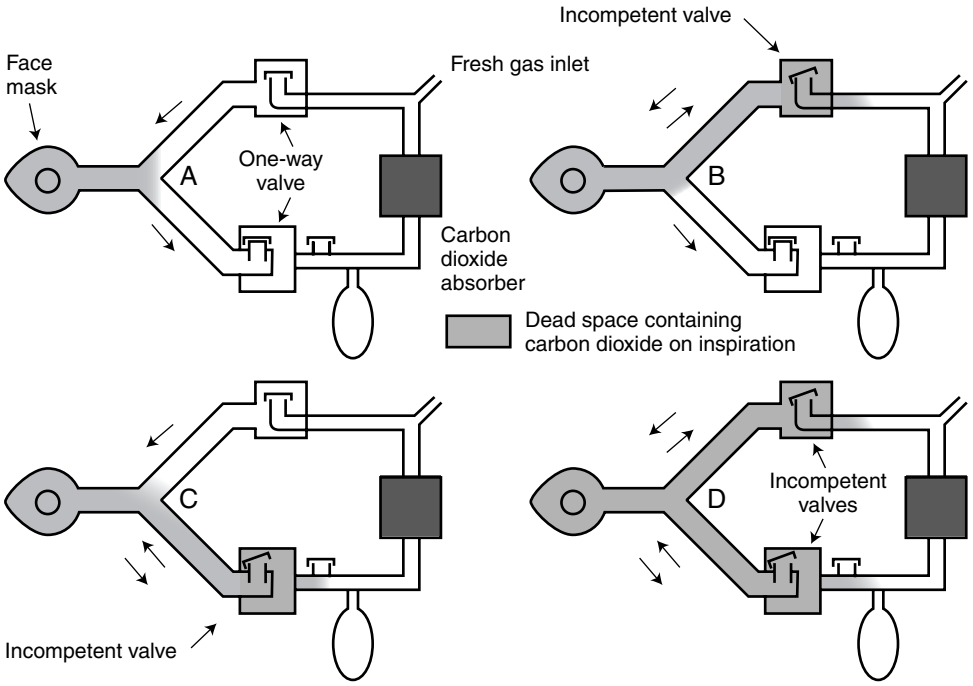

FIGURE **15-38** Incompetence of a unidirectional valve. **A,** Normal function. Incompetence of an inspiratory valve **(B),** an expiratory valve **(C),** or of both unidirectional valves **(D)** creates dead space *(stippled area)* that extends through the entire ipsilateral corrugated breathing hose. (Modified from Gravenstein JS, et al. *Capnography in Clinical Practice*. Boston: Butterworth; 1989.)

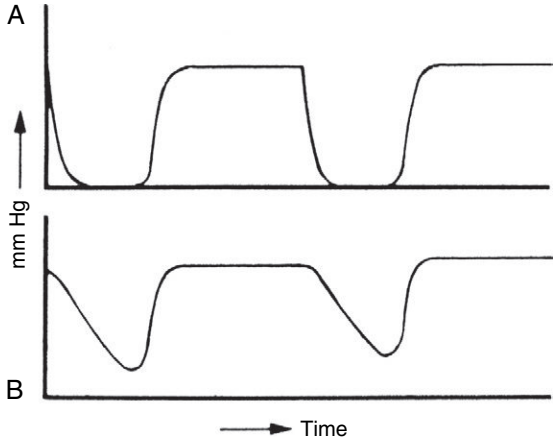

FIGURE **15-39** Compared with a normal capnogram **(A),** a capnogram recorded when the inspiratory unidirectional valve is incompetent **(B)** shows increases in inhaled and exhaled carbon dioxide pressure and an abnormally prolonged downstroke. The prolonged downstroke during the inspiratory phase occurs because the patient inspires mixed alveolar and fresh gas from the inspiratory limb rather than fresh gas alone. (Modified from Gravenstein JS, et al. *Capnography in Clinical Practice*. Boston: Butterworth; 1989.)

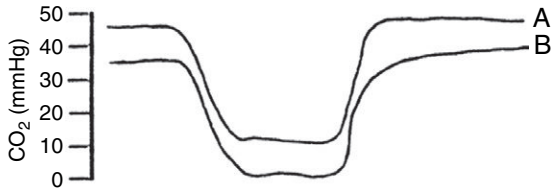

FIGURE **15-40** Compared with a normal capnogram *(B)*, a capnogram recorded with an incompetent expiratory unidirectional valve *(A)* shows increases in inspired and expired carbon dioxide concentration but no changes in morphology. (Modified from Gravenstein JS, et al. *Capnography in Clinical Practice*. Boston: Butterworth; 1989.)

contraindications to low fresh gas flows include when using older equipment that is less leak-proof; face mask anesthesia; during rigid bronchoscopy; and with the use of uncuffed endotracheal tubes.[156]

Humidification, and prevention of nosocomial infection, are desirable with the use of any respiratory apparatus. Both of these goals may be addressed with breathing circuit filters that incorporate heat and moisture exchange with filtration (HMEF).[157] The use of low flows during maintenance results in an increase in circuit humidity and a lower rate of use of volatile agents. Heat- and moisture-exchanging filters precipitate exhaled water vapor

BOX **15-11**

Circle System: Advantages and Disadvantages

Advantages

- Constant inspired concentrations
- Conservation of respiratory tract heat and humidity
- Minimal operating room and environmental pollution
- Useful for closed-system, low-flow, and semi-open configurations
- Low resistance (less than the endotracheal tube; not as low as in nonrebreathing circuits)

Disadvantages

- Relatively complex
- Opportunities for misconnection or disconnection
- Malfunctioning unidirectional valves cause serious problems
  - *Open:* Rebreathing
  - *Closed:* Occlusion
- Less portable than nonrebreathing circuits
- Increased dead space (true of all respiratory apparatus; extends to the point where inspired and expired gas streams diverge, i.e., at Y-piece)

BOX 15-12

Breathing System and Ventilator Design Features That Support Low-Flow Anesthesia

- Compliance and leak testing, automatic leak detection
- Fresh gas compensation or decoupling
- Warmed absorber heads (NM 6000, others)
- Low-volume absorber heads (allow faster equilibration of dialed and delivered agent concentration)
  - Narkomed 6000, Fabius GS—1500-mL canister (Fabius GS volume is 2800 mL, including bag for entire breathing system)
  - Aestiva 2700 mL (canisters alone)
  - ADU 750 mL (canister)
- No mandatory minimum oxygen flows (there are exceptions; Aespire and Aestiva, but these are only 50 mL/min)
- Point in the system where fresh gas enters is distal to inspiratory unidirectional valve (in ADU, Aisys); causes dialed changes to be reflected at airway more quickly when lower fresh gas flows are used

on their filter media. The next inhalation returns this water to the patient. These filters may slow the rate of heat loss from the patient, because they decrease the rate of evaporation of water from the tracheal mucosa. They may also confer the benefit of bacterial and viral filtration.[158,159] Cleaning the bellows is necessary after anesthesia has been provided to a patient with a disease transmitted by air or oral secretions. To limit contamination of the machine, consider avoiding the mechanical ventilator, using bacterial/viral filters on the Y-piece or on each limb, and changing the soda lime after the case.

The AANA (American Association of Nurse Anesthetists) Standards for Nurse Anesthesia Practice call on anesthetists to use safety precautions to minimize the risk of infection for the patient, the anesthetist, and other staff.[97,160] It is certain that anesthesia equipment, and providers, are contaminated with potential pathogens.[161] Furthermore, many of the surfaces of the anesthesia gas machine and monitors have been shown to be contaminated with blood—visible and occult.[162] It is therefore mandatory for patient safety to ensure that departmental cleaning and sterilization programs are adequate, that good housekeeping during administration of anesthesia is practiced, and that universal precautions are observed. For equipment, the AANA advocates a classification system and specific equipment recommendations that are published in their *Infection Control Guide*.[160] In addition, manufacturers include directions for cleaning and sterilizing equipment in their operation and maintenance manuals.

Electrically heated (active) breathing circuit humidifiers are no longer used. Problems associated with heated humidifiers included overhydration, underhydration, hypothermia, hyperthermia, melting of disposable breathing circuits, aspiration, interference with gas analysis accuracy (clogged lines or sensors) and infection.[163]

Carbon Dioxide Absorption

Carbon dioxide absorption makes rebreathing of exhalations possible. Thus it conserves agent, oxygen, nitrous oxide, and tracheal humidity, while preventing the respiratory acidosis that would result from the rebreathing of CO_2.

Fresh gas flow set on the flowmeters determines the amount of rebreathing in the circle system. A circle system with fresh gas flows of 0.3 to 0.5 L/min provides near-total rebreathing, and full reliance on absorbent for prevention of rebreathing of CO_2. At the other extreme, use of a circle system with fresh gas flows above minute ventilation (greater than 5 to 8 L/min for a traditional large, dual-canister absorber head) is associated with little if any reliance on absorbent granules, because exhaled carbon dioxide is rapidly diluted and sent to the scavenger with such high fresh gas inflows.[77,134,164] This relationship can be confusing. When faced with exhausted granules, which cause an increase in expired (and inspired) CO_2, one may be tempted to increase minute ventilation (V_E). This approach is ineffective with exhausted absorbent (even though it is the obvious response for controlling hypercarbia from other causes), because the patient simply inspires more of a gas mixture containing CO_2. The correct response to hypercarbia associated with exhausted absorbent is increasing fresh gas flow (and then changing the absorbent at the end of the case). With the newer absorbent canister designs, of course, this may be accomplished mid-case and without leaks or danger to the patient. Even with these newer designs, if a replacement canister is not immediately available, high fresh gas flows allow one to control inspired CO_2 while waiting for a replacement canister to be obtained.

BOX 15-13

Carbon Dioxide Absorption in Soda Lime

1. $CO_2 + H_2O \longleftrightarrow H_2CO_3$
2. $H_2CO_3 + NaOH \text{ (or } KOH) \longleftrightarrow Na_2CO_3 \text{ (or } K_2CO_3) + H_2O + \text{energy}$
3. $Na_2CO_3 \text{ (or } K_2CO_3) + Ca(OH)_2 \rightarrow CaCO_3\downarrow + NaOH \text{ (or } KOH)$

For soda lime, reaction 1 is also called *the first neutralization reaction;* reaction 3 is also called the *second neutralization reaction*. Note that activator is regenerated in step 3.

Chemistry

The chemistry of soda lime CO_2 absorption is shown in Box 15-13 (barium hydroxide lime reactions are not shown, because it has been withdrawn from the North American market by its manufacturer).[25,131] The ionic reactions take place on the surface of the granules in an aqueous medium. An appropriate water content (10% to 20%) is important for the speed and efficiency of the reactions. Dry granules become exhausted much more quickly than moist granules. Activators (NaOH, KOH) are added to increase the speed of the reaction. Potassium hydroxide is used much less frequently, because it has been implicated in reactions that produce carbon monoxide and compound A from degradation of inhaled anesthetic agents.[77] The activator combines with carbonate ions or CO_2 in a reversible reaction that produces water and energy. The absorption of 1 mole of CO_2 produces 13,000 kcal of heat energy.[131] Absorbents contain ethyl violet as an additive. The ethyl violet serves as an indicator of absorbent pH. Fresh CO_2 absorbent has a caustic alkaline pH because of the sodium hydroxide. As the reactions proceed, the pH becomes less alkaline. At a critical pH of 10.3, the ethyl violet changes from colorless to blue-purple.

Soda lime does not *regenerate* to any extent; in other words, it does not regain capacity to absorb CO_2 during periods when it is not in use. Its capacity is similar whether it is used continuously or intermittently. However, it does exhibit some *color reversion* (a change in appearance from blue-purple to white) during a rest period. The color of the absorbent at the beginning of the day may not reflect its remaining capacity because of this color reversion.[131] When a subsequent anesthetic is begun, the color of absorbent that had not seemed exhausted initially may quickly change

TABLE 15-5 Characteristics of Absorbents

Component	Sodasorb (WR Grace)	Medisorb (GE Medical)	Drägersorb 800 Plus (Dräger Medical)	Amsorb Plus (Armstrong Medical)	Litholyme (Allied Health Care)
$Ca(OH)_2$ %	50-100	70-80	75-83	>80	Contains lithium carbonate
NaOH %	3.7	<3.5	1-3	0	0
KOH %	0	0	0	0	0
$CaCl_2$ % (humectant)	—	—	—	1	—
$CaSO_4$ and Polyvinylpyrrolidine % (hardener)	—	—	—	1	—
Water content %	15-17	16-20	~16	13-18	16-20
Size (mesh)	4-8	4-8	4-8	4-8	4-10
Indicator	Yes	Yes	Yes	Yes	Yes

Data from Olympio MA. *APSF Newsl.* 2005;2:25-29; Higuchi H, et al. *Anesth Analg.* 2001;93:221-225; Wissing H, et al. *Anesthesiology.* 2001; 95:1205-1212; Yamakage M, et al. *Anesth Analg.* 2000;91:220-224.

Ca(OH)$_2$, Calcium hydroxide; *NaOH*, sodium hydroxide; *KOH*, potassium hydroxide; *CaCl*$_2$, calcium chloride; *CaSO*$_4$, calcium sulfate.

Numbers are approximations that may not sum to 100%.

to blue-purple. Therefore it is recommended that the user judge the degree of color change at the end of each case, and change the canister before the next case if necessary.[131]

Soda Lime

The characteristics of soda lime and other selected absorbents are listed in Table 15-5.[83,85,165-167] The main constituent of all absorbents is calcium hydroxide. Hardeners (silica and kieselguhr) may be added to soda lime. Soda lime is manufactured to have a water content between 13% and 20% by weight. The size of all absorbent granules is 4 to 8 mesh, meaning they will pass through screens with 4 to 8 holes per linear inch. The selection of granule size involves a compromise between resistance to flow and absorption efficiency. Larger granules have less resistance to gas flow; however, they are also less efficient because their surface area is relatively small with respect to their mass. Fine granules or soda lime dust would have a great deal of resistance to gas flow, but their efficiency would be high because of their increased surface area.

Soda lime degrades most current volatile agents to some extent,[54,85] with sevoflurane degraded most, and desflurane least. Degradation may produce compound A (sevoflurane), carbon monoxide (the ethyl methyl ethers), and other compounds. Degradation is favored by dry absorbent, and the presence and quantity of strong bases (potassium hydroxide more than sodium hydroxide).[82,85,166-170] Sevoflurane may be degraded so much at low flows in desiccated barium hydroxide lime that it is impossible to attain 1 MAC (minimum alveolar concentration) in the breathing circuit, regardless of the dial setting.[81]

Sevoflurane is unstable in soda lime, producing compound A. Compound A is lethal in rats at 130 to 340 ppm, and may cause renal injury at 25 to 50 ppm. Compound A concentrations of 25 to 50 ppm are easily achievable in normal clinical practice if extremely low fresh gas flows are used. The incidence of toxic (hepatic or renal) or lethal effects from sevoflurane, used in millions of humans, are comparable to desflurane.[171] The product insert does not recommend sevoflurane at total fresh gas flows less than 1 to 2 L/min for more than 2 MAC-hours.[172] The production of compound A may be affected by the particular gas machine used. At a constant fresh gas flow, it was least in the gas machine with the lower circuit and absorbent volume.[166]

BOX 15-14

Recommendations on the Safe Use of Carbon Dioxide Absorbents

1. Use carbon dioxide absorbents with lower (or no) amounts of strong bases (particularly potassium hydroxide [KOH]).
2. Create institutional, hospital, and/or departmental policies regarding steps to prevent desiccation of the carbon dioxide absorbent.
3. Turn off all gas flow when the machine is not in use.
4. Change the absorbent regularly—on Monday morning, for instance.
5. Change absorbent whenever the color change indicates exhaustion.
6. Change all absorbent, not just one canister in a two-canister system.
7. Change absorbent when uncertain of the state of hydration, such as when the fresh gas flow has been left on for an extensive or indeterminate time period.
8. If compact canisters are used, consider changing them more frequently.
9. Low flows also have a role in preserving humidity in absorbent granules. Use relatively low fresh gas flows for the majority of procedures, changing flows from high to low as soon as practical in any given case (after the patient has attained maintenance levels of volatile anesthetic).

Carbon monoxide is produced by desflurane, much more than isoflurane, when these agents are in contact with absorbent granules. Halothane or sevoflurane produce little, if any, carbon monoxide. Production of carbon monoxide is greatest in dry absorbent, or with barium hydroxide lime as compared with soda lime. It is recommended that oxygen be turned off at the end of each case, absorbents changed regularly (particularly if fresh gas flow is left on over the weekend or overnight), and low flows used (this will tend to keep granules moist). Current recommendations for avoiding problems with carbon monoxide are summarized in Box 15-14.*

*References 77, 78, 81, 83, 85, 173-175.

BOX 15-15

Clinical Signs of Carbon Dioxide–Absorbent Exhaustion

Early

- Increase in partial pressure of end-tidal carbon dioxide; may be accompanied by an increase in inspired carbon dioxide
- Respiratory acidosis
- Hyperventilation
- Signs of sympathetic nervous system activation (flushed appearance, cardiac irregularities, sweating)
- Increased bleeding at surgical site
- Color of indicator

Late

- Increase (and later a decrease) in heart rate and blood pressure
- Dysrhythmia

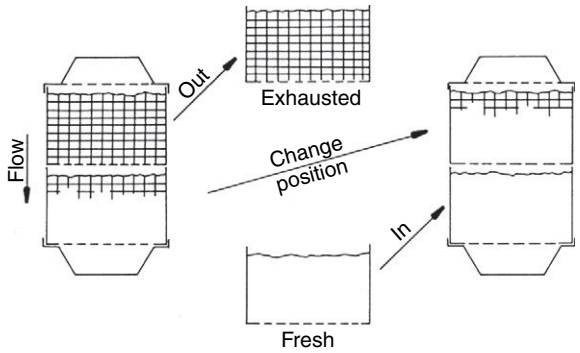

FIGURE **15-41** Changing dual-canister carbon dioxide absorbers. (From Schreiber P. *Safety Guidelines for Anesthesia Systems*. Telford, 1985, Drägerwerk AG & Co. KGaA, Lubeck.)

BOX 15-16

General Steps for Changing Carbon Dioxide–Absorbent Canisters

1. Protect eyes and skin with goggles and gloves. Wear a mask if pouring loose absorbent.
2. Note purple color, date last changed, or both.
3. Loosen clamp or screw.
4. Remove and discard top canister.
5. Remove plastic wrap and seals from new canister.
6. Insert new canister on bottom, and the old bottom canister on top.
7. Retighten screw.
8. Check breathing circuit for leaks.

NOTE: Do not change a dual canister in the middle of a case; convert to a semi-open breathing circuit by using 5 to 8 L/min fresh gas flow.

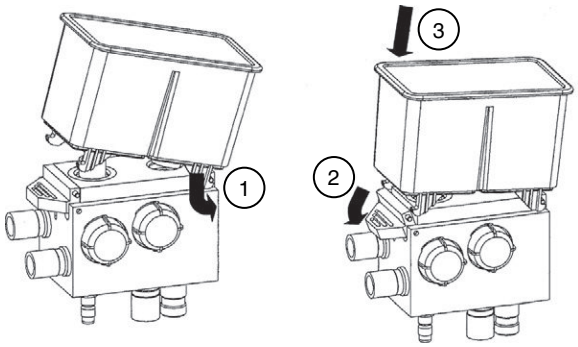

FIGURE **15-42** Changing carbon dioxide cassette in the ADU may be accomplished during a case. (From *S/5 Anesthesia Delivery Unit User's Reference Manual*, Catalog No. 8502304. Madison, Wis: Datex-Ohmeda; 2000.)

New Absorbents Lacking Strong Bases

The strongly basic activators (NaOH, and particularly KOH) have been convincingly implicated in the carbon monoxide problem with the methyl ethyl ethers (especially desflurane) and the generation of compound A by sevoflurane. Many absorbents available in North America lack KOH, and may have reduced amounts of NaOH (see Table 15-5). Eliminating both activators produces an absorbent that has similar physical characteristics and carbon dioxide absorption efficiency (the second is controversial) as compared with soda lime (Amsorb Plus [Armstrong Medical Ltd., Coleraine, Northern Ireland]).[80,85,165,176] Lithium hydroxide is also an effective carbon dioxide absorbent.

Because of the controversial efficiency of absorbents that lack all strong bases, most absorbents have been modified to include less NaOH, and no KOH (see Table 15-5). The goal is to maintain efficiency, while lessening the production of by-products. Dräger Medical makes an absorbent with decreased amounts of NaOH and no KOH: Drägersorb 800 Plus. GE Medical supplies Medisorb, which lacks KOH, in the prefilled canisters for all their gas machines (i.e., ADU, Aestiva, Aisys).

Using Carbon Dioxide Absorbents

Certain similarities are apparent with all absorbents. The resistance of filled canisters in a circle system is low (less than 1.5 cm H_2O at a flow rate of 100 L/min). Resistance of other breathing circuit components, particularly the endotracheal tube, is greater. Inhaled absorbent dust is caustic and a respiratory irritant (it may lead to laryngospasm, bronchospasm, and pneumonia).[131] A trap for water, which also prevents the passage of dust toward the patient, may be incorporated distal to the granules in circle systems; if present, it must be emptied periodically. In addition, when the breathing circuit is pressurized for checkout, the pressure should be released through the APL valve, rather than through the elbow at the patient's end. This technique not only prevents the propulsion of dust toward the patient, but also is useful for checking APL valve function.

Absorbent efficiency is decreased by channeling and the wall effect.[176,177] The amount of CO_2 absorbed varies throughout the canister. The inside edge of the canister wall is a low-resistance pathway. Exhaled gas follows this pathway, or other low-resistance pathways, through the canister, forming channels whose capacity to absorb CO_2 is exhausted before the capacity of the bulk of the absorbent is used. Thus the wall effect and channeling produce exhaustion of absorbent before its theoretic capacity has been reached. To help prevent these two effects, shake the canister before installation in the circle system, to promote uniform packing throughout.[131]

Exhaustion and Replacement of Canisters

The clinical signs of absorbent exhaustion are shown in Box 15-15. Some of these signs (e.g., hyperventilation) may be masked in the anesthetized patient. In practice, capnography and indicator color change are primary indications of exhaustion. It is unwise to rely on color change or canister temperature alone as a measure of exhaustion.[178] The process of canister replacement for Aestiva-style dual-canister absorbers is illustrated in Figure 15-41, and the steps for replacement are shown in Box 15-16. Canister replacement for the ADU is shown in Figure 15-42.

Do *not* change Aestiva-style canisters or loose fill in the middle of a case. If the new canister is placed in its clear plastic holder upside down, or if for any other reason the circuit cannot be reassembled promptly, resumption of ventilation might be delayed. If granules do become exhausted, a safer alternative strategy is to change fresh gas flow to one to two times the minute ventilation; this approach should ensure that expired CO_2 is reduced to acceptable levels. The granules can then be replaced after the case.

Each canister (top or bottom) in an Aestiva-style absorber contains 1.1 kg of granules in a volume of 1400 to 1500 mL.[68,71,179] This compares to 0.8 kg per canister in the Aisys, and 0.6 kg in the ADU canister.[179] Each 100 g of granules can absorb as much as 15 L of CO_2 before the outlet concentration is 1% (7.6 mmHg), assuming that no channeling occurs. The average to maximum production of CO_2 by the anesthetized adult is 12 to 18 L/hr.[131] Therefore, when total rebreathing is occurring during closed circuit anesthesia, the top canister in an Aestiva might be expected to last for 8 to 10 hours of continuous use. A much longer life is observed clinically for these large canisters, principally because higher flows are used (typically in many clinical settings, 2 to 4 L/min of fresh gas flow). These higher flows cause increases in both the dilution of exhaled CO_2, and the rate of washout of exhalations from the breathing circuit to the scavenger. In one study in which fresh gas flows of 4 L/min were used, two canisters were used for 67 and 79 hours (anesthesia time) over 2.5 weeks without exhaustion, with a final minimum water content in some segments of 4% to 8.5%.[180] As lower flows become more common for economic and environmental reasons, and canisters become smaller, anesthetists will need to become more aware of the signs of absorbent exhaustion, and realize that absorbent must be changed more frequently.[181]

The manufacturer of soda lime recommends that the absorbent be changed if it is left in the machine for longer than 48 hours.[131] Dräger recommends that absorbent in the Fabius be changed if the machine has been idle for 48 hours, or at least each week on Monday.[60] These extremely cautious guidelines are based on recognition of two problems that arise with extended use. First, the ethyl violet indicator present along the wall of the canister may be inactivated by drying, or intense light. Second, dehydration of the granules occurs over time, particularly if higher gas flows or an excessive amount of oxygen flush is used. It is not uncommon for gases to be left flowing accidentally overnight or over the weekend. The resultant dehydration of the granules reduces their efficiency, and makes production of carbon monoxide and compound A more likely.[85]

Ventilators

Classification and Theory of Operation—Gas-Driven Bellows Ventilators

Modern ventilators using compressible bellows are multimode, double-circuit, electronically controlled, volume- or pressure-limited ventilators. Because they are electronically controlled, these ventilators cannot operate without main electrical power or a backup battery. Ventilators in current use may be classified with respect to a number of parameters (Box 15-17).* Figure 15-35 shows gas flow in the breathing circuit with mechanical ventilation. The bellows is similar to the anesthetist's hand squeezing a breathing bag to assist the patient's respiration. The mechanical ventilator is a "bag in a bottle"; it uses the force of compressed gas (O_2 or air) as the driving mechanism to compress the bellows. Within the bellows is the gas inspired and expired by the patient. Thus the bellows contains what the patient breathes, and separates it from the surrounding driving gas. Leaks in the bellows may cause dilution of gas within the bellows by driving gas, or loss of agent and oxygen from within it.[182]

Without a means of escape, the continual addition of fresh gas flow into the breathing circuit would cause increased volume and pressure within it (and in the patient's lungs). A ventilator relief valve (also known as the *spill valve*, or *overflow valve*) maintains circuit volume and pressure by releasing gas to the scavenger, in an amount equal to the fresh gas flow per minute. The ventilator relief valve opens only during the expiratory phase (see Figure 15-35). During inspiration, driving gas closes this relief valve, inflating the lungs by preventing gas within the bellows from exiting to the scavenger as the bellows are compressed. During early expiration, a weight within the ventilator relief valve holds the pathway to the scavenger closed until the bellows have filled. This

*References 15, 20, 25, 46, 57, 60, 62, 66, 69, 72, 74, 77, 90.

BOX 15-17

Classification of Modern Ventilators

Power Source
- Gas-driven bellows—compressed gas and electricity
- Piston ventilator—electricity only

Drive Mechanism
- Double-circuit—Bellows compressed by driving gas, which surrounds and compresses the patient circuit gas within. The driving gas is 100% oxygen or compressed air (GE), or a Venturi mix of oxygen and room air (older Dräger).
- Piston ventilators (compression of patient gas is by an electrically driven piston)

Cycling Mechanism
- Electronically time-cycled. Flow can also terminate when a volume or pressure target is achieved.

Modes
- Manual/spontaneous
- Volume-controlled ventilation (VCV)
- Pressure-controlled ventilation (PCV)
- Synchronized intermittent mandatory ventilation (SIMV) in either volume or pressure mode, with or without pressure support of the patient's spontaneous breaths
- Pressure-support ventilation (PSV)
- Pressure–controlled ventilation with volume guarantee (PCV-VG)

Bellows Classification
- Gas-driven bellows
  - Most have ascending (standing) bellows.
  - Descending (hanging) bellows are seen less commonly.
- Piston ventilators are driven by electric motors.

Data from Dosch M. *The Anesthesia Gas Machine: Ventilators*, 2011. Accessed January 29, 2012 at: http://www.udmercy.edu/crna/agm/08.htm; Dorsch JA, Dorsch SE. *Understanding Anesthesia Equipment*. 5th ed. Philadelphia: LWW; 2008; Dorsch JA, Dorsch SE. *A Practical Approach to Anesthesia Equipment*. Philadelphia: LWW; 2011.

creates 2 to 3 cm water of positive end-expiratory pressure (PEEP) within the breathing circuit. This small amount of PEEP is inherent to the design when standing-bellows mechanical ventilation is used.[46,54,77,182,183] Note that the "Bag/Vent" switch set to "Vent" or "Auto" removes the reservoir bag and APL valve from the breathing circuit (not true for ventilators with fresh gas decoupling), so in a standing bellows ventilator, the APL valve can be open during mechanical ventilation without causing a leak.

Hanging Bellows. A few ventilators with gas-driven bellows have "hanging" bellows. To distinguish between ascending (standing) and descending (hanging) bellows, use the mnemonic, "Asc*e*nd and desc*e*nd contain *e*'s, so look at the bellows during *e*xpiration to distinguish them." Both standing and hanging bellows are safe, in that both are capable of alerting the user to a disconnection, so long as appropriate monitoring is used.[184] Standing bellows have an advantage in that they will not fill in the event of a disconnect, whereas hanging bellows may fill with room air even when completely disconnected from the patient.[183]

The hanging design may provide compactness and ease of sterilization of the entire breathing circuit. One machine with a hanging bellows incorporates disconnect alarms based on chemical (capnograph) and mechanical principles (pressure, volume, and flow sensors). Because this design uses fresh gas decoupling, the manual breathing bag is always in the circuit and fluctuates in volume while the mechanical ventilator is operating. Water may gather in the bellows (lessening tidal volume and creating an infection risk), but this should be lessened by the heated absorber head.[185]

Theory of Operation—Piston-Driven Ventilators

Piston ventilators use an electric motor to compress the gas in a rigid piston during inspiration. They use no driving gas and may be used without depleting the oxygen cylinder in case of oxygen pipeline failure.[186] Piston ventilators, like gas-driven bellows, are safe and effective.

In the Narkomed 6000/6400 Divan ventilator, the piston is out of view, because it is placed horizontally under the writing surface. Although the piston can be viewed by lifting the writing surface, the to-and-fro movement is not normally visible during mechanical ventilation. The anesthetist relies on pressure and capnography waveforms, plus the movement of the manual breathing bag, to guard against disconnects or other problems. The Fabius GS has a piston ventilator similar to the Divan, but the bellows travel vertically, and their movement is continuously visible through a window to the left of the flowmeter bank (see Figure 15-8).

The piston ventilator has positive and negative pressure relief valves built in. If the pressure within the piston reaches 75 ± 5 cm H_2O, the positive pressure relief valve opens. If the pressure within the piston declines to −8 cm H_2O, the negative pressure relief valve opens, and room air is drawn into the piston, protecting the patient from negative end-expiratory pressure (NEEP).[60,62]

There are several advantages to a piston ventilator.[186] It is quiet. There is no PEEP (2 to 3 cm H_2O is mandatory on standing bellows ventilators because of the design of the ventilator spill valve). There is great precision in delivered tidal volume, owing to compliance and leak compensation, fresh gas decoupling, and the rigid piston design. There are fewer compliance losses with a piston, as compared with a flexible standing bellows compressed by driving gas. Measuring compliance and leaks with a transducer near the piston eliminates a bulky, costly sensor close to the patient's airway (such as the D-Lite sensor on the ADU). Electricity is the driving force for the piston, so if oxygen pipeline pressure fails, or pipeline supplies are unavailable (as in office-based settings), mechanical ventilation may continue without exhausting the cylinder oxygen simply to drive the bellows. Piston ventilators (like gas-driven bellows) are capable of all modern ventilation modes.

The piston design also has some disadvantages.[25] They do not display the characteristic motions of a standing bellows during disconnects, or when the patient is breathing over and above the ventilator settings. But disconnects can be seen in a piston ventilator with fresh gas decoupling (see later), because the manual breathing bag remains in the breathing circuit during mechanical ventilation with a piston. The piston is quiet, so that it may be harder to hear its regular cycling. The piston ventilator design cannot easily accommodate nonrebreathing circuits, although this is also true of traditional absorber heads like the Ohmeda GMS, or newer ascending bellows ventilators like the ADU. The piston has the potential for NEEP and dilution of the patient's inspired gas with room air.

Typical Ventilator Alarms

Modern ventilators have safety alarms to protect the patient from a number of conditions (Box 15-18). One important safety feature of modern equipment is that apnea (disconnect) alarms are enabled with the first breath sensed.

Ventilator Modes and Settings

Besides increased tidal volume accuracy because of compliance and leak compensation, the most notable advance in current ventilators is their flexibility in modes of ventilation. Pressure-controlled ventilation (PCV) allows more efficient and safe ventilation for certain types of patients. Pressure-controlled ventilation with volume guarantee (PCV-VG) helps to maintain tidal volume in the face of changing lung compliance, for example, when pneumoperitoneum is applied or released. Pressure-support ventilation (PSV) is an important recent addition for patients who are spontaneously breathing, which is seen with much greater frequency since the adoption of the laryngeal mask airway. The improvement in accuracy afforded by modern ventilators at small tidal volumes means that switching of circuits (e.g., to a nonrebreather for small children) are not used as often. This helps avoid potential misconnects.

BOX 15-18

Typical Ventilator Alarms

Pressure Alarms
- High (isolated or continuing)
- Subatmospheric
  - Volume—low tidal or minute volume
  - Rate—high respiratory rate
  - Reverse flow (may indicate incompetence of expiratory unidirectional valve in the breathing circuit)

Apnea/Disconnect Alarms*

These may be based on the following:
- Chemical monitoring (lack of end-tidal carbon dioxide)
- Mechanical monitoring:
  - Failure to reach normal inspiratory peak pressure, or failure to sense return of tidal volume
  - Spirometry
  - Failure of standing bellows to fill during exhalation
  - Failure of manual breathing bag to move and fill during mechanical ventilation (machines with fresh gas decoupling—Apollo, Fabius, Narkomed 6000)
  - Other—lack of breath sounds or visible chest movement.

*Note that low readings of the pulse oximeter is less valuable, because it is a late sign of hypoventilation.

Volume-Controlled Ventilation. All ventilators offer volume-controlled ventilation (VCV). In this mode, the desired tidal volume (V_T) is delivered at a constant flow. The ventilator is volume limited, time cycled, and constant flow in VCV. Inspiration is terminated when the desired V_T is delivered or if an excessive pressure is reached (60 to 100 cm H_2O).[54,60,62,71] Patients under general anesthesia often have decreased functional residual capacity and compliance.[187] Because volume is controlled, alveolar ventilation and arterial carbon dioxide can be maintained despite changes in pulmonary function.[188] However, with VCV the peak inspiratory pressure is uncontrolled, and rises as the patient's compliance decreases, or airway resistance increases.

V_T is adjusted to prevent atelectasis, and respiratory rate (RR) is adjusted to keep end-tidal carbon dioxide at the desired value. Peak inspiratory pressure (PIP) is monitored but not controlled. Typical initial settings for VCV in an adult are V_T 6 to 12 mL/kg, RR 6 to 12 breaths per minute, and inspiratory:expiratory (I:E) ratio 1:2. PEEP of 5 cm H_2O may be added to prevent atelectasis.[189]

Pressure-Controlled Ventilation. In pressure-controlled ventilation (PCV) mode, PIP is limited, and the cycle is controlled by time, with a decelerating flow pattern. Inspiratory pressure is controlled rather than volume (as with VCV).[189,190] Tidal volume is uncontrolled, and increases if compliance increases, or airway resistance falls. The ventilator generates sufficient flow to attain the target pressure early in inspiration, then maintains this set pressure throughout the inspiratory time. High flow is needed at first, and less flow is required to maintain this pressure. If the desired tidal volume is not obtained, inspiratory rise can be increased. Target pressure is adjusted for the desired V_T; RR is adjusted to maintain a reasonable end-tidal carbon dioxide. V_T is monitored but not controlled. In patients with low compliance (e.g., morbidly obese), PCV may result in an increased tidal volume at a lower PIP, especially if PIP had been high when employing VCV (e.g., in laparoscopic abdominal or pelvic surgery). During PCV, if pulmonary compliance drops (e.g., application of pneumoperitoneum) or airway resistance increases (e.g., bronchospasm, kinked endotracheal tube), delivered V_T may drop substantially. Conversely, if pulmonary compliance improves (e.g., release of pneumoperitoneum, return to supine from steep Trendelenburg position) or airway resistance decreases, V_T may increase substantially.

There are several indications for PCV. Patients for whom high inspiratory pressure is particularly dangerous may benefit (e.g., laryngeal mask airway,[191] emphysema, neonates). In patients with low compliance, PCV can often produce higher tidal volumes than VCV (e.g., pregnancy, laparoscopic surgery, morbid obesity, or adult respiratory distress syndrome). PCV can compensate for leaks (e.g., infants with uncuffed endotracheal tubes, laryngeal mask airway). PCV may provide effective ventilation and lower airway pressure during one-lung ventilation.[190,192]

Typical initial settings for PCV in an adult include pressure limit 20 cm H_2O, RR 6 to 12 breaths per minute, I:E ratio 1:2. PEEP 5 cm H_2O may be added to help prevent atelectasis.[189] Pressure control has been incorporated into other modes, such as PCV-VG (which adjusts inspiratory pressure to prevent significant variation in delivered V_T; see later)[57,59] and as SIMV in pressure control mode.[62]

Pressure-Controlled Ventilation with Volume Guarantee. Pressure-controlled ventilation with volume guarantee (PCV-VG) was created to address the problem that V_T in pressure control mode varies, sometimes strikingly, when the patient's compliance changes. Like PCV, the basic controls are target pressure and rate, but in PCV-VG, a desired V_T is also set. Like PCV, the ventilator delivers breaths using a decelerating flow pattern at a constant pressure. But in PCV-VG, the inspiratory pressure is adjusted to deliver the set V_T, using the lowest possible pressure, and staying within the maximum pressure limit. PCV-VG begins by delivering a volume breath at the set V_T. The patient's compliance is determined from this volume breath, and the inspiratory pressure level is then adjusted for the next breath. PCV-VG combines the advantages of pressure-controlled ventilation, yet dynamically compensates for changes in the patient's lung characteristics (Figure 15-43).[73]

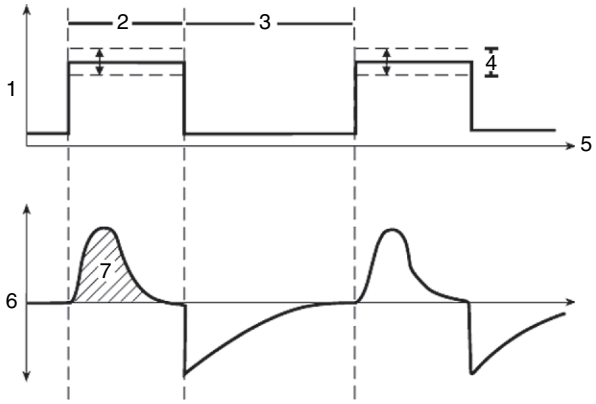

FIGURE **15-43** Pressure-controlled ventilation with volume guarantee. The pressure waveform at top (*1*) shows that peak inspiratory pressure is adjusted up and down to deliver the set tidal volume. The bottom (*6*) is the flow-time waveform. *1*, Paw waveform; *2*, Tinsp; *3*, Texp; *4*, Variable pressure to deliver desired TV; *5*, PEEP; *6*, Flow waveform; *7*, TV. *Paw,* Airway pressure; *Tinsp,* Time for inspiration; *Texp,* Time for expiration; *TV,* Tidal volume; *PEEP,* positive end-expiratory pressure. (From *Aisys User's Reference Manual,* part 2 of 2, Document No. M1122365 10 07 01 04 23. Tewksbury, Mass: Datex-Ohmeda Inc; 2008.)

Synchronized Intermittent Mandatory Ventilation. With the advent of the laryngeal mask airway (LMA) and the prevalence of short, ambulatory, or office-based surgical procedures, spontaneous unassisted breathing has become much more common during general anesthesia. But it is difficult to maintain a light enough plane of anesthesia to permit spontaneous ventilation, while still retaining sufficient depth for surgery to proceed. If the spontaneously breathing patient is maintained in a plane of anesthesia that is too deep, respiratory acidosis will occur; too light, bucking and awareness are risks. The traditional solution was to assist ventilation manually, because synchronized intermittent mandatory ventilation (SIMV) was all the mechanical ventilator could provide. Ventilation modes that could support a spontaneously breathing patient (i.e., provide normocapnia without bucking) include SIMV,[193] PSV,[194] continuous positive airway pressure (CPAP), and airway pressure release ventilation (APRV).[189,195,196] Of these modes, SIMV and PSV are currently available.

SIMV can be used for anything from full to partial support of ventilation. On newer gas machines, SIMV may be selected based on either pressure or volume modes. Whichever is selected, in SIMV the intermittent mandatory breaths are delivered in synchrony with, and triggered by, the patient's spontaneous efforts. Typical initial settings thus include not only volume (or pressure limit) and rate, but trigger window (percent) and sensitivity (Figure 15-44). The spontaneous breaths may also be pressure supported (SIMV-PS).[60]

Trigger window controls the amount of time during each expiratory cycle that the ventilator is sensitive to spontaneous breaths, by sensing the negative pressure generated by the patient's diaphragm. Sensitivity controls how much negative pressure the patient needs to generate before a breath is triggered. If

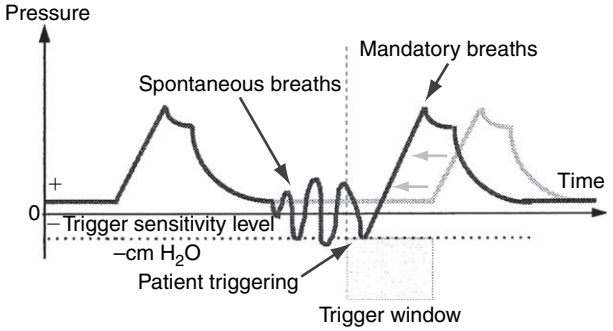

FIGURE **15-44** Trigger window and sensitivity may be set when choosing synchronized intermittent mandatory ventilation (SIMV) mode. (From *S/5 Anesthesia Delivery Unit User's Reference Manual*, Catalog No. 8502304. Madison, Wis: Datex-Ohmeda; 2000.)

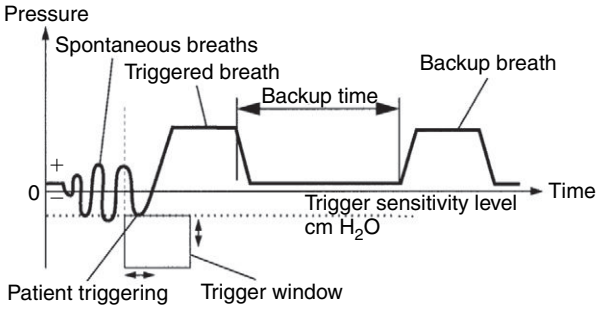

FIGURE **15-45** Trigger window and sensitivity settings interact with the patient's spontaneous breaths in pressure-support ventilation. (From *Datex-Ohmeda ADU Ventilation Supplement*, Document No. M1038740, Issue M1044700. Madison, Wis: Datex-Ohmeda; 2005.)

spontaneous breaths are triggered too often (e.g., by motion in the surgical field), the trigger window should be reduced, or the sensitivity made more negative.

When switching from SIMV to VCV, the I:E ratio does not reset to default values automatically (on the ADU), so I:E ratio should be checked as part of the review of all settings when placing a subsequent patient on the mechanical ventilator. Typical settings for SIMV mirror those used for VCV (or PCV if a pressure-controlled mode is chosen).

Pressure-Support Ventilation. Pressure-support ventilation (PSV) is like PCV in that it is a pressure-targeted ventilation mode—but with a RR of zero. It is like SIMV in that it is responsive to the patient's efforts, delivering a breath within a trigger window, provided the patient's negative inspiratory pressure meets the sensitivity setting. Thus it is *only* useful for patients who are breathing spontaneously. There is no minimum minute ventilation, although some ventilators allow setting an apnea backup rate or delay.[194]

PSV is useful to augment the V_T of a spontaneously ventilating patient during maintenance or emergence. The primary setting is the pressure-support level, which for adults may be started at 10 cm H_2O, and adjusted based on tidal volume and end-tidal carbon dioxide. Trigger window, sensitivity, maximum inspiratory flow, and apnea backup rate may also be set, depending on the particular ventilator (Figure 15-45).

Safety Features of Modern Ventilators

Flexibility. The appearance of PCV is a major advantage, allowing more challenging patients to be ventilated efficiently, such as patients with acute respiratory distress syndrome (ARDS) or morbid obesity who are difficult with VCV mode. PCV also increases safety for patients in whom excessive pressure must be strictly avoided, such as neonates and infants, and patients with emphysema. PSV and SIMV are quite valuable in supporting the patient with spontaneous respirations. Perhaps the biggest hurdle in implementation for all new modes is the education of generations of providers who are only familiar with "plain vanilla" volume control mode.

Accuracy at Lower Tidal Volumes. Factors contributing to a discrepancy between set and delivered tidal volumes are especially acute in pediatrics, and include the large compression volume of the circle system relative to the infant's lung volume, leaks around uncuffed endotracheal tubes, the augmentation of delivered V_T produced by fresh gas flow, and the difficulty of setting a small V_T using an adult bellows assembly.[15]

Modern ventilators have an unprecedented V_T range for two reasons; greatly increased accuracy in V_T delivery achieved through electronic compliance and leak testing, and V_T that is compensated for these factors, as well as changes in fresh gas flow. They are able to ventilate smaller patients much more accurately than any previous anesthesia ventilator could. This has significantly lessened the need for nonrebreathing (Mapleson) circuits and made care safer, because anesthetists will no longer have to disassemble and reconfigure a nonrebreathing circuit for a child in the middle of several adult cases. However, it is mandatory to substitute pediatric circle disposable hoses for tidal volumes less than 200 mL with the Narkomed 6000 and the Fabius.[197] Smaller filters, a pediatric D-Lite sensor, and less compliant pediatric circle breathing systems must be used on the ADU for V_T less than 150 mL.[54] The lower limit of accuracy for V_T is 10 mL (for the Narkomed 6000[66]), and 20 mL (for the Fabius,[60] Aestiva,[71] ADU,[54] Apollo,[62] Avance,[57] and Aisys[73]). When sensors or disposable breathing circuit types are changed for a pediatric case, users must repeat the leak and compliance tests of the preanesthesia check, so that maximum V_T accuracy is ensured. Likewise, these must be repeated when returning to the adult configuration.

Compliance and Leak Testing. Accuracy in delivered V_T comes with a price. An electronic leak and compliance test is part of the morning checklist, and it must be repeated every time the circuit is changed to a circuit with a different configuration (adult circle to pediatric circle, or adult to long circuit). Users must familiarize themselves with whether vaporizers and other components are included in the leak and compliance test, because what is actually checked varies between different models.

The placement of the sensor used to compensate tidal volumes for compliance losses and leaks has some interesting consequences. The Aestiva flow sensors are placed between the disposable corrugated breathing circuit limbs and the absorber head. Here they are able to compensate tidal volumes for fresh gas flow, compliance losses, and leaks internal to the machine and absorber head—but not for any of these that occur distally (in the breathing hoses). The D-Lite sensor (ADU) is placed at the Y-piece. In this position, it can compensate for all leaks and compliance losses out to the Y-piece (thus including the breathing circuit hoses). However, at this point, it adds appreciable bulk and weight close to the patient's face. This may make mask ventilation more cumbersome. Further, a sensor closer to the patient is exposed to more exhaled moisture, but the impact on monitoring integrity can be lessened with a heat and moisture exchanger between patient and sensor. Unfortunately, this adds further bulk and weight. The Narkomed 6000, Apollo, and Fabius test compliance and leaks of all components to the Y-piece via a pressure transducer within the internal circuitry near the bellows. Here the sensor is relatively protected from moisture.

Fresh Gas Decoupling Versus Tidal Volume Compensation. A final factor adding to modern ventilator accuracy is that they compensate delivered tidal volume for changes in fresh gas flow. In older

ventilators, the delivered V_T is the sum of the volume delivered from the ventilator and the fresh gas flowing during the inspiratory phase, so the actual delivered $V_T$may change as fresh gas flow is changed. For example, consider a patient with a fresh gas flow of 4 L/min, an RR of 10, an I:E ratio of 1:2, and a V_T of 700 mL. During each minute, the ventilator spends a total of 20 seconds in inspiratory time and 40 seconds in expiratory time (as a result of the 1:2 ratio). During this 20 seconds, the fresh gas flow is 1320 mL (one third of 4000 mL/min fresh gas flow). So each of the 10 breaths of 700 mL is augmented by 132 mL of fresh gas flowing while the breath is being delivered, and the actual delivered V_T is 832 mL/breath (a 19% increase).

What happens when we decrease the fresh gas flow? Assume the same parameters, but a fresh gas flow of 1000 mL/min. During each minute, the ventilator spends 20 seconds in inspiratory time and 40 seconds in expiratory time (1:2 ratio). During this 20 seconds, the fresh gas flow is 330 mL (one-third of 1000 mL/min fresh gas flow). So each of the 10 breaths of 700 mL is augmented by 33 mL of fresh gas flowing while the breath is being delivered, making the total delivered tidal volume 733 mL/breath. This means that changing fresh gas flow from 4000 mL/min to 1000 mL/min, *without changing ventilator settings*, has resulted in a 14% decrease in delivered V_T (832 to 733 mL). It would not be surprising if the end-tidal carbon dioxide rose as a result.

The situation is more acute with a child ventilated without fresh gas flow compensation. Assume a 10-kg patient with a fresh gas flow of 4 L/min, an RR of 20, I:E ratio of 1:2, and a V_T of 100 mL. During each minute, the ventilator spends 20 seconds in inspiratory time and 40 seconds in expiratory time (1:2 ratio). During this 20 seconds, the fresh gas flow is 1320 mL (one third of 4000 mL/min fresh gas flow). So each of the 20 breaths of 100 mL is augmented by 66 mL of fresh gas flowing while the breath is being delivered, making the total delivered V_T 166 mL/breath. This is a 66% increase above what is set on the ventilator. Decreasing fresh gas flow from 4 to 1 L/min, again without changing ventilator settings, decreases minute ventilation from 3320 to 2333 mL (a 30% reduction).

There are two approaches to dealing with the problem. The Apollo, Narkomed 6000, and Fabius use fresh gas decoupling (Figure 15-46). Fresh gas flow during inspiration is not added to the delivered V_T, because it is diverted (by the closed decoupling

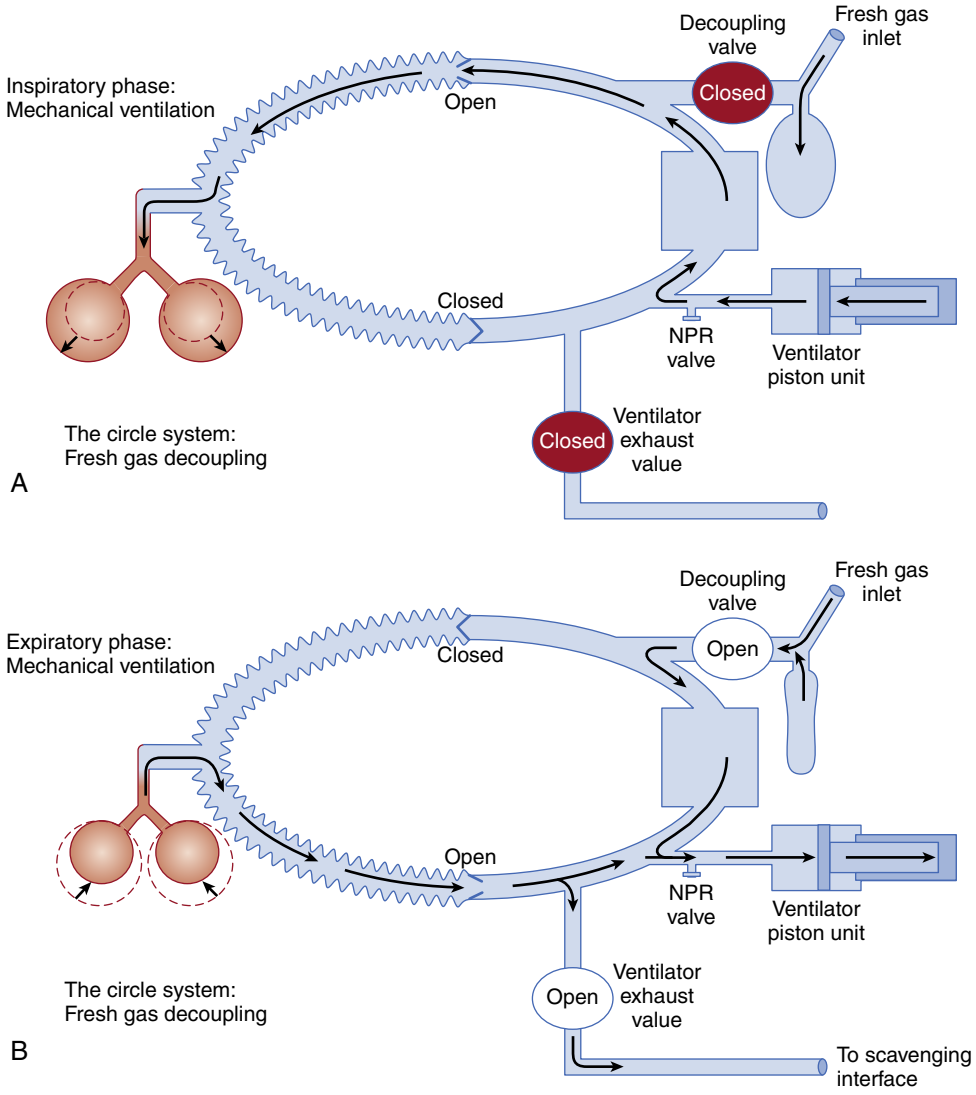

FIGURE **15-46** Circle breathing system with fresh gas decoupling. See text for explanation. *NPR*, Negative pressure relief valve. (From Miller RD, et al, eds. *Miller's Anesthesia*. 7th ed. Philadelphia: Churchill Livingstone; 2010.)

valve) to the manual breathing bag, which remains in circuit during mechanical ventilation. Thus fresh gas decoupling helps ensure that the set and delivered tidal volumes are equal. The visual appearance of the circuit during mechanical ventilation is unusual in that the manual breathing bag (normally quiescent) moves with each breath. Further, this manual breathing bag movement is opposite to the movement seen in a mechanical ventilator bellows, which empties during inspiration, and fills during expiration. With fresh gas decoupling, the manual breathing bag inflates during inspiration (due to fresh gas flow) and deflates during expiration as the contents empty into the piston. With fresh gas decoupling, if there is a disconnect, the manual breathing bag rapidly deflates because the piston retraction draws gas from it.

The same fresh-gas decoupled circuit is shown during expiration in the bottom panel of Figure 15-46. The piston refills with the patient's exhaled gas, and also fresh gas contained in the manual breathing bag (now returned to the rest of the breathing circuit by the open decoupling valve). The ventilator relief valve is now open, allowing excess gas to exit to the scavenger.

The second approach to preventing augmentation of delivered V_T by fresh gas flow is called tidal volume compensation, which is used in the Aestiva and ADU (among others). The volume and flow sensors at the Y-piece provide feedback that allows the ventilator to adjust the delivered V_T so that it matches the set V_T, in spite of changes in fresh gas flow.

Suitability for Low Flows. Low fresh gas flow is desirable to reduce pollution, reduce the cost of volatile agents and nitrous oxide, preserve tracheal heat and moisture, prevent soda lime granules from drying, and help preserve patient body temperature. Factors that enhance the safety and efficiency of low-flow anesthesia in modern ventilators are shown in Box 15-12. As you can see, a traditional-sized absorber head like the Aestiva is roughly twice the volume of some of the newer designs. All newer nondisposable portions of the breathing circuit are designed to be more leak-proof than earlier designs.

Electronic Selection of Positive End-Expiratory Pressure. Electronic selection of positive end-expiratory pressure (PEEP) is safer than previous approaches, which involved adding adapters to the breathing circuit. Add-on adapters came in different varieties, depending on how much PEEP was desired (e.g., 5 or 10 cm H_2O). They were intended to be placed between the expiratory limb of the breathing hoses and the expiratory unidirectional valve. They have been placed accidentally in the inspiratory limb, where they cause complete obstruction to flow in the breathing circuit.[198] Although it would seem easy to find this fault immediately, in the heat of the moment with a patient who is already hypoxemic, the clinician may become distracted and unable to focus effectively on the problem. This is an example of a clinical pearl: When a change in the patient's condition is noticed, think back to the last alteration made to the equipment (or to the last drug *thought* to be given), and determine whether it might have contributed to the change.

Current Ventilator Designs

GE Healthcare 7900 "SmartVent." The 7900 was designed to provide consistent delivered V_T in spite of changes in fresh gas flow, small leaks, and absorber or bellows compliance losses. It uses variable-orifice flow sensors (proximal to the inspiratory and expiratory limbs) and pressure sensors to accomplish this. Compliance losses in the corrugated hoses are not corrected for, but these are a relatively small portion of compliance losses.[199] Available modes include manual/spontaneous, volume control, pressure control, pressure support, and SIMV (in either volume or pressure mode with pressure support). PCV-VG is available on the Aisys and Avance. PEEP is integrated and electronically controlled. Spirometry loops are available. It is found on a variety of machines, including Aestiva, Aisys, and Avance. Typical Aestiva controls are shown in Figure 15-47.

GE Healthcare 7100. The 7100 is similar to the 7900, except that the selection of modes is not as extensive. The 7100, like the 7900, features tidal volume compensation. It is found on the Aespire.

GE Healthcare ADU Ventilator. The design of the ADU ventilator and gas machine system has many innovative features.[54] The ventilator (like most modern designs) is activated by a single switch (setting the "Bag/Vent" switch to "Auto"). The ventilator can use either oxygen or air as a driving gas, and will switch automatically to air if oxygen pipeline pressure is lost. Delivered V_T is adjusted to compensate for changes in fresh gas flow and total (absorber head and corrugated limbs) breathing circuit compliance losses (through the D-Lite sensor at the elbow). Entering the patient's weight will suggest appropriate ventilator settings. Volume control, pressure control, pressure support, manual/spontaneous, and SIMV modes are offered, along with integrated electronic PEEP. Flow-volume (resistance) or pressure-volume (compliance) spirometry loops may be displayed breath by breath. The controls are straightforward (Figure 15-48).

Users should exercise caution with regard to the displayed oxygen concentration. "Calc. O_2%," which is optionally displayed in the mid–lower left of the primary (left) machine status screen, is

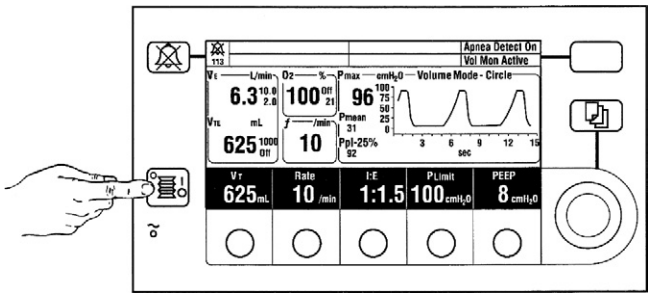

FIGURE 15-47 Display and control panel of the Datex-Ohmeda 7900 ventilator. (From *Ohmeda 7900 Ventilator Operation and Maintenance Manual*. Madison, Wis: Datex-Ohmeda; 1997.)

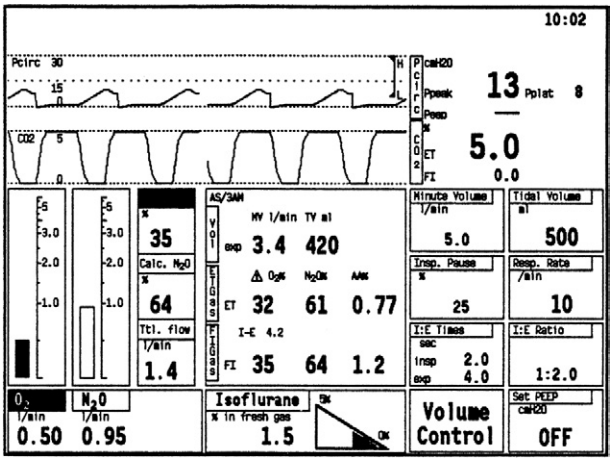

FIGURE 15-48 Machine monitors and ventilator controls are on the left display screen of the Datex-Ohmeda ADU. (From *Datex-Ohmeda AS/3 Anesthesia Delivery Unit User's Reference Manual*. Tewksbury, Mass: Datex-Ohmeda; 1998.)

based on the flowmeter settings only, unlike the oxygen analysis results displayed in the lower center area of the same screen. The danger arises in a crossover situation, in which the pipeline oxygen supply is lost and replaced with another gas (e.g., nitrogen). In this emergency, two sections of the same display may offer conflicting information. Because it is based on flowmeter settings, Calc. O_2% will indicate only the intended inspired oxygen concentration, not the actual. The oxygen analyzer display will simultaneously alarm, accurately showing a dangerous hypoxic mixture. Although the manual clearly warns of this problem, the design may confuse providers in this rare emergency situation, delaying the correct response, which might lead to patient injury.[50,54]

Dräger Divan Ventilator. The Divan ventilator is a piston ventilator found on the Narkomed 6000/6400.[66] It offers pressure control, volume control, manual/spontaneous, and SIMV modes. There is no mechanical Bag/Vent switch. Switching between modes is accomplished by electronic keypad. The Divan corrects delivered V_T for compliance losses by measuring circuit compliance, and for fresh gas flow by fresh gas decoupling. Electronic PEEP is integrated. The absorber head is warmed. The Divan is limited to a pressure of 70 cm H_2O, so like most ventilators, it cannot ventilate patients in volume-controlled mode beyond this pressure (but it is possible and perhaps preferable to ventilate the ARDS patient with pressure-controlled mode). It is accurate to very low tidal volumes (range 10 to 1400 mL). Use pediatric circle system (low compliance) hoses for tidal volumes less than 200 mL, and remember to repeat the ventilator self-test when changing circuits.

Unlike most other anesthesia ventilators, there are no visible bellows on the Divan ventilator. It is unique among current models in having a horizontal piston, which is hidden within the writing surface of the gas machine. To provide a visible indication of lung inflation, fresh gas is diverted to the manual breathing bag, which inflates during mechanical ventilator inspiration and deflates during expiration. The piston design avoids NEEP by entraining room air if pressure within the bellows is less than atmospheric pressure. The "Fresh gas low" error message warns of this condition.

Fabius GS Ventilator. The Fabius GS ventilator is another piston ventilator.[60,200] It offers pressure control, volume control, pressure support, SIMV/PSV, and manual/spontaneous modes. There is no mechanical Bag/Vent switch. Switching between modes is accomplished by electronic keypad. It corrects delivered V_T for compliance losses by measuring circuit compliance, and for fresh gas flow changes by fresh gas decoupling. Electronic PEEP is integrated. One can view measured respiratory parameters or ventilator settings (but not both simultaneously) on the monitor screen. It is accurate to very low tidal volumes (range 20 to 1400 mL). Use pediatric circle system (low compliance) hoses for tidal volumes less than 200 mL, and remember to repeat the ventilator self-test when changing circuits.

The piston movement is visible in a window to the left of the flowmeter bank. Like the Divan, it provides a visible indication of lung inflation and potential disconnects in that fresh gas is diverted to the manual breathing bag, which inflates during mechanical ventilator inspiration and deflates during expiration. The piston design avoids NEEP by entraining room air if pressure within the bellows is less than atmospheric pressure. The "Fresh gas low" error message warns of this condition.

Apollo Ventilator. The Apollo ventilator is a piston similar to the Fabius, except that spirometry is displayed. It is similar to the Narkomed 6000 in that the absorber head is heated. Modes are manual/spontaneous, volume and pressure control, pressure support, and SIMV in either volume or pressure mode.[15,62]

Traditional Anesthesia Ventilators

The Datex-Ohmeda 7000 and 7800, and the Dräger AV-2 and AV-E ventilators were covered in previous editions of this text. Departments who still retain or use these ventilators should ensure that all personnel are familiar with them and can use them safely in an emergency.[1]

Critical Incidents Related to Ventilation

Disconnects and Other Causes of Low Pressure in the Breathing Circuit. Clinical experience with anesthesia ventilators and breathing circuits has identified several situations that have led to critical incidents. Vigilance directed toward situations that have the potential to cause patient injury may contribute to the prevention of future occurrences (Box 15-19). Failure to ventilate caused by disconnection has been called the most common preventable equipment-related cause of mishaps.[25] The most common site for disconnection is between the breathing circuit and the endotracheal tube (at the Y-piece).[184] Disconnects can be

BOX 15-19

Causes of Critical Incidents

Underlying Causes of All Critical Incidents

- Improper or infrequent maintenance
- Inadequate in-service education
- Substandard equipment monitoring
- Failure to check equipment before use
- Lack of familiarity with equipment standards

Mechanisms of Critical Incidents

Failure to Ventilate

- Disconnection
- Failure to initiate ventilation or resume it after an interruption
- Misconnections of breathing circuit
- Occlusion or obstruction of breathing circuit
- Kinking or plugging of endotracheal tube
- Kinking of fresh gas delivery hose
- Mold flash or plastic emboli from wrapping material
- Leaks
- Failure or improper reassembly of bellows after cleaning
- Damage to or disconnection of pressure monitoring or other hoses
- Failure of pipeline and tank oxygen supply
- Driving a vent with cylinders (when pipeline is unavailable) causes rapid tank depletion
- Inadvertent application of suction to the breathing circuit
- Failure of scavenger interface negative-pressure relief valve
- Intubation of trachea with nasogastric tube, which is then connected to suction

Barotrauma

- Excess inflow to breathing circuit (flushing during ventilator inspiration)
- Ventilator relief valve may stick closed
- Control assembly problems

partial or complete. Recent reported causes of low pressure (leak) conditions are many: absorbent granules changed between cases by ancillary personnel but improperly reassembled or even left open[201,202]; defective absorber canister[203]; failure of the Bag/Vent switch[204,205]; leaks in corrugated hoses[206]; incompetent ventilator relief valve[207]; leaks from a hot-wire anemometer sensor[208]; the gas sampling line preventing manual ventilation by preventing closure of an APL[209-213]; and ventilator failure due to moisture in flow sensors.[70]

A proposed protocol for dealing with leaks and other causes of low pressure in the breathing circuit has been published.[214] Prevention of disconnects involves a thorough preanesthesia check of equipment, including testing the breathing circuit with a second breathing bag as an artificial lung (or breathing through the circuit). A primary monitor for disconnection is continuous auscultation of breath sounds with a precordial or esophageal stethoscope, as well as direct visual observation of chest movement (both are recommended by standard).[96,97] Electronic monitors for disconnection include capnography and pressure-based and volume-based alarms (see Box 15-18).[38,184] Because electronic monitors may have alarms disabled, either inadvertently or intentionally (because of artifacts and because of monitor failure), there is no substitute for the anesthetist's vigilance in remaining in touch with the patient through the five senses.

To manage inability to ventilate due to low pressure in the breathing circuit, first ensure ventilation is occurring by checking breath sounds. If not, and the circuit has obviously lost volume, check for leaks quickly (e.g., disconnect, suction in trachea, scavenger settings, incompetent ventilator relief valve), then try to ventilate manually using the anesthesia breathing circuit. If no volume loss is apparent, check settings of fresh gas flow, scavenger, and ventilator, as well as monitor artifact.[38] Do not interrupt ventilation for diagnosis of machine problems; proceed to manual ventilation with backup ventilation equipment (Ambu bag) without delay.[214]

Failure to Initiate or Resume Ventilation. Failure to initiate or resume ventilation may be less likely in the future because of the incorporation of modern monitoring in current gas machines. All possess common features that add to patient safety.[54,60] They have a centralized data and alarm display, as well as alarms prioritized to warnings, cautions, and advisories. They provide electronic pre-use checklists.[98,215] Furthermore, the apnea and disconnect alarms are typically placed on standby when the system's main power switch is activated, and their alarms are enabled once a breath is sensed. Therefore the anesthesia gas machine should alert the operator to a failure to turn on a mechanical ventilator after intubation, or to a failure to resume ventilation after the ventilator is shut off either temporarily (in the middle of a case for radiography) or permanently (during emergence). If turning off a mechanical ventilator temporarily mid-case, it is safest to leave one's finger on the switch until it is time to resume ventilation.

The number of different alarm conditions programmed into a modern anesthesia gas machine with integrated monitoring is staggering. It is absolutely necessary to read the manuals and participate in training for machines of such complexity.[216] Although equipment has improved dramatically, some of the underlying causes of failure to ventilate and of barotrauma will likely remain problems for the foreseeable future (e.g., lack of knowledge or training, and failure to use checklists).

Barotrauma and High Pressure in the Breathing Circuit. Although such problems as misconnections are less likely now than in the past because of improvements in design, other possible causes of failure to ventilate, or barotraumas, are still hazards: occlusion, bellows leaks, failure of gas supply, failure of the ventilator relief valve, and inadvertent application of suction or positive pressure to the airway.[138,143,153,217-224]

Unlike disconnects and other low-pressure breathing circuit problems, high pressure in the breathing circuit can evolve quickly and produce devastating consequences, allowing little time for diagnosis or correction. The causes of sustained high pressure in the breathing circuit are diverse. Obstruction to exhalation (but not inhalation) has been caused in recent times by direct connection of wall oxygen to a tracheal tube,[224] improper manufacture of a scavenger assembly,[225] failure to remove plastic wrap around a soda lime canister before installing it in the machine,[226,227] malfunctioning ventilator relief valve,[143] occlusion of the lumen of a breathing circuit extender adaptor by mold flash or other plastic debris,[150,152,153] insertion of an occluded disposable PEEP valve into the breathing circuit,[150] and an occluded expiratory unidirectional valve.[147] Most of these obstructions would have easily been detected by a preinduction high-pressure check of the breathing circuit, with release of pressure through the APL valve, using an artificial lung during checkout to ensure gas flows properly in the breathing circuit, or simply by breathing through the circuit. Consequences included high PEEP, decreased venous return, cardiovascular collapse, pneumothorax, massive subcutaneous emphysema, or death.

The algorithm for responding to sustained high pressure in the breathing circuit is as follows.[38] Assess patient-related causes such as bronchospasm. Try manually ventilating the patient with the breathing circuit (in "Bag" mode). If the high pressure is relieved, it is likely that the ventilator relief valve is at fault. The ventilator is unusable until this valve is serviced. If circuit pressure is sustained during manual ventilation with the circuit, it is likely that the scavenger is obstructed or that its relief valves have failed. In either case, attempt to disconnect the scavenger gas collection tubing from the back of the APL if possible. If the tubing cannot be disconnected, disconnect the patient from the breathing circuit and continue ventilation by Ambu bag.[38]

Fire in the Breathing Circuit. Although rare, fires in the breathing circuit have been reported in vivo[84,86,228] and in vitro.[81,86,229,230] These events are often associated with first cases on Monday, sevoflurane, and desiccated barium hydroxide lime. The most important preventive actions include (1) turning off all gas flows and vaporizers between cases and at the end of the day and (2) ensuring that carbon dioxide absorbents are changed regularly.[79,84,85] The response to breathing circuit fires is the same as for airway fires.[86]

The Anesthesia Gas Machine and Malignant Hyperthermia. When an unexpected malignant hyperthermia (MH) crisis arises, one follows a protocol including (as far as equipment is concerned) withdrawal of triggering agents. This would include stopping the administration of volatile agents, hyperventilating with oxygen 100%, increasing fresh gas flow, and (if time and help are available and can be spared from other more important tasks such as mixing dantrolene) changing the disposable breathing circuit components and granules.[77,231] When preparing the gas machine for a patient who is known to be susceptible, one changes the breathing circuit and granules, disables or removes the vaporizers, and flushes all traces of volatile agent from its internal circuitry. The old guideline for flushing was a fresh gas flow rate of 10 L/min for 20 minutes. New evidence indicates that this may be very inadequate for some machines, with the Fabius requiring as much as 104 minutes.[231-234] Keep fresh gas flows high during maintenance.[232]

DISPOSAL

The final *D* of the SPDD model is concerned with a simple but vital question: How are gases disposed of?

Disposal of Gases in Scavenging Systems

Scavenging is the collection of waste anesthetic gases from the breathing circuit and ventilator and their removal from the operating room. An amount equal to the fresh gas flow must be scavenged each minute.[89,235-237] Otherwise, the breathing circuit and the patient's lungs will either gain or lose volume, resulting in barotrauma or failure to ventilate. The components of the scavenger are listed in Box 15-20 and shown in Figure 15-49.

BOX 15-20

Components of the Scavenger System

Gas collection assembly—at adjustable pressure-limiting (APL) valve and ventilator relief valve
Transfer tubing—19 or 30 mm, sometimes color-coded yellow
Scavenging interface (most important part)
- Closed interface (all older models)
  - Communicates to atmosphere only through valves
  - If used with passive disposal system, must have positive pressure relief
  - Used with active (suction) disposal system; must have positive *and* negative pressure relief
- Open interface (most new models)
  - No valves; open to atmosphere (both negative and positive pressure relief "built in")
  - Must be used *only* with active systems
  - Reservoir required

  Safety:
  - Safer than closed interface for the patient; no barotrauma
  - Less safe than closed interface for the caregiver (if used improperly)

Gas disposal tubing
Gas disposal assembly—active disposal (common) or passive disposal

A standard for exposure to waste anesthetic gases is published by the Occupational Safety and Health Administration (OSHA).[238] OSHA directs that no worker be exposed to more than 2 ppm halogenated agents (0.5 ppm if used with nitrous oxide), and no more than 25 ppm nitrous oxide, based on a time-weighted 8-hour average concentration. Levels in unscavenged anesthetizing locations may be as high as 7000 ppm (0.7%) N_2O and 85 ppm (0.008%) halothane.[21] The highest levels are found in the anesthetist's workstation, and between the anesthesia gas machine and the wall.[20] Operating-room personnel (anesthesiologists, surgeons, and nurses) working in ear, nose, and throat operating rooms had measurable levels of exhaled sevoflurane higher than controls up to 18 hours after being on duty, although this study did not report what type of scavenging, if any, was employed.[239] The health effects of chronic exposure to volatile agents are unproved, though it is clear that occupational exposure to nitrous oxide should definitely be avoided.[171]

Several variables determine the attainable reduction in waste anesthetic gases in the operating room, including the degree of room ventilation, the condition of anesthesia equipment, the effectiveness of the scavenger, and the anesthetic techniques of the user. However, with appropriate attention to these areas, trace gas levels within the operating room can meet OSHA requirements.[21]

The most important component of the scavenger system is the interface, because it protects the patient from excessive buildup of positive pressure, and from exposure to suction. There are two types of interfaces: closed and open. The closed interface is found on older machines, though it is available as an option on new models.[240,241] A closed interface is useful where passive scavenging is used (no dedicated suction line for the scavenger, and waste gases flow passively along with room ventilation exhaust). A closed interface communicates with the atmosphere only through valves (Figure 15-50). A means for relief of positive pressure is mandatory for all closed interfaces. If the suction attached to the scavenger fails or if a hose distal to it becomes kinked, positive pressure relief

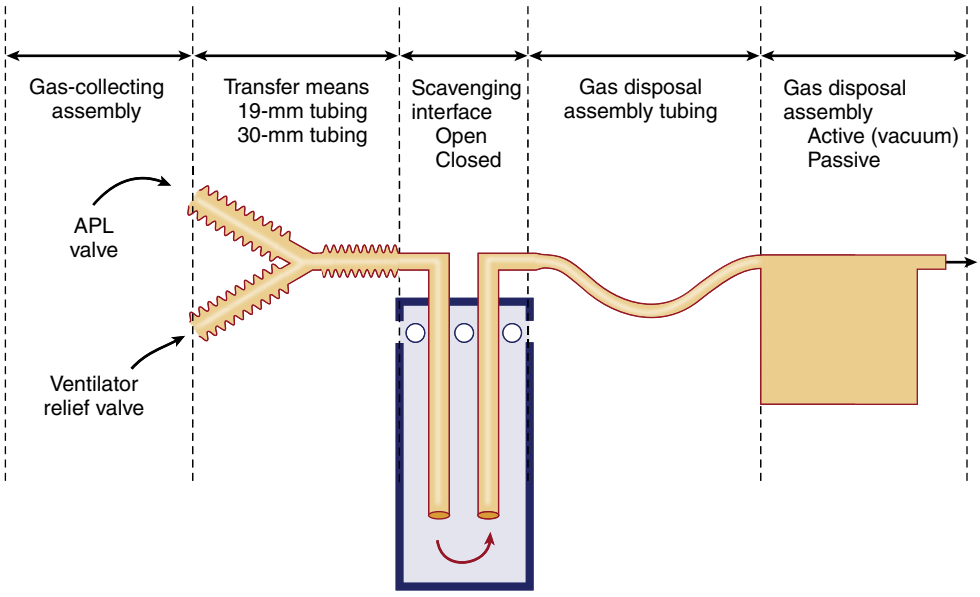

FIGURE **15-49** Components of the scavenging system. (Barash PG, ed: *Clinical Anesthesia*. 5th ed. Philadelphia: LWW; 2006:589.)

valves operate before the pressure buildup within the scavenger is transmitted to the breathing circuit and the lungs. In this case, the positive pressure relief valve opens and allows the release of waste gases into the operating-room air. If the closed interface is attached to suction, a negative pressure relief valve is also mandatory. The positive-pressure relief valve on the closed interface opens to draw in room air when suction is excessive, preventing the emptying of gas from the patient circuit. Suction should be adjusted as fresh gas flows change, so that the scavenger reservoir bag is neither flat nor overdistended.[241]

Because the closed-interface relief valves can fail,[242] an open scavenger interface is much more common on new machines (Figure 15-51). The open interface has large open holes or ports around the top. There are no valves, such as those found in closed-interface systems, to impede the flow of gases into, or out of, the reservoir. Each patient exhalation is led to the bottom of the open-interface reservoir, where a second tube withdraws it by suction before the next exhalation arrives. Use of the device with appropriate suction is critical to its proper function.[240] Yet because the device is so different from the closed interface, errors in its use have already been reported. In one report, 10 of 10 newly purchased machines equipped with open interfaces had the suction to the scavenger turned off, resulting in the release of all patient exhalations into the operating room.[242] This error in use may be related to the sounds produced by the two different interfaces. When a closed interface is leaking gas into the room through the positive pressure relief valve, one can hear a soft, intermittent hiss. The open interface, on the other hand, may hiss continuously when it has been properly adjusted.

The open interface affords patient safety advantages. With the open interface, there is no chance of relief valve failure, which can cause barotrauma or the application of suction to the breathing circuit. The device is perhaps less safe for the operator who is unfamiliar with its use; however, the only danger of this ignorance is increased occupational exposure to waste anesthetic gases. The smell of volatile agent during a case is abnormal, and its cause must be sought. The threshold for smelling volatile agents is variously stated as 5 to 300 ppm.[21,134,236] Thus if any agent is smelled, the concentration is excessive (i.e., above that described in the OSHA standard).

Many factors in addition to the scavenger affect exposure to waste anesthetic gases. Guidelines for limiting exposure are listed in Box 15-21.[21,236,237,243-245] Some may be applied generally, whereas others are applicable only to selected practice settings.

RISK MANAGEMENT

Department-Level Aspects

Risk management is defined as a detection system designed to predict failures and ensure that precautions to prevent patient harm are taken.[134] Typical anesthesia risk management components include preoperative and postoperative rounds, avoiding indifferent treatment of patients, maintaining vigilance and high standards of care, peer review, continuing education, and the commitment to delivery of high-quality and humane patient care. In terms of equipment, risk management includes cleanliness, daily performance of equipment checklists, familiarity with equipment manuals, and appropriate maintenance.[134,246]

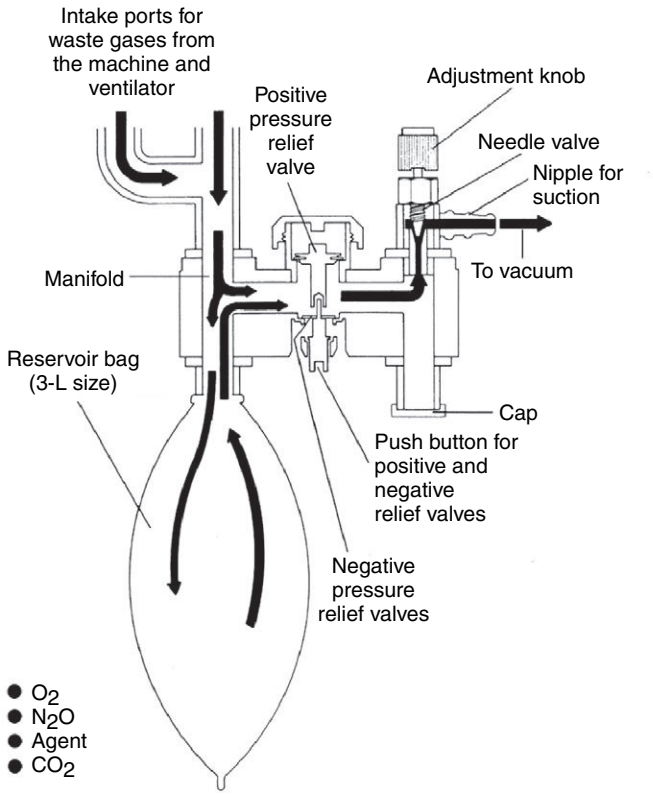

FIGURE **15-50** Closed scavenger interface attached to suction. Note the reservoir, the positive and negative pressure relief valves, and the capped extra port. (From Bowie E, Huffman LM. *The Anesthesia Machine: Essentials for Understanding*. Madison, Wis: Datex-Ohmeda; 1985.)

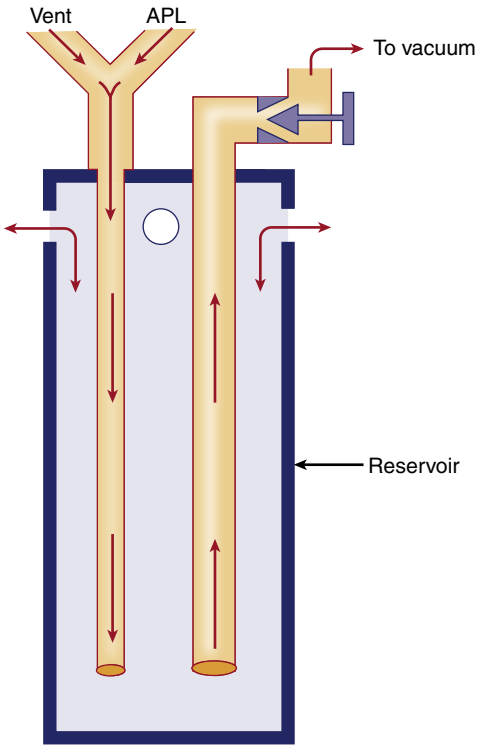

FIGURE **15-51** The open scavenger interface. (Modified from Dorsch JA, Dorsch SE, eds. *Understanding Anesthesia Equipment*. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 1999:355.)

BOX **15-21**

Means of Limiting Exposure to Waste Anesthetic Gases

- Check the scavenger before use.
- Perform regular preventive maintenance of room ventilation systems.
- Perform regular preventive maintenance of all anesthesia equipment.
- Conduct personnel monitoring and ambient trace gas monitoring.
- Seek the source of the smell of anesthetics noted during a case.
- Keep a good mask fit.
- Avoid unscavengeable techniques (open drop, insufflation).
- Prevent flow from breathing system into room air.
- Turn on anesthetic gases only after the mask is on the patient.
- Turn off anesthetic gases before suctioning.
- Wash out anesthetics into the scavenger at the end of the case.
- Do not spill liquid agent.
- Use cuffed endotracheal tubes.
- Use low fresh gas flows.
- Check the machine regularly for leaks.
- Disconnect nitrous oxide at wall outlet at end of day.
- Use total intravenous anesthesia.
- Avoid use of nitrous oxide.

The Safe Medical Device Act of 1990 requires hospitals to report instances in which medical devices cause or contribute to death, serious illness, or serious injury.[247] All medical personnel who become aware of a problem with a device must remove the equipment from contact with patients and report the problem to their supervisors. The hospital risk manager then conducts an investigation and reports the results to the FDA within 10 working days. The most common barrier to investigation of a critical incident, and the degree to which anesthesia equipment may have contributed to it, is alteration of the equipment (i.e., it has been cleaned, disassembled, or tested).[248] In the case of patient injury in which equipment may be at fault, it is most helpful if equipment (including wastebaskets and syringes in the anesthesia work area) is sequestered "as is," pending a forensic evaluation conducted by the representatives of the hospital, the manufacturer, and perhaps the patient. Equipment logs should be kept for each anesthesia machine and include reports of maintenance, critical incidents, additions or alterations, pollution control, and vaporizer calibration. Preventive maintenance should be done at intervals specified by the manufacturer (usually two to four times per year) by qualified, factory-trained technicians.[134]

Individual Risk Management

The department-level risk management plan requires the active involvement of all department members. In addition to participation in the department-level activities noted earlier, individuals play a vital role in three further aspects: performance of the machine checklist before use, limiting equipment-related disease transmission, and reducing trace and waste gas exposure through alteration of work practices (the latter two were discussed earlier in this chapter).

Anesthesia Gas Machine Checklist

Reports of equipment problems surfacing in the 1980s prompted the professional societies and government to develop a recommended anesthesia checklist.[249-251] Although equipment failures are rare, they are often the result of human error in the use of the equipment.[4,11,249] Failure to check anesthesia equipment adequately has been reported as a factor in up to 30% of critical incidents.[252,253] Users report that they often do not perform the FDA checklist, and many do not feel competent in their ability to perform it correctly.[3] When a checklist is performed, 30% of the gas machines in one study had serious faults discovered.[2] Checklists have been the focus of several studies of fault-detection ability* and much comment.[260] It is probable, but as yet unproved, that proper and consistent use of checklists will not only prevent critical incidents but also help teach and reinforce knowledge of the function and use of the anesthesia gas machine.[14] Performance of the pre-use anesthesia checkout is required by various standards.[261]

New developments in the pre-use anesthesia checkout are the publication of a new PreAnesthesia Checkout (PAC) in 2008 (see Boxes 15-22 and 15-23 at the end of the chapter).[99] It became necessary to abandon the 1990s FDA checklist because it no longer worked for different models. Considering the significant differences between models, and variations in their self-test routines, no one set of *procedures* will cover all gas machines. This new checklist is a statement of *principles* of what should be checked, and who should check it, rather than a procedures list. For example, the availability of backup ventilation equipment and backup oxygen supplies, and the calibration of the oxygen analyzer and other monitors must be checked, regardless of which machine is used. But *how* these actions are performed varies from machine to machine. If they have not done so already, anesthesia departments will need to develop specific procedures and training for the machines they use, in consultation with manufacturers and the operator's instruction manuals.

The Aestiva is a system that must be manually checked—there are no electronic aspects to the checklist.[46] At the other extreme, some gas machines checkout procedures rely almost exclusively on electronic checklists. These electronic self-check routines (like that in the ADU, Aisys, Fabius, and Apollo) may help prevent errors and omissions in the preanesthesia checklist.[262] Electronic checklists of this type are not all identical, but they do cover most essential functions, can detect leaks, and can measure breathing circuit compliance. The ADU and Fabius checklist warn if leaks greater than 150 mL/min are detected.[54] If leaks are detected, users must check the tightness of all connections—respiratory and patient circuit tubing and bellows (bellows, bellows block, ventilator relief valve, and bellows chamber). Ensure that the Y-piece is properly occluded, gas flows are closed, and the gas sampling lines in the D-Lite sensor are not still connected to the circuit. In the Apollo, these must be connected. The user performs a few manual tests at the end—suction, cylinder pressure, unidirectional valves, and gas analysis. All of these new machine checklists require that the circuit be occluded for compliance and leak testing, then reconfigured for use.

It is critical that the anesthetist can answer several questions in the affirmative at the end of a properly performed checkout. For example, is there oxygen in the oxygen line? Can the patient breathe unobstructed through the circuit? Can the patient be

*References 9, 10, 13, 14, 254-259.

BOX **15-22**

Summary of Preanesthesia Checkout Recommendations

To Be Completed Daily	TO BE REPEATED BEFORE EACH CASE
1. Verify that auxiliary oxygen cylinder and self-inflating manual ventilation device are available and functioning.	
2. Verify that patient suction is adequate to clear the airway.	*
3. Turn on anesthesia delivery system and confirm that AC power is available.	
4. Verify availability of required monitors, including alarms.	*
5. Verify that pressure is adequate on the spare oxygen cylinder mounted on the anesthesia machine.	
6. Verify that the piped gas pressures are 50 or greater psi.	
7. Verify that vaporizers are adequately filled, and if applicable, that the filler ports are tightly closed.	*
8. Verify that there are no leaks in the gas supply lines between the flowmeters and the common gas outlet.	
9. Test scavenging system function.	
10. Calibrate, or verify calibration of, the oxygen monitor and check the low oxygen alarm.	
11. Verify that carbon dioxide absorbent is not exhausted.	*
12. Conduct breathing system pressure and leak testing.	*
13. Verify that gas flows properly through the breathing circuit during both inspiration and exhalation.	*
14. Document completion of checkout procedures.	*
15. Confirm ventilator settings and evaluate readiness to deliver anesthesia care. (ANESTHESIA TIME OUT)	*

From Sub-Committee of the American Society of Anesthesiologists (ASA) Committee on Equipment and Facilities: Recommendations for Pre-Anesthesia Checkout Procedures, 2008. Available at http://www.asahq.org/For-Members/Clinical-Information/2008-ASA-Recommendations-for-PreAnesthesia-Checkout.aspx.
psi, pounds per square inch.

given a positive pressure breath? Are there leaks in the breathing circuit once reassembled? Is backup ventilation equipment present in the room?

To ensure these basic requirements are met, a few activities must be part of the PAC, or be performed manually by the anesthetist after it is complete: (1) checking the oxygen analysis; (2) checking that the circuit is unobstructed and that the unidirectional valves are functioning properly; and (3) checking the reassembled breathing circuit for leaks with high pressure.[263] Check that the oxygen analyzer reads 21% when exposed to room air, and the reading increases when the sensor is exposed to gas from the oxygen pipeline. Test the unidirectional valves with an artificial lung (or by breathing through the circuit) to ensure that the circuit is not obstructed by mold flash or plastic wrapping.[150,151] To ensure that all breathing circuit connections are gas-tight, always perform a high-pressure check after the checklist is complete. While checking for backup ventilation equipment (e.g., Ambu bag) and cylinder oxygen, walk around the machine, checking for suction and an extra circuit, the location of circuit breakers, the presence of a cylinder wrench and head strap, and whether gas analysis monitors are scavenged. Because in some machines the vaporizers must be individually checked for leaks, it is possible that care of a patient could begin with the vaporizers inadvertently turned on. So the anesthetist must check that vaporizers are off during the checklist.

There is no "minimum" test other than that suggested by the operator's instruction manuals. In administering an anesthetic for an emergency surgical procedure, one should always check the suction, check for a backup means of ventilation (e.g., Ambu bag), and perform a high-pressure leak test of the breathing circuit. During preoxygenation, (whether in emergencies, or as a matter of routine in any case), observe the breathing bag for fluctuations. Respiratory effort that is visible in the breathing bag before induction begins ensures that the patient is breathing, the mask fit is good, and oxygen is flowing. A situation in which any of these conditions is absent requires immediate attention.

SUMMARY

Compared with its forebears, the anesthesia gas machine available today is a system of tremendous capability, power, safety, and complexity. The machine is a result both of improvements in design and of the integration of physiologic monitors and machine function monitors. Use of an anesthesia gas machine was more straightforward in the past because all types of anesthesia machines contained simpler, similar elements. With the introduction of new designs, this is no longer the case. The days when a few "wizards" in an anesthesia department could specialize in equipment operation and maintenance and could instruct or troubleshoot for all of his or her co-workers have likewise passed. Equipment competency must be a part of everyone's toolkit of patient-care skills. It is hoped that through study of this chapter, current equipment will be more widely understood. In this manner, our future patients may "sleep" in safety, afforded the level of care that we all wish for ourselves and our loved ones.

BOX **15-23**

Recommendations for Preanesthesia Checkout Procedures

General Considerations

The following document is intended to serve not as a preanesthesia checkout (PAC) itself, but rather as a template for developing checkout procedures that are appropriate for each individual anesthesia machine design and practice setting. When using this template to develop a checkout procedure for systems that incorporate automated checkout features, items that are not evaluated by the automated checkout need to be identified, and supplemental manual checkout procedures included as needed.

Simply because an automated checkout procedure exists does not mean it can completely replace a manual checkout procedure or that it can be performed safely without adequate training and a thorough understanding of what the automated checkout accomplishes. An automated checkout procedure can be incomplete and/or misleading. For example, the leak test performed by some current automated checkouts does not test for leaks at the vaporizers. As a result, a loose vaporizer filler cap, or a leak at the vaporizer mount, could easily be missed.

Ideally an automated checkout procedure should clearly reveal to the user the functions that are being checked, any deficient function that is found, and recommendations for correcting the problem. Documentation of the automated checkout process should preferably be done in a manner that can be recorded on the anesthesia record.

Operator's manuals, which accompany anesthesia delivery systems, include extensive recommendations for equipment checkout. Although these recommendations are quite extensive and typically not used by anesthesia providers, they are nevertheless important references for developing machine-specific and institution-specific checkout procedures.

Personnel Performing the PAC

The previously accepted *Anesthesia Apparatus Checkout Recommendation* placed all of the responsibility for pre-use checkout on the anesthesia provider. This guideline identifies those aspects of the PAC that could be completed by a qualified anesthesia and/or biomedical technician. Critical checkout steps (e.g., availability of backup ventilation equipment) will benefit from intentional redundancy (i.e., having more than one individual responsible for checking the equipment). *Regardless of the level of training and support by technicians, the anesthesia care provider is ultimately responsible for proper function of all equipment used to provide anesthesia care.*

Adaptation of the PAC to local needs, assignment of responsibility for the checkout procedures, and training are the responsibilities of the individual anesthesia department. Training procedures should be documented. Proper documentation should include records of completed coursework (e.g., a manufacturer course) or for in-house training, a listing of the competency items taught and records of successful completion by trainees.

Objectives for a New PAC

1. Outline the essential items that need to be available and functioning properly prior to delivering every anesthetic.
2. Identify the frequency with which each of the items needs to be checked.
3. Suggest which items may be checked by a qualified anesthesia technician, biomedical technician, or a manufacturer-certified service technician.

Basic Principles

The anesthesia care provider is ultimately responsible for ensuring that the anesthesia equipment is safe and ready for use. This responsibility includes adequate familiarity with the equipment, following relevant local policies for performing and documenting the PAC, and being knowledgeable about those procedures.

Depending upon the staffing resources in a particular institution, anesthesia technicians and/or biomedical technicians can participate in the PAC. Each department should decide whether or not the available technicians can or should be trained to assist with checkout procedures.

- Critical items will benefit from redundant checks to avoid errors and omissions.
- When more than one person is responsible for checking an item, all parties should perform the check if intentional redundancy is deemed important, or either party may be acceptable, depending upon the available resources.
- Whoever conducts the PAC should provide documentation of successful performance. The anesthesia provider should include this documentation on the patient chart.
- Whenever an anesthesia machine is moved to a new location, a complete beginning-of-the-day checkout should be performed.
- Automated checks should clearly distinguish the components of the delivery system that are checked automatically from those that require manual checkout.
- Ideally, the date, time, and outcome of the most recent check(s) should be recorded and the information made accessible to the user.
- Specific procedures for pre-use checkout cannot be prescribed in this document because they vary with the delivery systems. Clinicians must learn how to effectively perform the necessary pre-use check for each piece of equipment they use.
- Each department or health care facility should work with the manufacturer(s) of their equipment to develop pre-use checkout procedures that satisfy both the following guidelines and the needs of the local department.
- Default settings for ventilators, monitors, and alarms should be checked to determine whether they are appropriate.
- These checkout recommendations are intended to replace the pre-existing FDA-approved *Anesthesia Apparatus Checkout Recommendations.* They are not intended to be a replacement for required preventive maintenance.
- The PAC is essential to safe care but should not delay initiating care if the patient needs are so urgent that time taken to complete the PAC could worsen the patient's outcome.

Guidelines for Developing Institution-Specific Checkout Procedures Prior to Anesthesia Delivery

These guidelines describe a basic approach to checkout procedures and rationale that will ensure that these priorities are satisfied. They should be used to develop institution-specific checkout procedures designed for the equipment and resources available. (Examples of institution-specific procedures for current anesthesia delivery systems are published on the same website as this document.)

Requirements for Safe Delivery of Anesthesia Care

- Reliable delivery of oxygen at any appropriate concentration up to 100%
- Reliable means of positive pressure ventilation
- Backup ventilation equipment available and functioning
- Controlled release of positive pressure from the breathing circuit
- Anesthesia vapor delivery (if intended as part of the anesthetic plan)
- Adequate suction
- Means to conform to standards for patient monitoring

BOX **15-23**

Recommendations for Preanesthesia Checkout Procedures—cont'd

Specific Items

The following fifteen items need to be checked as part of a complete PAC. The intent is to identify what to check, the recommended frequency of checking and the individual(s) who could be responsible for the item. For these guidelines, the responsible party would fall into one of four categories: Provider, Technician, Technician or Provider, or Technician and Provider. The designation "Technician and Provider" means that the provider must perform the check whether or not it has been completed by a technician. It is not intended to make the use of technician checks mandatory. The intent is not to specify how an item needs to be checked, because the specific checkout procedure will depend upon the equipment being used.

1. Verify auxiliary oxygen cylinder and self-inflating manual ventilation device are available and functioning.
   Frequency: Daily.
   Responsible Parties: Provider and Technician.
   Rationale: Failure to be able to ventilate is a major cause of morbidity and mortality related to anesthesia care. Because equipment failure with resulting inability to ventilate the patient can occur at any time, a self-inflating manual ventilation device (e.g., AMBU bag) should be present at every anesthetizing location for every case and should be checked for proper function. In addition, a source of oxygen separate from the anesthesia machine and pipeline supply, specifically an oxygen cylinder with regulator and a means to open the cylinder valve, should be immediately available and checked. After checking the cylinder pressure, it is recommended that the main cylinder valve be closed to avoid inadvertent emptying of the cylinder through a leaky or open regulator.
2. Verify that patient suction is adequate to clear the airway.
   Frequency: Prior to each use.
   Responsible Parties: Provider and Technician.
   Rationale: Safe anesthetic care requires the immediate availability of suction to clear the airway if needed.
3. Turn on anesthesia delivery system and confirm that AC power is available.
   Frequency: Daily.
   Responsible Parties: Provider or Technician.
   Rationale: Anesthesia delivery systems typically function with backup battery power if AC power fails. Unless the presence of AC power is confirmed, the first obvious sign of power failure can be a complete system shutdown when the batteries can no longer power the system. Many anesthesia delivery systems have visual indicators of the power source showing the presence of both AC and battery power. These indicators should be checked, and connection of the power cord to a functional AC power source should be confirmed.
   Desflurane vaporizers require electrical power and recommendations for checking power to these vaporizers should also be followed.
4. Verify availability of required monitors, including alarms.
   Frequency: Prior to each use.
   Responsible Parties: Provider or Technician.
   Rationale: Standards for patient monitoring during anesthesia are clearly defined. The ability to conform to these standards should be confirmed for every anesthetic. The first step is to visually verify that the appropriate monitoring supplies (BP cuffs, oximetry probes, etc.) are available. All monitors should be turned on and proper completion of power-up self-tests confirmed. Given the importance of pulse oximetry and capnography to patient safety, verifying proper function of these devices before anesthetizing the patient is essential. Capnometer function can be verified by exhaling through the breathing circuit or gas sensor to generate a capnogram, or verifying that the patient's breathing efforts generate a capnogram before the patient is anesthetized. Visual and audible alarm signals should be generated when this is discontinued. Pulse oximeter function, including an audible alarm, can be verified by placing the sensor on a finger and observing for a proper recording. The pulse oximeter alarm can be tested by introducing motion artifact or removing the sensor.
   Audible alarms have also been reconfirmed as essential to patient safety by ASA, AANA, APSF, and The Joint Commission. Proper monitor functioning includes visual and audible alarm signals that function as designed.
5. Verify that pressure is adequate on the spare oxygen cylinder mounted on the anesthesia machine.
   Frequency: Daily.
   Responsible Parties: Provider and Technician.
   Rationale: Anesthesia delivery systems rely on a supply of oxygen for various machine functions. At a minimum, the oxygen supply is used to provide oxygen to the patient. Pneumatically powered ventilators also rely on a gas supply. Oxygen cylinder(s) should be mounted on the anesthesia delivery system and determined to have an acceptable minimum pressure. The acceptable pressure depends on the intended use, the design of the anesthesia delivery system, and the availability of piped oxygen.
   Typically, an oxygen cylinder will be used if the central oxygen supply fails.
   If the cylinder is intended to be the primary source of oxygen (e.g., remote site anesthesia), then a cylinder supply sufficient to last for the entire anesthetic is required. If a pneumatically powered ventilator that uses oxygen as its driving gas will be used, a full "E" oxygen cylinder may provide only 30 minutes of oxygen. In that case, the maximum duration of oxygen supply can be obtained from an oxygen cylinder if it is used only to provide fresh gas to the patient in conjunction with manual or spontaneous ventilation. Mechanical ventilators will consume the oxygen supply if pneumatically powered ventilators that require oxygen to power the ventilator are used. Electrically powered ventilators do not consume oxygen, so the duration of a cylinder supply will depend only on total fresh gas flow. The oxygen cylinder valve should be closed after it has been verified that adequate pressure is present, unless the cylinder is to be the primary source of oxygen (i.e., piped oxygen is not available). If the valve remains open and the pipeline supply should fail, the oxygen cylinder can become depleted while the anesthesia provider is unaware of the oxygen supply problem.
   Other gas supply cylinders (e.g., Heliox, CO_2, Air, N_2O) need to be checked only if that gas is required to provide anesthetic care.
6. Verify that piped gas pressures are 50 or greater psi/g.
   Frequency: Daily.
   Responsible Parties: Provider and Technician.
   Rationale: A minimum gas supply pressure is required for proper function of the anesthesia delivery system. Gas supplied from a central source can fail for a variety of reasons. Therefore the pressure in the piped gas supply should be checked at least once daily.
7. Verify that vaporizers are adequately filled, and if applicable, that the filler ports are tightly closed.
   Frequency: Prior to each use.
   Responsible Parties: Provider. Technician if redundancy desired.

Continued

BOX **15-23**

Recommendations for Preanesthesia Checkout Procedures—cont'd

Rationale: If anesthetic vapor delivery is planned, an adequate supply is essential to reduce the risk of light anesthesia or recall. This is especially true if an anesthetic agent monitor with a low agent alarm is not being used. Partially open filler ports are a common cause of leaks that may not be detected if the vaporizer control dial is not open when a leak test is performed. This leak source can be minimized by tightly closing filler ports. Newer vaporizer designs have filling systems that automatically close the filler port when filling is completed.

High and low anesthetic agent alarms are useful to help prevent over- or under-dosage of anesthetic vapor. Use of these alarms is encouraged, and they should be set to the appropriate limits and enabled.

8. Verify that there are no leaks in the gas supply lines between the flowmeters and the common gas outlet.
   Frequency: Daily and whenever a vaporizer is changed.
   Responsible Parties: Provider or Technician.
   Rationale: The gas supply in this part of the anesthesia delivery system passes through the anesthetic vaporizer(s) on most anesthesia delivery systems. In order to perform a thorough leak test, each vaporizer must be turned on individually to check for leaks at the vaporizer mount(s) or inside the vaporizer. Furthermore, some machines have a check valve between the flowmeters and the common gas outlet, requiring a negative pressure test to adequately check for leaks. Automated checkout procedures typically include a leak test but may not evaluate leaks at the vaporizer especially if the vaporizer is not turned on during the leak test. When relying upon automated testing to evaluate the system for leaks, the automated leak test would need to be repeated for each vaporizer in place. This test should also be completed whenever a vaporizer is changed. The risk of a leak at the vaporizer depends upon the vaporizer design. Vaporizer designs where the filler port closes automatically after filling can reduce the risk of leaks. Technicians can provide useful assistance with this aspect of the machine checkout because it can be time consuming.
9. Test scavenging system function.
   Frequency: Daily.
   Responsible Parties: Provider or Technician.
   Rationale: A properly functioning scavenging system prevents room contamination by anesthetic gases. Proper function depends upon correct connections between the scavenging system and the anesthesia delivery system. These connections should be checked daily by a provider or technician. Depending upon the scavenging system design, proper function may also require that the vacuum level is adequate, which should also be confirmed daily. Some scavenging systems have mechanical positive and negative pressure relief valves. Positive and negative pressure relief is important to protect the patient circuit from pressure fluctuations related to the scavenging system. Proper checkout of the scavenging system should ensure that positive and negative pressure relief is functioning properly. Due to the complexity of checking for effective positive and negative pressure relief, and the variations in scavenging system design, a properly trained technician can facilitate this aspect of the checkout process.
10. Calibrate, or verify calibration of, the oxygen monitor and check the low oxygen alarm.
    Frequency: Daily.
    Responsible Parties: Provider or Technician.
    Rationale: Continuous monitoring of the inspired oxygen concentration is the last line of defense against delivering hypoxic gas concentrations to the patient. The oxygen monitor is essential for detecting adulteration of the oxygen supply. Most oxygen monitors require calibration once daily, although some are self-calibrating. For self-calibrating oxygen monitors, they should be verified to read 21% when sampling room air. This is a step that is easily completed by a trained technician. When more than one oxygen monitor is present, the primary sensor that will be relied upon for oxygen monitoring should be checked.

    The low oxygen concentration alarm should also be checked at this time by setting the alarm above the measured oxygen concentration and confirming that an audible alarm signal is generated.
11. Verify that carbon dioxide absorbent is not exhausted.
    Frequency: Prior to each use.
    Responsible Parties: Provider or Technician.
    Rationale: Proper function of a circle anesthesia system relies on the absorbent to remove carbon dioxide from rebreathed gas. Exhausted absorbent as indicated by the characteristic color change should be replaced. It is possible for absorbent material to lose the ability to absorb CO_2, yet the characteristic color change may be absent or difficult to see. Some newer absorbents do change color when desiccated. Capnography should be used for every anesthetic, and when using a circle anesthesia system, rebreathing carbon dioxide as indicated by an inspired CO_2 concentration greater than 0 can also indicate exhausted absorbent.
12. Conduct breathing system pressure and leak testing.
    Frequency: Prior to each use.
    Responsible Parties: Provider and Technician.
    Rationale: The breathing system pressure and leak test should be performed with the circuit configuration to be used during anesthetic delivery. If any components of the circuit are changed after this test is completed, the test should be performed again. Although the anesthesia provider should perform this test before each use, anesthesia technicians who replace and assemble circuits can also perform this check and add redundancy to this important checkout procedure. Proper testing will demonstrate that pressure can be developed in the breathing system during both manual and mechanical ventilation and that pressure can be relieved during manual ventilation by opening the adjustable pressure-limiting (APL) valve.

    Automated testing is often implemented in the newer anesthesia delivery systems to evaluate the system for leaks and also to determine the compliance of the breathing system. The compliance value determined during this testing will be used to automatically adjust the volume delivered by the ventilator to maintain a constant volume delivery to the patient. It is important that the circuit configuration that is to be used be in place during the test.
13. Verify that gas flows properly through the breathing circuit during both inspiration and exhalation.
    Frequency: Prior to each use.
    Responsible Parties: Provider and Technician.
    Rationale: Pressure and leak testing does not identify all obstructions in the breathing circuit or confirm proper function of the inspiratory and expiratory unidirectional valves. A test lung or second reservoir bag can be used to confirm that flow through the circuit is unimpeded. Complete testing includes both manual and mechanical ventilation. The presence of the unidirectional valves can be assessed visually during the PAC. Proper function of these valves cannot be visually assessed because subtle valve incompetence may not be detected. Checkout procedures to identify valve incompetence that may not be visually obvious can be implemented but are typically

BOX **15-23**

Recommendations for Preanesthesia Checkout Procedures—cont'd

too complex for daily testing. A trained technician can perform regular valve competence tests. Capnography should be used during every anesthetic and the presence of carbon dioxide in the inspired gases can help to detect an incompetent valve.

14. Document completion of checkout procedures.
Frequency: Prior to each use.
Responsible Parties: Provider and Technician.
Rationale: Each individual responsible for checkout procedures should document completion of these procedures. Documentation gives credit for completing the job and can be helpful if an adverse event should occur. Some automated checkout systems maintain an audit trail of completed checkout procedures that are dated and timed.
15. Confirm ventilator settings and evaluate readiness to deliver anesthesia care. (ANESTHESIA TIME OUT)
Frequency: Immediately prior to initiating the anesthetic.
Responsible Parties: Provider.
Rationale: This step is intended to avoid errors due to production pressure or other sources of haste. The goal is to confirm that appropriate checks have been completed and that essential equipment is indeed available. The concept is analogous to the "time out" used to confirm patient identity and surgical site prior to incision. Improper ventilator settings can be harmful, especially if a small patient is following a much larger patient or vice versa. Pressure limit settings (when available) should be used to prevent excessive volume delivery from improper ventilator settings.

Items to check:
- Monitors functional?
- Capnogram present?
- Oxygen saturation by pulse oximetry measured?
- Flowmeter and ventilator settings proper?
- Manual/ventilator switch set to manual?
- Vaporizer(s) adequately filled?

From Sub-Committee of the American Society of Anesthesiologists (ASA) Committee on Equipment and Facilities: Recommendations for Pre-Anesthesia Checkout Procedures, 2008. Available at http://www.asahq.org/For-Members/Clinical-Information/2008-ASA-Recommendations-for-PreAnesthesia-Checkout.aspx.

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CHAPTER 16

Clinical Monitoring I

Cardiovascular System

◆ *Mark A. Kossick*

Monitoring of anatomic and physiologic variables during an anesthetic procedure is vital to patient safety and meeting established standards of care.[1] Many different monitors are commonly used to assist in the delivery of an anesthetic, and clinicians assimilate the data provided to make appropriate clinical judgments. Consequently, the application of critical thinking skills, thorough physical assessment, vigilance, and the appropriate selection and application of monitors are key requirements in the process of anesthesia monitoring.

Fundamental monitoring/assessment techniques include inspection, auscultation, and palpation. They provide essential objective and subjective data not available from advanced monitoring modalities and can alert the anesthetist to occult problems in select patients. *Inspection* of the patient can provide information regarding the adequacy of oxygen delivery and carbon dioxide elimination, fluid requirements, and positioning and alignment of body structures. *Auscultation* is used to verify correct placement of airway devices such as the endotracheal tube and laryngeal mask airway, to assess arterial blood pressure, and to continually monitor heart sounds and air exchange through the pulmonary system. *Palpation* can aid in assessing the quality of the pulse and degree of skeletal muscle relaxation, as well as locating major vascular structures when placing central venous lines or performing regional anesthesia techniques.

Critical thinking skills are cardinal prerequisites for successful monitoring of a patient's anesthetic. In addition, it is well known that errors in anesthesia care are minimized when clinicians remain alert and vigilant. This chapter reviews the more commonly used noninvasive and invasive cardiovascular monitors in anesthesia practice.

ECG MONITORING

The continuous monitoring of the cardiovascular status via the electrocardiogram (ECG) is a requirement for any patient receiving an anesthetic. This includes assessment of heart rate, rhythm, and in particular for some patients, ST segments. Computerized real-time ST-segment analysis continues to be incorporated in operating rooms (ORs), intensive care units (ICUs), and postanesthesia care units (PACUs) across the country. Many factors support this trend, including the development of practice guidelines by professional societies that advocate such monitoring techniques in select patient populations[2] and the demographics of the general surgical population. Approximately one third of patients scheduled for noncardiac surgery have risk factors for coronary artery disease (CAD), and postoperative myocardial infarction is three times as frequent in patients with ischemia.[3] Research has shown prolonged stress-induced ischemia (i.e., ST-segment depression) to be the major cause for cardiac morbidity (myocardial infarction) after major vascular surgery.[4] The overall incidence of perioperative ischemia in patients with CAD scheduled for cardiac or noncardiac surgery ranges from 20% to 80%.[5,6]

Because of its low cost, noninvasiveness, widespread availability, and designation as a standard of care for monitoring of all anesthetized patients,[1] the ECG remains a common and required diagnostic tool in the operating room. Compared with Holter monitors, ST-segment trending monitors have on average a sensitivity of 74% and specificity of 73% in detecting myocardial ischemia.[7] When used in high-risk cardiac patients to guide early treatment, they may reduce morbidity.[4]

Current recommendations for ST-segment deviation thresholds account for the *influence* of gender, ECG lead, age, and race on position of the ST segment.[8-11] In particular, two chest leads (V_2 and V_3) have been shown to exhibit the greatest shift of the ST junction and as such must be accounted for in applying diagnostic criteria for myocardial injury. Otherwise the proportion of false positives would increase.

The degree of elevation (or depression) is relative to an isoelectric line, which is commonly referenced as the PR segment. The PR segment extends from the end of the P wave to the start of ventricular depolarization (e.g., appearance of a Q wave) (Figure 16-1). The ST junction is defined as the point at which the QRS complex ends and the ST segment begins. It is also synonymous with the J point. In the clinical setting some biomedical engineers have eliminated the J point in their computerized ST-segment analysis software algorithms (Figure 16-2). Recommended threshold values for ST-segment changes are listed in Table 16-1.[8] When these threshold values are met, an imbalance between oxygen supply and demand *may* exist (e.g., myocardial injury).

It should be appreciated when critiquing the literature that researchers may use the J point in combination with the ST point as a means to determine the degree of ST-segment deviation. Examples would include assessing the extent of ST-segment shift by measuring 60 ms (1.5 mm) or 80 ms (2 mm) from the J point. Figure 16-2 contrasts these two means of calculating ST-segment deviation. Measuring the degree of ST-segment depression or elevation at the J point is the author's preferred method to most accurately assess ST-segment deviation values.

For anesthesia providers who use ST-segment analysis software that incorporates a J point in combination with an ST point, caution should be exercised in blindly accepting numeric ST-segment deviation values. Shortened ST segments are predictably associated with tachyarrhythmias, which can result in T waves encroaching on ST segments. Should this occur, the use of a J + 80-ms or even J + 60-ms distance could lead to an ST point intersecting a T wave instead of the ST segment. In this circumstance, the computer-derived ST-segment deviation value would reflect a *false* significant shift in the ST segment, suggesting myocardial injury (false positive) or masking a significant ST-segment depression (false negative) (Figure 16-3).

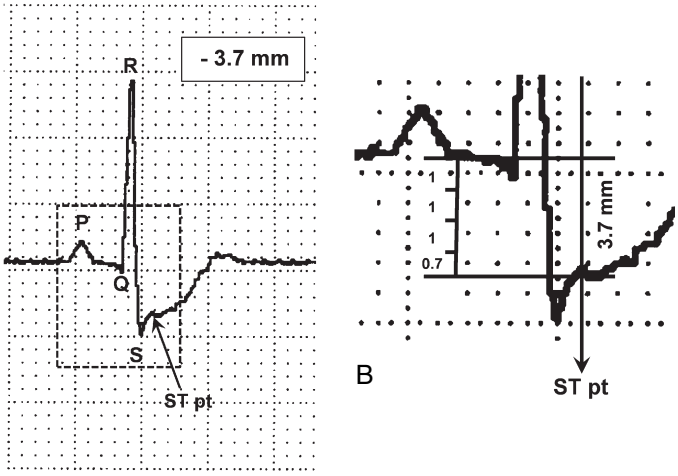

FIGURE **16-1** A single cardiac cycle (ST snippet) and enlarged section of the snippet providing greater details. The PR segment is measured from the end of the *P* wave to the beginning of the QRS complex. **A,** Depicts a depressed ST-segment that is upsloping. The junction between the *S* wave and ST segment defines the ST *point*. **B,** The PR segment is extended out via a horizontal line. This serves as an isoelectric reference (no deviation of the ECG stylus upward or downward) to determine the degree of ST-segment shift. The distance from the extended PR segment to the ST point demonstrates that the ST segment is 3.7 mm depressed (i.e., J point depression of 3.7 mm). (Reprinted with permission from Kossick MA. *EKG Interpretation: Simple, Thorough, Practical.* 3rd ed. Park Ridge, Ill: AANA Publishing. In press.)

TABLE 16-1 Threshold Values for ST-Segment Deviation

Gender and Age	ECG Leads	J-point elevation
Males > 40 years of age	I, II, III, aVR, aVL, aVF	1 mm (0.1 mV)
	V_1, V_4, V_5, V_6	
	V_2, V_3	2 mm (0.2 mV)
Males < 40 years of age	V_2, V_3	2.5 mm (0.25 mV)
Females	I, II, III, aVR, aVL, aVF	> 1 mm (0.1 mV)
	V_1, V_4, V_5, V_6	
	V_2, V_3	1.5 mm (0.15 mV)
Males and females	V_3R, V_4R*	0.5 mm (0.05 mV)
Males < 30 years of age	V_3R, V_4R*	1 mm (0.1 mV)
Males and females	V_7, V_8, V_9†	0.5 mm (0.05 mV)
Males and females of all ages	V_2, V_3	– 0.5 mm (– 0.05 mV)
	All other leads	– 1 mm (– 0.1 mV)

From Galen SW, et al. AHA/ACCF/HRS Expert Consensus Document: AHA/ACCF/HRS Recommendations for the standardization and interpretation of the electrocardiogram. Part VI: Acute ischemia/infarction: A Scientific Statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society. Endorsed by the International Society for Computerized Electrocardiology. *J Am Coll Cardiol.* 2009;53:1003-1011.
mV, Millivolt; *, right ventricular ECG leads; †, posterior chest leads.

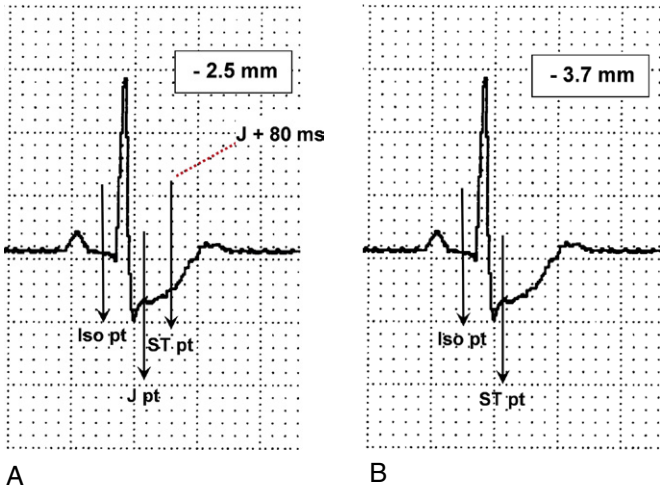

FIGURE **16-2** Two ST snippets illustrating two different techniques to calculate ST-segment depression values. ST snippet (**A**) measures ST-segment deviation 80 ms (2 mm) from the J point. ST snippet (**B**) measures ST-segment depression at the J point. The most recent American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society recommendations for standardizing and interpreting the electrocardiogram advocate measuring ST-segment changes at the J point (i.e., **B**). (Reprinted with permission from Kossick MA. *EKG Interpretation: Simple, Thorough, Practical.* 3rd ed. Park Ridge, Ill: AANA Publishing. In press.)

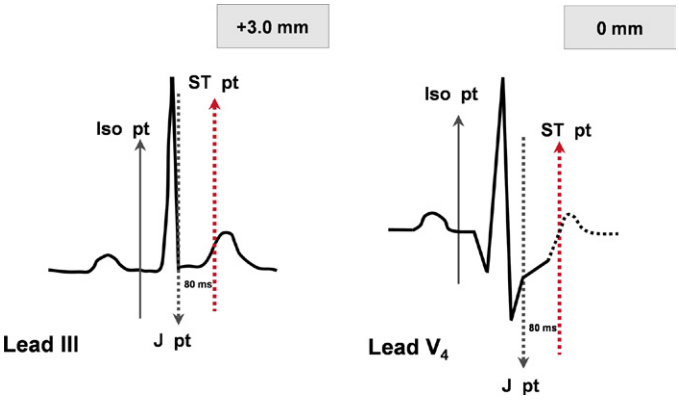

FIGURE **16-3** Two cardiac cycles from lead III and V_4 illustrating a shortened ST segment. Use of a J + 80 ms value to measure ST-segment deviation in each lead results in the ST point intersecting the T wave, thus producing inaccurate ST-segment deviation values. For lead III the misplaced ST point produces a false positive and for lead V_4 a false negative. (Reprinted with permission from Kossick MA. *EKG Interpretation: Simple, Thorough, Practical.* 3rd ed. Park Ridge, Ill: AANA Publishing. In press.)

Regarding the significance of the various forms of ST-segment depression, it is important to recall that a horizontal or downsloping depressed ST segment has greater specificity (fewer false positives) than an upsloping depressed ST segment. Adding upsloping ST-segment changes to myocardial injury diagnostic criteria does improve overall sensitivity but at a sacrifice to specificity and positive predictive value.[12,13]

Setting the ST-Segment Parameters

Most manufacturers of computerized ST-segment analysis monitors have sophisticated algorithms that allow fairly consistent and accurate placement of ST measurement points. Nevertheless, these parameters should be periodically assessed these parameters and changed as needed; responding to false trends secondary to incorrectly placed ST measurement points could lead to iatrogenic injury. In fact, manufacturers have incorporated software that permits

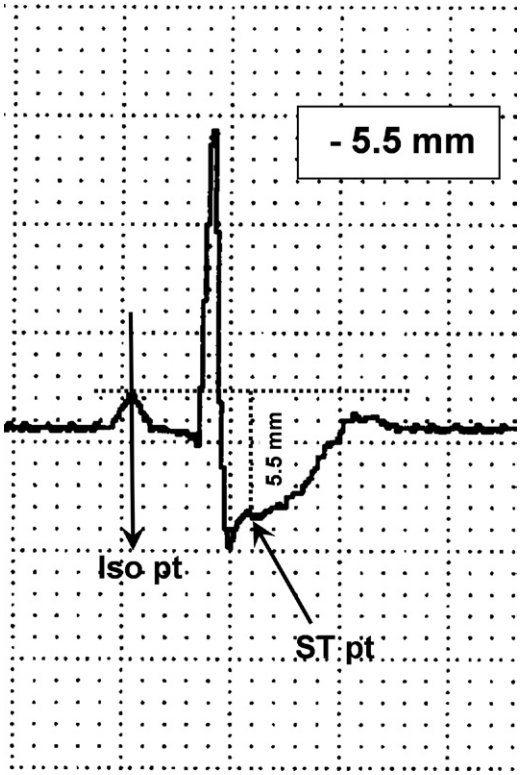

FIGURE **16-4** Iso point incorrectly placed on top of the P wave by an electrocardiogram (ECG) monitor, producing an exaggerated ST-segment deviation value. (Reprinted with permission from Kossick MA. *EKG Interpretation: Simple, Thorough, Practical*. 3rd ed. Park Ridge, Ill: AANA Publishing. In press.)

healthcare providers to override the monitor's placement of ST measurement points. A common technique for setting ST measurement points involves adjustment of two (Iso point and ST point) or three (Iso point, J point, and ST point) variables. Manipulation of a keypad or touchscreen device on the ECG monitor permits the operator to scroll each of these "points" along a horizontal axis. The "points" are depicted as vertical lines that intersect various components of a single cardiac cycle (Figure 16-2). Figure 16-4 illustrates the consequences when real-time ST-segment analysis software incorrectly places the Iso point on the apex of the P wave. The application of an ST-segment deviation algorithm can reduce the occurrence of such mishaps and improve overall management of patients at risk for ischemic changes (Figure 16-5).

Other significant variables to account for when monitoring patients at risk for ischemic events include ECG electrode placement, ECG lead selection, gain setting, and frequency bandwidth. Each of these is briefly reviewed here.

Electrocardiograph Electrode Placement

It is fairly common to see ECG electrodes placed incorrectly on a patient in an attempt to "move an operating room schedule along." Many times with a physical status (PS) I or II patient, accurate ECG electrode placement is not a critical issue. However, in patients with risk factors for CAD, such inattentiveness can lead to iatrogenic injury by producing deviated ST segments, inverted T waves, or pathologic Q waves that can be viewed as "real" problems. Proper placement of the limb lead and chest lead electrodes is described in Table 16-2. For emphasis, the precordial leads should be placed via palpation of the costae, not by gross visual estimation of an intercostal space (Figure 16-6). Understandably, some surgical procedures do not permit the use of optimal ECG lead selection and placement; ECG electrode(s) can interfere with skin preparation and surgical incision. Under these circumstances, a less than optimal ECG lead placement is acceptable and rationale should be documented.

Electrocardiographic Lead Selection

The decision regarding which ECG leads to monitor during the course of an anesthetic can be extremely important relative to the medical history of the patient. Improper selection can result in unrecognized myocardial ischemia, injury, or infarction. Research has validated that use of a single ECG lead for ischemic monitoring in patients with documented CAD is inadequate; monitoring with multiple leads enhances patient safety. In patients at risk for ischemic events, this author recommends the maximum number of ECG leads be displayed (e.g., 3, 7, 12 [derived 12-lead]) during the perioperative period to enhance continuous and comprehensive assessment of ST-segment and T-wave changes (Figures 16-7 and 16-8). Which lead(s) is/are best in detecting significant ST-segment changes remains somewhat controversial. First and foremost, if a preoperative 12-lead ECG has been done, "fingerprinting" of this tracing should serve as the primary guide for lead selection during the perioperative period. If the baseline 12-lead shows significant primary ST-segment changes in limb leads III and aVF, then this lead set should be prioritized for continuous display in the operating room. The ECG monitoring system software will dictate what lead display options can be configured. For example, with Philips software and a five-cable ECG lead system, a derived 12-lead (EASI) can be continuously displayed (see Figure 16-8). With other manufacturers and a five-cable ECG lead system, a true V lead (e.g., V_3), a modified chest lead V_5 (e.g., central subclavicular 5 [CS_5]), and a bipolar limb lead (e.g., lead II) can be configured for ECG monitoring (Figure 16-9).

In patients without a preoperative 12-lead or those who have a baseline 12-lead that is unremarkable, the literature suggests leads V_3, V_4, V_5, limb lead III, and aVF (in this order of preference) be selected for continuous monitoring for ST-segment elevation or depression.[14-18] Lead II is recommended for assessment of narrow QRS complex rhythms, particularly if the P wave is significant for diagnostic criteria (e.g., atrial flutter, atrial fibrillation, junctional rhythms).

The 1988 recommendation for V_5 and limb lead II as preferred ECG leads[19] in patients where ST-segment monitoring is desired has been mitigated by other researchers, critical care task forces, and major publications.[2,15,17,20,21] In 2002 Landesberg and colleagues studied 185 consecutive patients undergoing vascular surgery who were monitored by continuous 12-lead ST-trend analysis during the perioperative period and up to 72 hours postoperatively. Chest lead V_3 was found to detect ischemia earliest and most frequently (86.8%). Lead V_4 was the second most diagnostic lead (78.9%), and V_5 was third (65.8%). With those patients sustaining a myocardial infarction, V_4 was the most sensitive lead (83.3%), with V_3 and V_5 being the second most sensitive (75%).[17] In this study, myocardial infarction was diagnosed if cardiac troponin I levels were greater than 3.1 ng/mL and were accompanied by symptoms of ischemia or the presence of ECG criteria (i.e., ST-segment elevation, ST-segment depression, or large Q waves). Of interest was the observation that 97% of ischemic events were expressed as ST-segment depression—not elevation—and ST shifts were considered significant if their duration of change exceeded 10 minutes. As reported elsewhere in the literature, monitoring in multiple leads was advocated as a means to improve sensitivity for detecting ST-segment changes.[4,17-19]

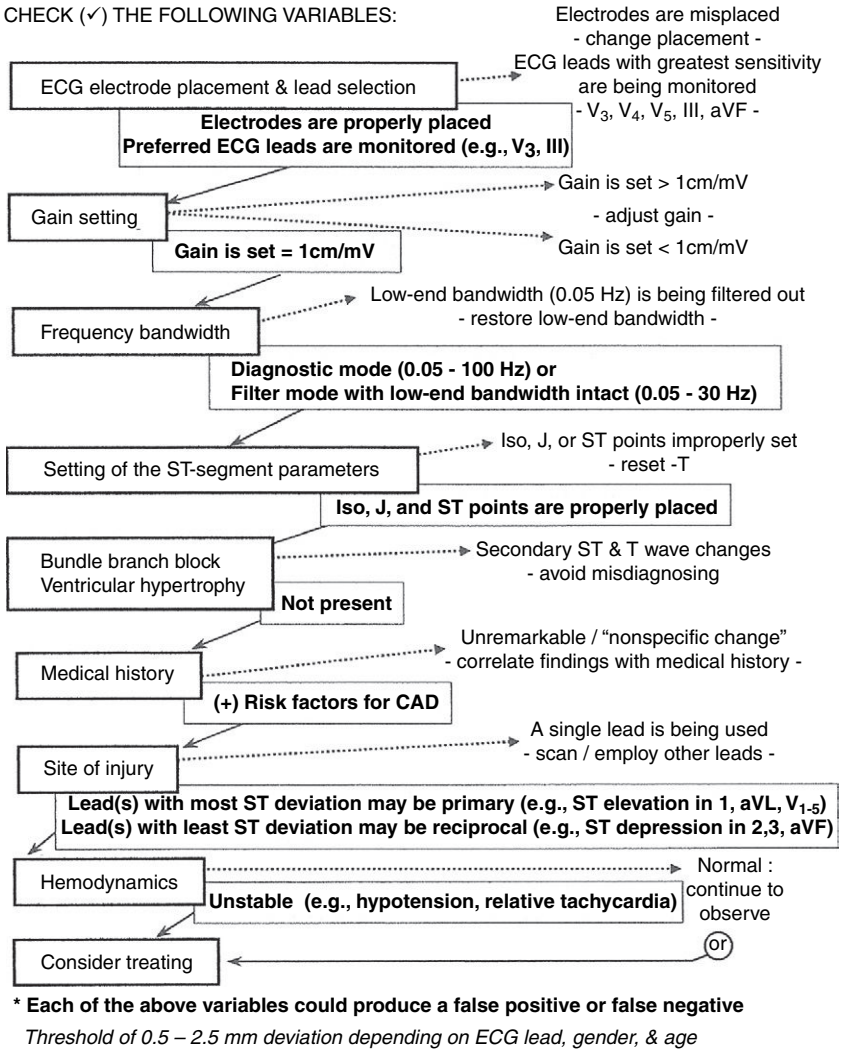

FIGURE **16-5** An ST-segment deviation assessment and treatment algorithm. (Reprinted with permission from Kossick MA. *EKG Interpretation: Simple, Thorough, Practical.* 3rd ed. Park Ridge, Ill: AANA Publishing. In press.)

Given this information, it is prudent for anesthesia providers to monitor and assess multiple ECG leads in the operating room. In the absence of an ST-segment fingerprint, this author advocates the following ECG lead combinations (for ST-segment elevation or depression) in patients with documented or identified significant risk factors for ischemic heart disease:

1. For a five-cable ECG recording system, the three-lead set of V_3, MCL_5, and aVF (the use of MCL_5 precludes the use of limb lead III) or V_3 combined with limb lead III and aVF.
2. For a three-cable ECG recording system, a two-lead set comprising MCL_5 combined with limb lead aVF.

Extended monitoring capabilities help to optimize detection of regionalized myocardial ischemia. Many times this entails nothing more than changing the lead selector switch to another ECG lead (e.g., III changed to aVF) or displaying a multilead ECG when indicated or continuously during an anesthetic (Figure 16-10). The latter produces an ECG recording of all six limb leads and a single chest lead, permitting the anesthetist to more comprehensively assess ECG data, including arrhythmias, the mean QRS axis (limb leads I and aVF), T-wave morphology, ST-segment changes, QT intervals, and the presence of right bundle branch block.

With the introduction into clinical practice of the derived 12-lead system (EASI), nurses and physicians now have a convenient method with which to globally assess the overall well-being of the myocardium (see Figure 16-8). The 12-lead is derived from modified vectorcardiographic leads and requires the use of a five-cable ECG lead system.[22] To monitor with this system, the five ECG electrodes are placed in the following locations: LA electrode over the manubrium; chest (V) electrode over the lower body of the sternum; LL electrode, left midaxillary, horizontal to the chest electrode; RA electrode, right midaxillary, also horizontal to the chest electrode; and RL electrode in any convenient location. Current and past research suggests the derived 12-lead is comparable (but not equivalent) to the standard 12-lead for multiple cardiac diagnosis in adults and children (e.g., ST-segment changes, myocardial infarction, wide QRS-complex tachycardia, QT-interval measurements).[23-25] It is possible that patients at substantial risk for CAD would benefit from global ischemic monitoring via a derived 12-lead. This software option also eliminates any need to consider "preferred" ECG leads because all six limb leads and six chest leads can be viewed during an anesthetic.

TABLE 16-2 Proper Placement of Electrocardiographic Electrodes for Monitoring Chest Leads and Limb Leads via the Mason-Likar Lead Position

Lead Name	Placement
RA	Over the outer right clavicle*
LA	Over the outer left clavicle*
LL	Near the left iliac crest or midway between the costal margin and left iliac crest, anterior axillary line*
RL	At any convenient location on the body (e.g., upper right shoulder)
V_1	Fourth intercostal space right of the sternal border
V_2	Fourth intercostal space left of the sternal border
V_3	Equal distance between V_2 and V_4
V_4	Midclavicular line at the fifth intercostal space
V_5	Horizontal to V_4 on the anterior axillary line or if difficult to identify (anterior axillary line), then midway between V_4 and V_6
V_6	Horizontal to V_5 on the midaxillary line
V_7	Horizontal to V_6 on the posterior axillary line
V_8	Horizontal to V_7 below the left scapula
V_9	Horizontal to V_8 at the left paravertebral border
V_3R	Placed right side of chest wall in mirror image to chest lead V_3
V_4R	Placed right side of chest wall in mirror image to chest lead V_4

From Krucoff MW, et al. Simultaneous ST-segment measurements using standard and monitoring-compatible torso limb lead placements at rest and during coronary occlusion. *Am J Cardiol*. 1994; 74(10):997-1001; Paul K, et al. AHA/ACC/HRS scientific statement: Recommendations for the standardization and interpretation of the electrocardiogram. Part I: The electrocardiogram and its technology: A Scientific Statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society. Endorsed by the International Society for Computerized Electrocardiology. *Heart Rhythm*. 2007;4:394-412.
LA, Left arm electrocardiographic (ECG) electrode; *LL*, left leg ECG electrode; *RA*, right arm ECG electrode; *RL*, right leg ECG electrode; *, Mason-Likar ECG electrode placement.

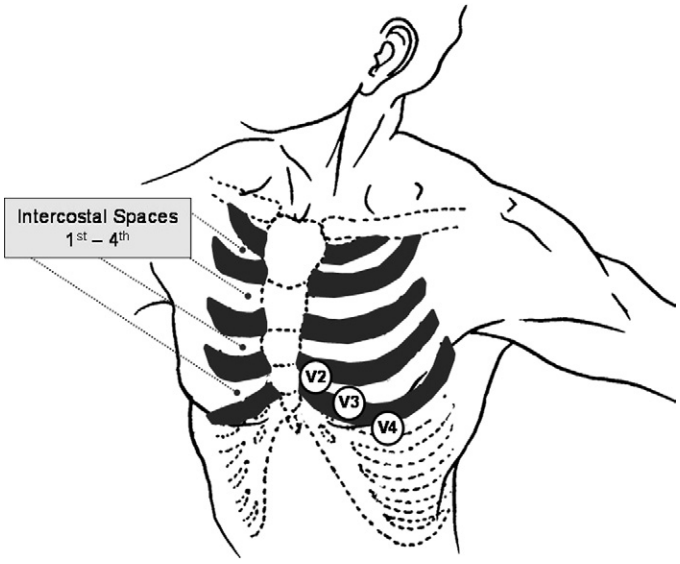

FIGURE **16-6** Precordial electrodes V_2, V_3, V_4 positioned across the ventrolateral aspect of the thorax. V_2 placement: 4th intercostal space (ICS) left of the sternum; V_3: equal distance between V_2 and V_4.; V_4: left midclavicular line at the 5th ICS. (Reprinted with permission from Kossick MA. *EKG Interpretation: Simple, Thorough, Practical*. 3rd ed. Park Ridge, Ill: AANA Publishing. In press.)

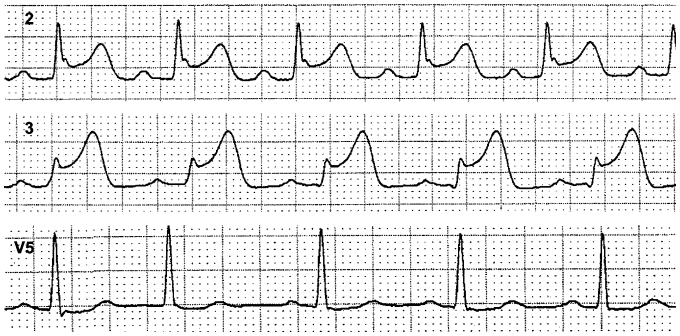

FIGURE **16-7** Monitoring in three electrocardiogram (ECG) leads during anesthetic administration captured significant ST-segment elevation. The greatest change in ST segments occurred in limb lead III, followed by limb lead II. Noteworthy was the failure of lead V_5 to demonstrate any appreciable change in the ST segment. Postoperatively a cardiology consultation resulted in a diagnosis of Prinzmetal angina.

In contrast to a derived 12-lead or five-cable ECG electrode system, a three-cable system offers challenges to anesthesia providers concerning potential errors with ECG lead configuration. The literature documents that healthcare providers consistently struggle with modified chest lead configuration—even those who routinely monitor the ECG.[26] Modified chest leads offer an alternative to true chest leads when only a three-cable ECG recording system is available. Recently introduced into clinical practice is the modified chest lead $MAC_{1(L)}$ (modified augmented chest lead V_1). This modified chest lead is configured using limb lead aVL and has been shown to have a diagnostic accuracy similar to true chest lead V_1. The internal validity of this finding was based on His-bundle recordings, used as the gold standard for distinguishing between premature ventricular ectopy and premature aberrantly conducted beats.[27] The simplicity of this unique ECG lead has the potential to reduce modified chest lead configuration errors. Research would need be done to substantiate this theoretical advantage (e.g., ease of configuration of $MAC_{1(L)}$ versus modified chest lead V_1 [MCL_1]). Figure 16-11 illustrates the ECG configuration of $MAC_{1(L)}$, as well as the similarities in morphologic characteristics of single cardiac cycles recorded in V_1 and $MAC_{1(L)}$.

In summary, practitioners who limit ECG monitoring and assessment to a single lead or pair of leads *in patients with documented or recognized risk factors for ischemic heart disease* are potentially compromising patient safety by not using (when available) multiple-ECG-lead display configuration options.[2] In such patients, the continuous display of three-ECG leads, a multilead ECG (six limb leads and one true chest lead), or a derived 12-lead could be of clinical benefit. The literature substantiates myocardial ischemia (T-wave and/or ST-segment changes) can be regionalized and completely missed when viewing two or fewer ECG leads. Similar concerns exists when three-cable ECG lead systems are used in place of available five-cable ECG lead systems. The latter permits the viewing of a true chest lead, which is always preferable over a modified chest. Unarguably, critical assessment of all available patient data will help anesthetists exercise better judgment during an anesthetic and potentially improve anesthetic outcome.

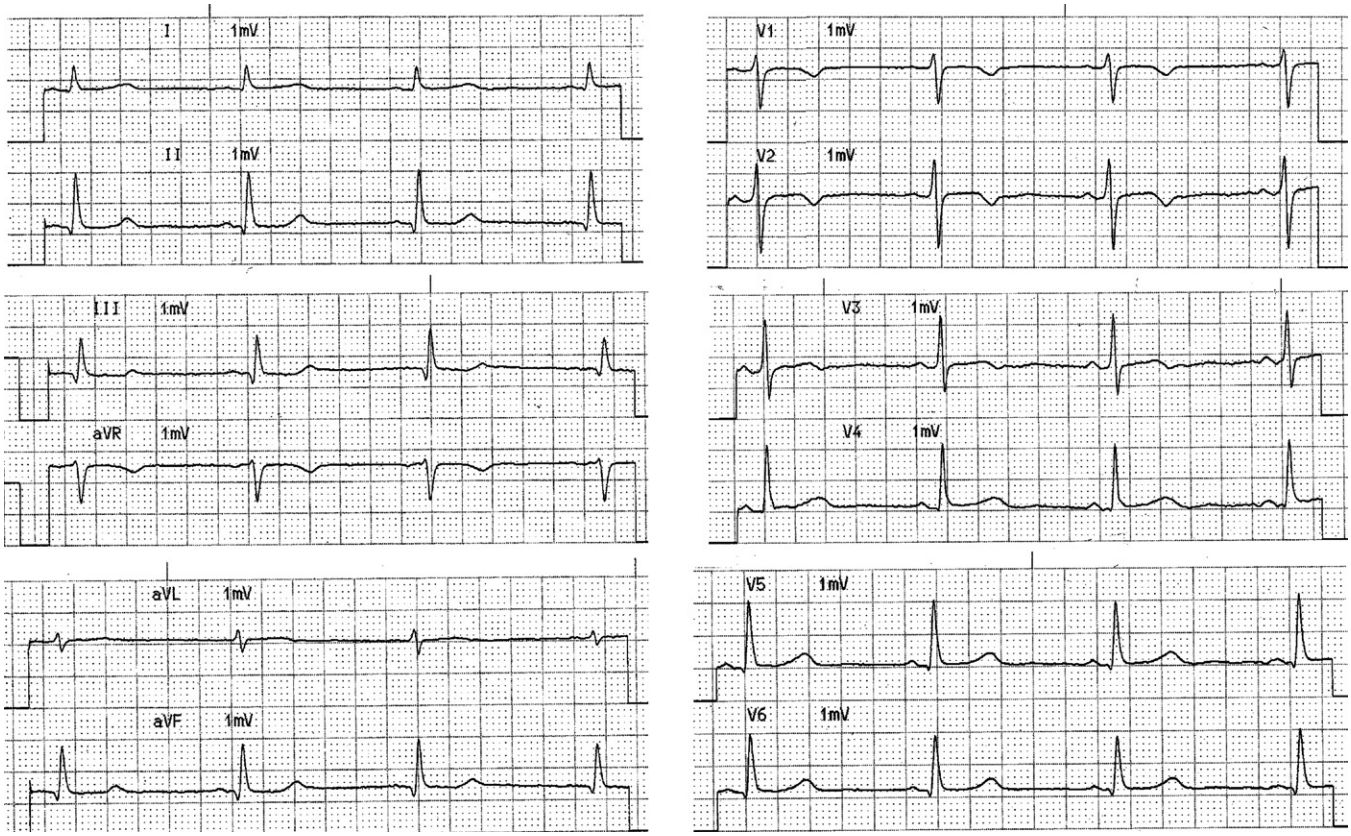

FIGURE **16-8** Derived 12-lead electrocardiogram (ECG [EASI]) recorded just prior to anesthetic induction in the operating room. The ECG monitor can be configured to continuously display all 12 leads for comprehensive assessment of ST segments and rhythm changes.

Gain Setting and Frequency Bandwidth

Two other potential problems with continuous ST-segment monitoring relate to the amplitude at which the ECG monitor has been set and whether filtering of the electrical signal is excessive. When accurate visual assessment of ST segments is a priority during an anesthetic, the gain of the ECG monitor should be set at standardization (i.e., a 1-mV signal delivered by the ECG monitor produces a 10-mm calibration pulse). This gain setting fixes the ratio of the ST-segment and QRS-complex size so that a 1-mm ST-segment change is accurately assessed (e.g., potential myocardial injury). Failure to recognize the use of other gain settings can lead to overdiagnosis or underdiagnosis of myocardial injuries (ST-segment changes). Figure 16-12 illustrates how changes in gain settings and incorrect ECG electrode and/or lead wire placement can confound ST-segment assessment.[28-30]

The filtering capacity of the ECG monitor is yet another potential source of artifact. Research has demonstrated that filtering out the low end of the frequency bandwidth (e.g., 0.05 to 0.5 to produce a new bandwidth range of 0.5 to 40 Hz) of the monitor's electrical signal can lead to distortion of the ST segment (elevation or depression) and T wave (inverted).[31,32] For this reason in many (but not all) cases, the *diagnostic mode* of an ECG monitor should be used when ST-segment analysis is a priority during an anesthetic.

Clearly, the sensitivity and specificity of computerized real-time ST-segment analysis software is dependent on the ability of the anesthetist to critically analyze the large number of factors that influence ST-segment values. Attentiveness to such variables as the patient's physical status, ECG lead placement and selection, verification of proper placement of the Iso point, ST point, type of electronic filtering used by the ECG monitor, and gain setting may affect anesthetic outcome in patients at risk for myocardial ischemia or injury.

CENTRAL VENOUS AND ARTERIAL HEMODYNAMIC MEASUREMENTS

Central venous and pulmonary artery catheters (PAC) are not commonly used in the general surgical population. In fact, since the introduction of the PAC in 1970, the frequency of its use as a monitoring tool for significant surgical procedures has significantly diminished. Even during cardiac or large invasive vascular surgical procedures, many surgeons and anesthesia providers have opted for less invasive means to assess hemodynamic measurements (e.g., Flo Trac sensor). Part of the rationale for this change in practice relates to insufficient evidence demonstrating clinical benefit from use of the PAC.[33,34] The literature is clear in regard to numerous challenges healthcare providers face in accurately interpreting data derived from PACs and central venous lines[35]; cardinal concepts that relate to critical assessment of hemodynamic data are reviewed in this section of the clinical monitoring chapter.

Practice guidelines for PAC use have been recommended and established by various professional societies.[36] It is also recognized that the competency of healthcare providers to manage central venous and arterial hemodynamic parameters can vary significantly. In one study, attending physicians from the departments of medicine, surgery, and anesthesia were unable to demonstrate the basic skill of correctly determining the pulmonary artery occlusive pressure [PAOP] from a clear tracing and applying PAC data for proper patient treatment.[37] Research with anesthesiologists who specialize in cardiovascular anesthesia care also demonstrated cognitive deficits with the use of the PAC (e.g., 39% of cardiovascular anesthesiologists could not correctly interpret a

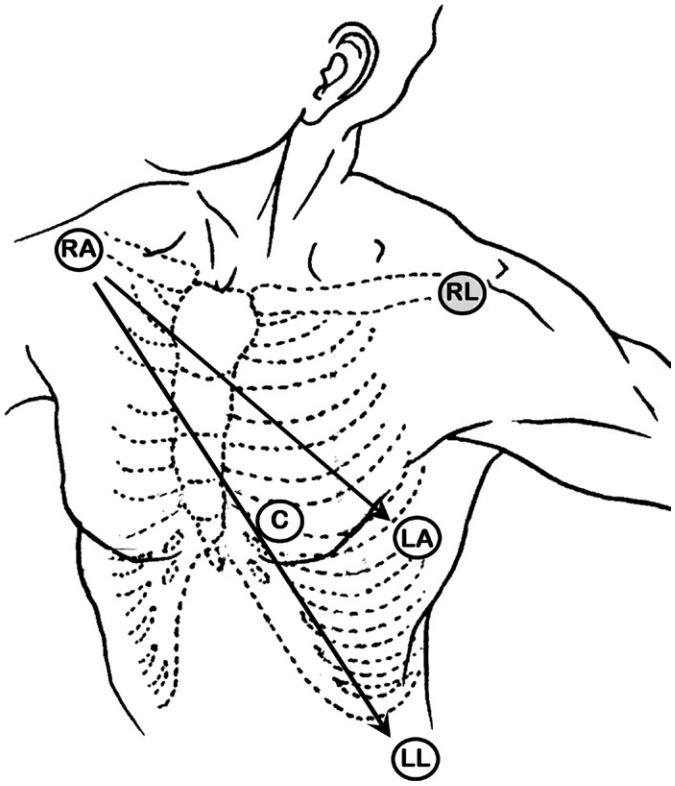

FIGURE **16-9** Preoperative electrocardiogram (ECG) configured with a five-cable ECG system to continuously display limb lead II (right arm *[RA]* negative and left leg *[LL]* positive), true V_3 chest lead (C), and modified chest lead 5 (MCL_5, i.e., central subclavicular 5 *[*CS_5*]*). V_3 electrode placement *(C)*: equal distance between V_2 and V_4. Lead selector switch set to display lead I causes the RA electrode to become negative and the left arm *(LA)* electrode (placed in the V_5 position) to become positive (CS_5). (Reprinted with permission from Kossick MA. *EKG Interpretation: Simple, Thorough, Practical.* 3rd ed. Park Ridge, Ill: AANA Publishing. In press.)

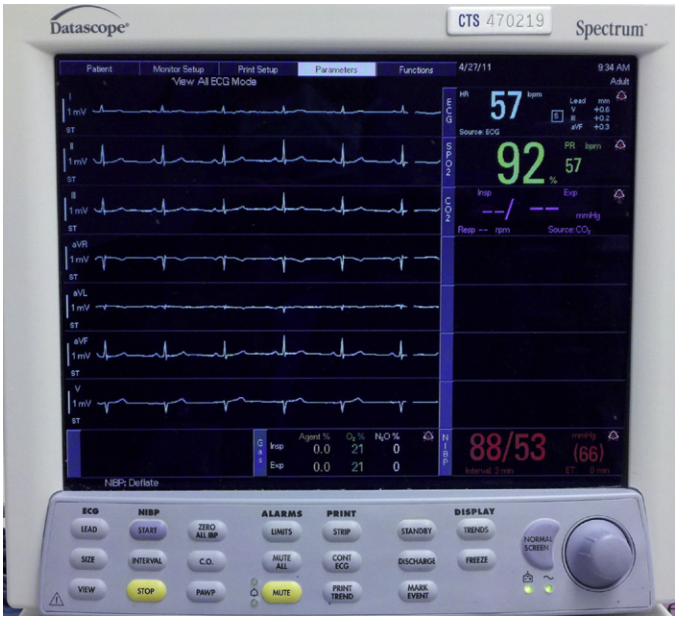

FIGURE **16-10** Multilead electrocardiogram (ECG) displayed in the operating room. ECG leads displayed include limb leads I, II, III, aVR, aVL, aVF, and true chest lead V_3. This configuration permits a more comprehensive view of cardiac anatomy. (Reprinted with permission from Kossick MA. *EKG Interpretation: Simple, Thorough, Practical.* 3rd ed. Park Ridge, Ill: AANA Publishing. In press.)

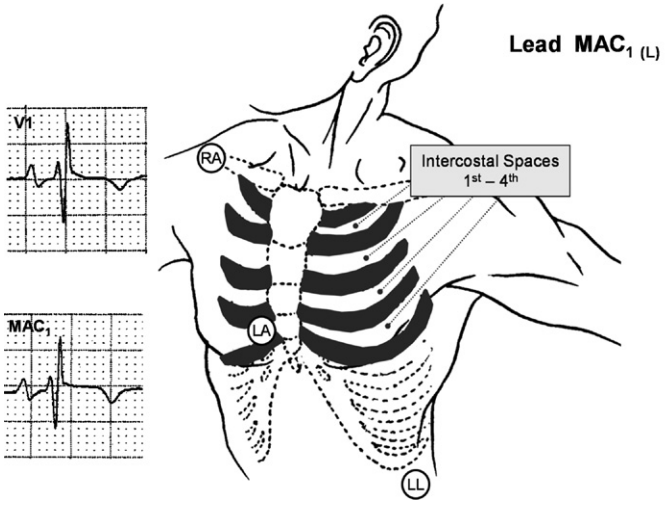

FIGURE **16-11** Modified augmented chest lead V_1 ($MAC_{1\ [L]}$). It is configured by (1) using limb lead aVL, which causes the left arm (*LA*) electrode to become positive, and (2) placing the LA electrode in the V_1 position. The remaining ECG electrodes are placed in their normal positions. The two single cardiac cycles shown above illustrate great similarity in cardiac cycle morphology (rSR_1) between V_1 and $MAC_{1(L)}$. (Modified and reprinted with permission from Kossick MA. *Evaluation of a New Modified Chest Lead in Diagnosing Wide Complex Beats of Unknown Origin.* Dissertation. Memphis, Tenn: The University of Tennessee Health Science Center; 2003:2, 9.)

PAOP waveform).[38] Results from these two studies suggest that the understanding of PAC data among healthcare providers is extremely variable, and misinterpretation of PAC data may result in increased morbidity and mortality. It is likely that similar deficiencies in the application and interpretation of PAC data exists for advanced practice nurses (including Certified Registered Nurse Anesthetists [CRNAs]), knowing failing scores were noted on competency tests used to assess other areas of critical care.[26] Such research findings have caused several groups to develop guidelines for the indications of a PAC, along with competency requirements for interpretation of data.[36,39]

Physiology and Morphology of Hemodynamic Waveforms

Essential to accurate interpretation of hemodynamic data derived from central venous lines is a solid foundation in what constitutes "normal" distances, pressures, and waveform morphology for central venous pressure (CVP), right ventricular (RV), PA, and PAOP recordings. Table 16-3 illustrates the approximate distances for reaching the junction of the venae cavae and the right atrium (RA) from various distal anatomic sites. Table 16-4 lists the anticipated distances for reaching various cardiac and pulmonary structures from the right internal jugular vein. Advancement of a catheter 10 cm beyond these distances without the production of a characteristic waveform could indicate coiling of the central line. If this problem arises with a PAC, the balloon should be deflated and the catheter withdrawn. If any resistance is met during withdrawal, a chest radiograph should be taken to rule out knotting or entanglement with the chordae tendineae.

Right Atrial Pressure Waveform

Familiarity with the anticipated distances of relevant hemodynamic anatomy, normal intracardiac pressures, pulmonary pressures (Table 16-5), and waveform morphology facilitates accurate interpretation of PAC data and placement of central lines. For example, under normal circumstances, a CVP tracing will generate mean RA

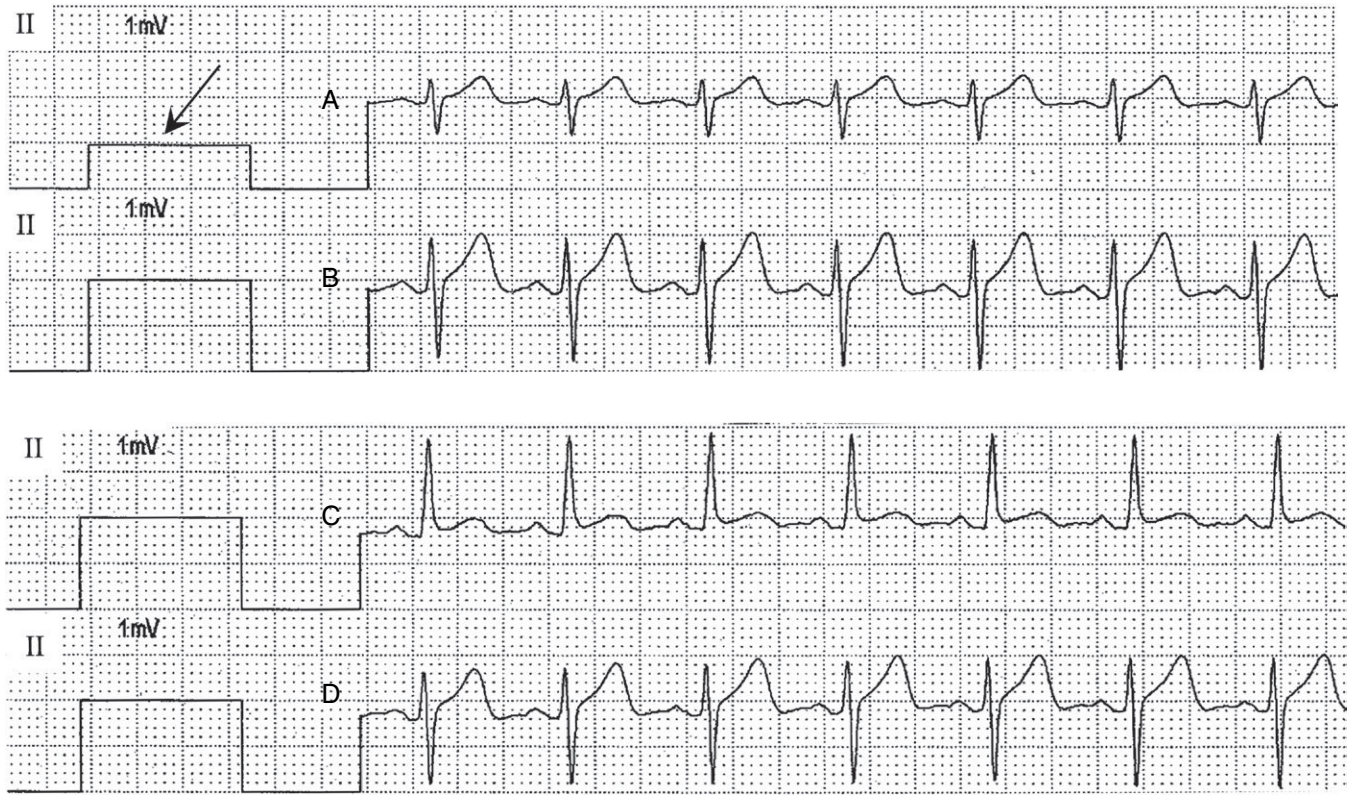

FIGURE **16-12** Series of electrocardiographic (ECG) recordings illustrating how the gain setting and incorrect ECG electrode placement can lead to misinterpretation of ST-segment changes. In strip A, the gain setting *(arrow)* on the ECG monitor has been set at half standardization (1 mV = 5 mm); it grossly gives the appearance of a minor ST-segment change. When concurrent strip *B* is compared with strip A, it becomes apparent that use of smaller gain settings can mask ST-segment deviation. Therefore if a 0.5-mm ST-segment deviation in ECG strip *A* were to occur, it would equate with a 1-mm change. A similar error in assessment of ST-segment changes can occur secondary to misplaced ECG electrodes. ECG strip recording C has all limb lead electrodes properly placed and displays an ST-segment elevation of approximately 0.75 mm. In contrast, ECG rhythm strip *D* mistakenly has the left leg electrode placed in the second intercostal space, midclavicular line, and therefore is not representative of a lead II. The end result is an ST segment that is falsely elevated (approximately 1.5 mm), suggesting inferior transmural myocardial injury. (Reprinted with permission from Kossick MA. *EKG Interpretation: Simple, Thorough, Practical.* 2nd ed. Park Ridge, Ill: AANA Publishing; 1999:26-27.)

TABLE 16-3 Distance to the Junction of the Venae Cavae and Right Atrium from Various Distal Anatomic Sites

Location	Distance (cm)
Subclavian	10
Right internal jugular vein	15
Left internal jugular vein	20
Femoral vein	40
Right median basilic vein	40
Left median basilic vein	50

TABLE 16-4 Distance from the Right Internal Jugular Vein to Distal Cardiac and Pulmonary Structures

Location or Structure	Distance (cm)
Junction venae cavae and right atrium	15
Right atrium	15-25
Right ventricle	25-35
Pulmonary artery	35-45
Pulmonary artery wedge position	40-50

pressures in the range of 1 to 10 mmHg. The fidelity of the transducing system determines whether discernible *a*, *c*, and *v* waves will be displayed once the distal tip of a central line lies just above the junction of the venae cavae and the RA (Figure 16-13). The *a* wave is produced by contraction of the RA, the *c* wave by closure of the tricuspid valve, and the *v* wave by passive filling of the RA (which encompasses a portion of RV systole). The reason the *a* wave is commonly larger than the *c* wave is based on the position of the catheter relative to the physiologic event responsible for the pressure change. In essence, RA systole and the subsequent increase in atrial pressure is detected by a catheter positioned just above (or inappropriately within) the RA, whereas RV systole (a more distal physiologic event relative to the position of a CVP catheter) indirectly increases RA pressure by closure of the tricuspid valve.

Right Ventricular Pressure Waveform

Further advancement of a PAC (approximately 10 cm) produces dramatic changes in the morphology of the hemodynamic waveform. As shown in Figure 16-14, a brisk upstroke (isovolumetric contraction and rapid ejection [RV systole]) and steep downslope (reduced ejection and isovolumetric relaxation [RV systole and diastole]) are viewed on an oscilloscope when a PAC is advanced through the right intraventricular cavity. A PAC with the distal balloon inflated should remain in the RV for as short a time as possible to reduce the incidence of ventricular ectopy, or the development of a conduction defect such as bundle branch block. Because it is undesirable to leave the tip of a central line in the RV, pressures generated during RV systole and RV diastole are assessed indirectly via the CVP port of a PAC and distal tip of the PAC. The former is used to estimate RV end-diastolic pressure (EDP) and the latter RV systolic pressure via the PA systolic recording. Thus RVEDP is used to estimate RVED volume (RVEDV), which approximates RV preload (and less accurately left ventricular [LV] preload).

TABLE 16-5 Normal Intracardiac and Pulmonary Pressures

Location	Absolute Value (mmHg)	Range (mmHg)
MRAP	5	1-10
RV	25/5*	15-30/0-8
PA S/D	25/10*	15-30/5-15
MPAP	15	10-20
PAOP	10	5-15
MLAP	8	4-12
LVEDP	8	4-12

LVEDP, Left ventricular end-diastolic pressure; *MLAP*, mean left atrial pressure; *MPAP*, mean pulmonary artery pressure; *MRAP*, mean right atrial pressure; *PA*, pulmonary artery; *PAOP*, pulmonary artery occlusive pressure; *RV*, right ventricular; *S/D*, systolic/diastolic.
*Values are systolic pressure/diastolic pressure.

Pulmonary Artery Pressure Waveform

When a catheter enters the PA, the diastolic pressure is acutely increased with little change in systolic pressure. The upstroke of the PA tracing is produced by opening of the pulmonic valve, followed by RV ejection. The downstroke contains the dicrotic notch, which is produced by sudden closure of the pulmonic valve leaflets (the beginning of diastole).

Pulmonary Artery Occlusive Pressure Waveform

Final advancement of a PAC by 5 to 10 cm should produce a PAOP tracing. This waveform is similar to a CVP (the *a* wave is produced by left atrial [LA] systole, the *c* wave by closure of the mitral valve, and the *v* wave by filling of the LA, as well as upward displacement of the mitral valve during LV systole), except that the pressure values are somewhat greater. In addition, it is less common to detect a *c* wave on a PAOP tracing, because retrograde transmission of LA pressure (produced by closure of the mitral valve) is significantly attenuated within the pulmonary circulation. The characteristic waveform morphologies of a PAOP tracing are shown in Figure 16-14.

Negative Waveforms

The descents that follow the *a*, *c*, and *v* waves of a CVP or PAOP tracing are labeled as *x*, x^1, and *y* (see Figure 16-13). The *x* descent corresponds to the start of atrial diastole (its terminal component

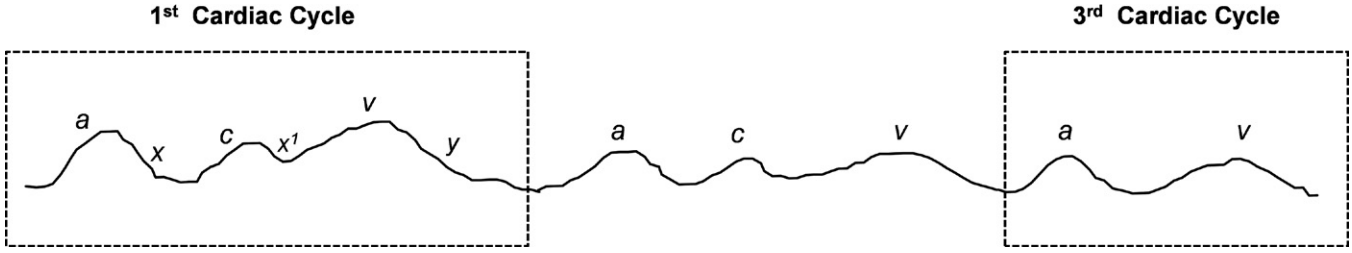

FIGURE 16-13 Positive and negative waveforms of a central venous pressure (CVP) tracing. The third cardiac cycle in this figure does not produce a *c* wave.

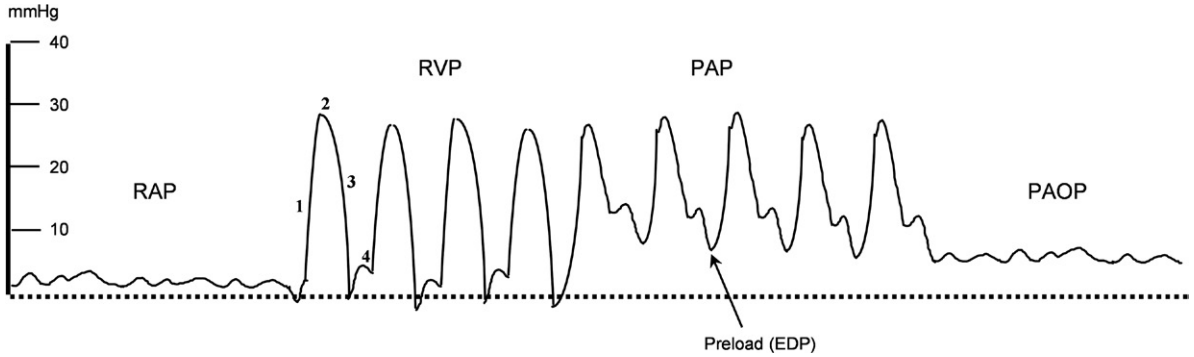

FIGURE 16-14 Pressure waveforms during positioning of a pulmonary artery catheter (PAC). *EDP*, End-diastolic pressure; *PAOP*, pulmonary artery occlusive pressure; *PAP*, pulmonary artery pressure; *RAP*, right atrial pressure; *RVP*, right ventricular pressure. *1*, Isovolumetric contraction (ascent of pressure waveform); *2*, rapid ejection; *3*, isovolumetric relaxation (mid-descent of pressure waveform); *4*, atrial systole (slight increase in pressure).

[just before the upstroke of the *c wave* (or in its absence, the *v* wave)] with RVEDP and LVEDP); the *x*[1] descent is produced by downward pulling of the septum during ventricular systole; and the *y* descent corresponds to opening of the tricuspid valve.

Correlation of Pressure Waveforms and the Electrocardiogram

The interpretation of hemodynamic waveforms can be facilitated by correlating their morphology and timeline with the ECG. The *a* wave of a CVP tracing, which is produced by atrial contraction, will follow depolarization of the atria (P wave on the ECG). The *c* and *v* waves occur after the beginning of ventricular depolarization (QRS complex), or the *v* wave may not appear until shortly after the T wave (Figures 16-15 and 16-16). When compared with the CVP tracing, the PAOP recording shows greater hysteresis between the waveforms of the ECG and the display of *a*, *c*, and *v* waves—meaning there is a greater distance between ECG activity and the subsequent pressure waveform. Identification of abnormal waveforms is greatly facilitated by the use of the ECG; for example, without an ECG recording, large positive waveforms on a PAOP tracing can be diagnosed as either cannon *a* waves or large *v* waves.

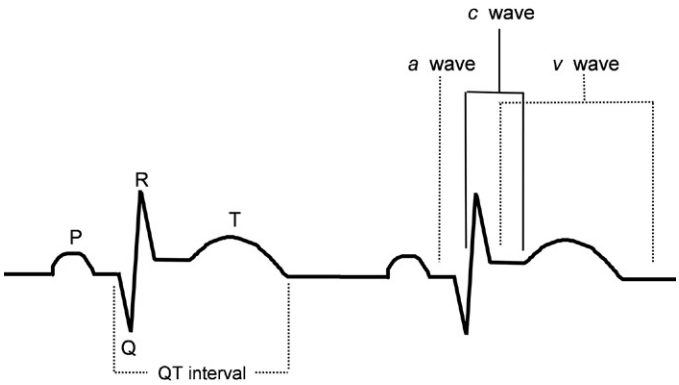

FIGURE **16-15** Temporal relationship between the electrocardiogram and hemodynamic waveforms.

Distortion of Pressure Waveforms

Arrhythmias can produce significant alterations in hemodynamic waveforms. Atrial fibrillation, junctional rhythms, and premature ventricular contractions (PVCs) can alter the shape of *a* waves. With atrial fibrillation, no synchronized atrial contraction occurs. In the CVP or PAOP tracing, this can lead to the loss of *a* waves or the appearance of small fibrillatory *a* waves. Complete atrioventricular block and some forms of junctional arrhythmias cause the atria to contract against a closed tricuspid valve, which can produce large cannon *a* waves (Figure 16-17). Ventricular pacing can be associated with both the presence of cannon *a* waves and loss of *a* waves. The former occurs if a patient does not have an atrioventricular sequential pacemaker; the latter when ventricular pacing is used in the setting of asystole (neither atrial or ventricular depolarization is occurring). Valvular defects can also produce dramatic changes in the CVP and PAOP tracings, causing an increase in the amplitude of the *v* wave secondary to regurgitation (e.g., with mitral regurgitation a portion of the stroke volume is ejected retrograde into the pulmonary circuit, owing to an incompetent mitral valve). Recognition of such abnormalities is critical for accurate recording of pressure measurements and proper placement of central lines. Significant tricuspid regurgitation can cause a CVP recording to mimic an RV tracing, and mitral regurgitation can lead to a PAOP recording to appear as a PA tracing. Specifically, large *v* waves become superimposed on *a* waves. For the indistinguishable PA and PAOP recording, analysis of an SvO_2 (venous oxygen saturation) blood sample can assist in making a differential diagnosis. The saturation will be elevated (greater than 77%) if the catheter is in a wedged position, assuming the distal tip is not in a region of the lung that is atelectatic; which in contrast would produce a false-negative result (normal or low SvO_2). As a precautionary measure, a catheter suspected of being in a wedged position should not be flushed with the fluid contained in the pressurized transducing system. Although the overall incidence of PA rupture is low (0.064%),[40] flushing of a wedged catheter (as well as balloon overinflation) can result in vascular damage ranging from minor endobronchial hemorrhage to massive hemoptysis.

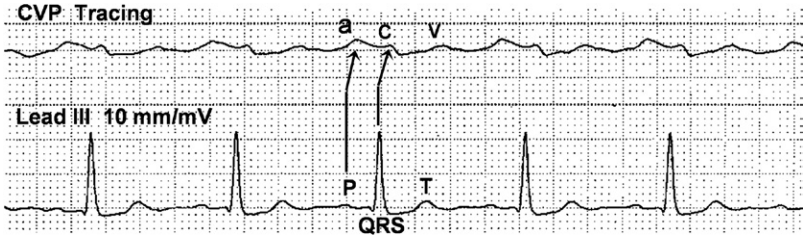

FIGURE **16-16** Electrocardiographic recording with a concurrent central venous pressure tracing that demonstrates hysteresis between atrial depolarization (P wave) and the production of an *a* wave, as well as the QRS complex and the associated *c* and *v* waves.

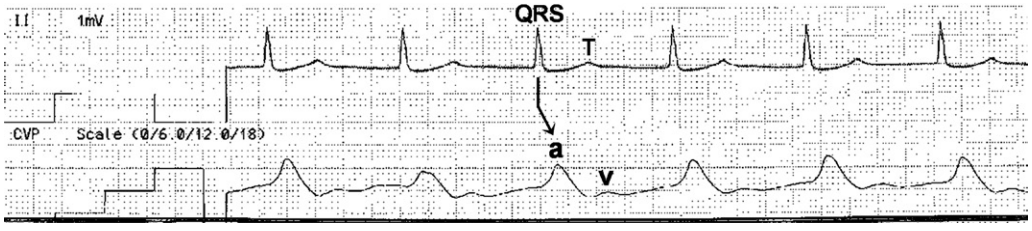

FIGURE **16-17** Electrocardiographic recording of a junctional rhythm *(top)* in which there is simultaneous retrograde atrial and antegrade ventricular depolarization (as evidenced by the lack of a P wave in each cardiac cycle). This results in the right atrium contracting against a closed tricuspid valve. As a consequence, the central venous pressure (CVP) tracing *(bottom)* has cannon *a* waves.

Significant tricuspid regurgitation and mitral regurgitation may also be associated with normal CVP and PAOP tracings.[41] These occur in patients with a low volume status and compliant atria. In addition, a poor correlation has been found between the size of the *v* wave and the degree of regurgitation. Also of interest is the finding that large *v* waves can be observed in the absence of significant regurgitation. This phenomenon can occur whenever an acute increase in preload occurs, which dynamically reduces atrial and pulmonary vascular compliance.[41]

Whenever large *v* waves are detected on a CVP or PAOP tracing, estimates of preload should be measured just before the upstroke of the *v* wave (or *c* wave when present). This point on the pressure recording equates with the EDP, the moment just before ventricular systole that ultimately produces the large *v* waves. Box 16-1 indicates how various rhythm disturbances, pacing, and valvular defects can distort the CVP tracing.

Implications of Abnormal Hemodynamic Values

The CVP serves as an estimate of right ventricular preload (RVEDP). Table 16-6 lists the causes of an elevated CVP. A low CVP correlates with hypovolemia of any cause. As stated previously, RV pressures can be assessed indirectly from the CVP and PA pressure (PAP) recordings. Right ventricular values can be elevated secondary to pulmonary hypertension, ventricular septal defect, pulmonary stenosis, RV failure, constrictive pericarditis, or cardiac tamponade.

Like the RV waveform, the PA tracing occurs within the QT interval of the ECG. LVEDP can be estimated by measuring the pressure value that exists just prior to the upstroke of the PA waveform (Figure 16-14). See Table 16-6 for a list of causes of an increase in the PAP. A false high value can also be produced by a phenomenon called *catheter whip*, which is exaggerated oscillation of the PA tracing. This can occur with excessive catheter coiling if the tip of the PA catheter is near the pulmonic valve; it also occurs in patients with dilated pulmonary arteries. The latter may occur if pulmonary hypertension exists.

When properly used, the PAOP recording has the potential to improve the clinician's ability to make a differential diagnosis in critically ill patients. Like the CVP, it indirectly assesses ventricular function and therefore has distinct limitations. To ensure that accurate pressure recordings are documented, the mean or diastolic pressure should always be determined at end-expiration (whether the patient is spontaneously breathing or receiving positive pressure ventilation). This is the time when pleural pressures are approximately equal to atmospheric pressures (except when positive end-expiratory pressure [PEEP] is being used). The rationale for this timing relates to the fact that vascular pressure recordings are calibrated relative to atmospheric pressure. As stated previously, the correct area on the pressure recording to determine preload (e.g., LVEDP) is just before the upstroke of the *v* wave (or *c* wave if present). Causes of an elevated PAOP are listed in Table 16-6.

Variables That Influence Hemodynamic Measurements

Essential for proper management of hemodynamic parameters is the recognition of how numerous variables can skew recorded pressure values. The foundation for understanding PAC data begins with the recognition that absolute numbers are generally not as important as trends. In addition, most of the data obtained from a PAC allows for only *indirect* assessment of cardiovascular function and pulmonary indices. For example, PA diastolic pressure (PADP) approximates PAOP, which approximates LA pressure, which approximates LVEDP, which provides an estimate of left ventricular end-diastolic volume (LVEDV). Table 16-7 lists clinical factors that can skew these pressure and volume relationships. Obviously, reliance on indirect pressure measurements mandates that the anesthetist understand how to interpret these data in light of such limitations. It should be assumed that for most patients who require a PAC or CVP that several, if not numerous, pathophysiologic states exist (e.g., cardiovascular disease, pulmonary dysfunction) that will skew the pressure-to-pressure and pressure-to-volume relationships.

Of the variables listed in Table 16-7, several require further discussion. Many of the factors listed can be viewed as disruptions or obstructions of the continuous column of blood that exists between the RA and LV. This is the case for valvular defects and pulmonary factors.

The goal for placement of a PAC is to have it reside in a West zone III[42] of the lung; this usually does occur, because the bulk of pulmonary blood flow lies within this region of the lung. In this

BOX 16-1

Factors That Can Distort Central Venous Pressure and Pulmonary Artery Occlusive Pressure Tracings

Loss of *a* Waves or Only *v* Waves
- Atrial fibrillation
- Ventricular pacing in the setting of asystole

Giant *a* Waves—"Cannon" *a* Waves
- Junctional rhythms
- Complete AV block
- PVCs (simultaneous atrial and ventricular contraction)
- Ventricular pacing (asynchronous)
- Tricuspid or mitral stenosis
- Diastolic dysfunction
- Myocardial ischemia
- Ventricular hypertrophy

Large *v* Waves
- Tricuspid or mitral regurgitation
- Acute ↑ in intravascular volume

↑, Increase; *AV*, atrioventricular; *PVCs*, premature ventricular contractions.

TABLE 16-6 Potential Causes of Elevated Central Venous Pressure, Pulmonary Artery Pressure, and Pulmonary Artery Occlusive Pressure

CVP	PAP	PAOP
RV failure	LV failure	LV failure
Tricuspid stenosis or regurgitation	Mitral stenosis or regurgitation	Mitral stenosis or regurgitation
Cardiac tamponade	L-to-R shunt	Cardiac tamponade
Constrictive pericarditis	ASD or VSD	Constrictive pericarditis
Volume overload	Volume overload	Volume overload
Pulmonary HTN	Pulmonary HTN	Ischemia
LV failure (chronic)	"Catheter whip"	

ASD, Atrial septal defect; *CVP*, central venous pressure; *HTN*, hypertension; *L*, left; *LV*, left ventricular; *PAOP*, pulmonary artery occlusive pressure; *PAP*, pulmonary artery pressure; *R*, right; *RV*, right ventricular; *VSD*, ventricular septal defect.

position, the PAP is greater than the pulmonary venous pressure, which is greater than the alveolar pressure. This zone corresponds to a complete circuit or conduit that allows for direct communication between right-sided heart and pulmonary pressures with left-sided intraventricular pressures (Figure 16-18). It is important to recall that each of the lung zones is physiologically—not anatomically—defined; thus a zone III can change into a zone II (PAP > alveolar pressure > pulmonary venous pressure) or zone I (alveolar pressure > PAP > pulmonary venous pressure).

TABLE 16-7 Factors That Alter the Relationships Among Central Cardiovascular Pressures and Volumes

CVP ≠ PADP	Change in RV compliance (e.g., PS) Tricuspid valve disease
PADP ≠ PAOP	Pulmonary HTN MR or AR Lung zone I or II Tachycardia ARDS RBBB
PAOP ≠ MLAP	Juxtacardiac pressure (e.g., PEEP) Lung zone I or II Mediastinal fibrosis RBBB
MLAP ≠ LVEDP	Juxtacardiac pressure (e.g., PEEP) Mitral valve disease Change in LV compliance (e.g., AS)
LVEDP ≠ LVEDV	Juxtacardiac pressure (PEEP) Ventricular interdependence Change in LV compliance (e.g., ischemia)

AR, Aortic regurgitation; *ARDS*, acute respiratory distress syndrome; *AS*, aortic stenosis; *CVP*, central venous pressure; *HTN*, hypertension; *LVEDP*, left ventricular end-diastolic pressure; *LVEDV*, left ventricular end-diastolic volume; *MLAP*, mean left atrial pressure; *MR*, mitral regurgitation; *PADP*, pulmonary artery diastolic pressure; *PAOP*, pulmonary artery occlusive pressure; *PEEP*, positive end-expiratory pressure; *PS*, pulmonic stenosis;; *RBBB*, right bundle branch block; *RV*, right ventricular.

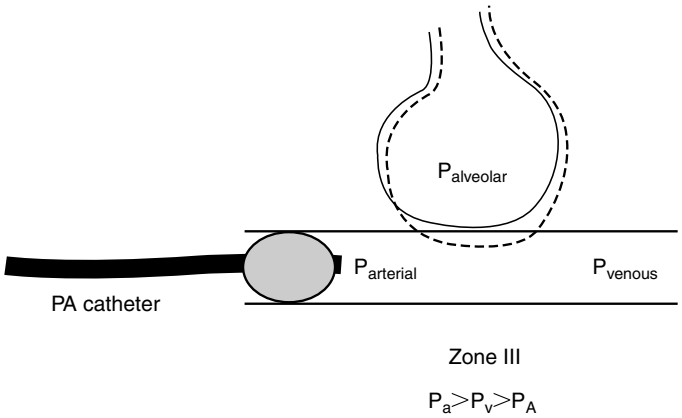

FIGURE 16-18 Pulmonary artery catheter with balloon inflated (wedging) in a West lung zone III. In this zone, pulmonary pressures equilibrate during diastole because both arterial and venous pulmonary pressures are greater than alveolar pressures. The addition of positive end-expiratory pressure *(dashed-line alveolus)* or hypovolemia can convert a zone III to a zone I or II and lead to distended alveoli and inaccurate estimates of pressures distal to the invagination. P_a, Arterial pressure; P_A, alveolar pressure; P_v, venous pressure; *PA*, pulmonary artery.

Factors that contribute to the dynamic state of zone III include the application of PEEP (Figure 16-18), significant diuresis, hemorrhage, and a change in patient position (e.g., supine to sitting). The influence of PEEP is contingent on the quantity applied, intravascular volume status, and pulmonary compliance. Normally, less than 50% of PEEP is transmitted to the microvasculature—even less if pulmonary compliance is poor (e.g., patients with adult respiratory distress syndrome).[43] In contrast, patients with decreased volume status (e.g., left atrial pressure less than 5 mmHg) who receive PEEP as low as 7.5 cm H_2O can have collapse of the pulmonary capillaries, which distorts the PAOP.[44] A PAC located in zone I or II will produce marked variations in the PAOP waveform recording during the ventilatory cycle. In addition, *a* and *v* waves (cardiac influences) are lost, and the PAOP exceeds the PADP. This is in contrast to a PAOP recording produced by a catheter located in a true wedge position. The distinguishing criteria include the development of a characteristic waveform with balloon inflation and a PAOP reading less than or equal to the PADP. The latter criterion assumes that no valvular defect is present, which could also cause the mean PAOP to exceed the PADP.

A rapid heart rate (HR) can also skew the relationship between PADP and the PAOP. Research has demonstrated that left-atrial-paced induced tachycardia (increased HR from 74 to 124 beats per minute) can produce an 11-mmHg gradient between the PADP and LVEDP. The increase in PADP and decrease in LVEDP result from the shortening of diastole, which reduces the amount of blood being transported from the pulmonary circulation to the LV.[45] Also, as HR increases, the left atrium begins to contract against a partially closed mitral valve.[46]

Another variable that significantly influences PAC data is a change in ventricular compliance. To illustrate this point, consider the fact that a high PAOP (or LVEDP) can exist in patients with an elevated preload with normal ventricular compliance, as well as in patients with a low preload with poor ventricular compliance. A patient with reduced ventricular compliance (e.g., myocardial ischemia, left ventricular hypertrophy, cardiac tamponade, ventricular interdependence) has a high PAOP or PADP that results in overestimation of LVEDV (Figure 16-19) and underestimation of LVEDP. In the setting of poor compliance, PAOP is not a reliable index for LVEDV.[47] In fact, it has been shown that during myocardial revascularization procedures, high PAOP values exist more than 50% of the time in conjunction with a low volume status (as determined by echocardiography), with patients responding favorably (despite a high PAOP) to an increase in intravascular volume.[48]

To summarize, the PADP correlates poorly (by 5 mmHg or more) with the PAOP under the following circumstances: when pulmonary vascular resistance (PVR) is elevated (e.g., chronic obstructive pulmonary disease, human papillomavirus, pulmonary embolus, adult respiratory distress syndrome, hypercarbia), when heart rates exceed 130 beats per minute, when severe mitral or aortic regurgitation is present, or when a lung zone III has changed to a zone II or I (e.g., in the presence of hypovolemia, PEEP). Increases in PVR and HR cause the PADP to exceed PAOP. Severe regurgitation and lung zone changes produce the opposite effect, with PADP being less than the PAOP; this may also hold true for right bundle branch block, based on one researcher's findings of how this conduction defect caused the PADP (in the setting of normal PVR) to be up to 7 mmHg less than the mean left atrial pressure.[49] A review of the gross interpretation of CVP and PAOP values is presented in Table 16-8.

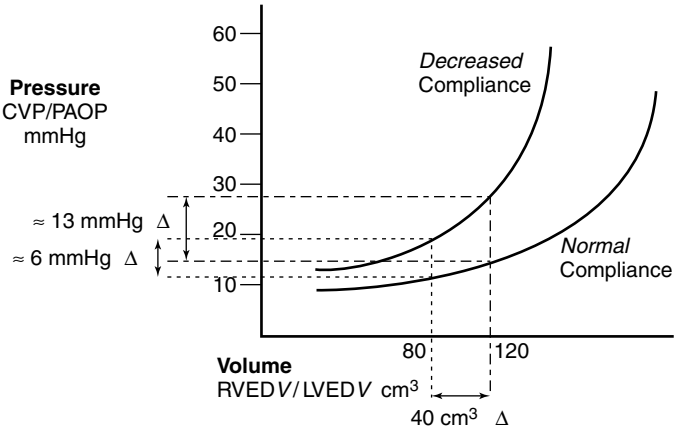

FIGURE **16-19** Effect of changes in ventricular compliance on CVP (which estimates RVEDP) and PAOP (which estimates LVEDP). The curve with *decreased compliance* distorts the relationship between pressure values and estimated ventricular volume. A preload of 80 cm^3 in a compliant versus noncompliant ventricle generates a pressure difference of ≈ 6 mmHg *(flat portion of each curve)*. On the steeper portion of both curves, the relationship between volume and pressure is skewed even more dramatically. A preload of 120 cm^3 generates a pressure difference of ≈ 13 mmHg, which can ultimately lead to a gross overestimation of ventricular preload. Δ, Change; *CVP*, central venous pressure; *LVEDP*, left ventricular end-diastolic pressure; *PAOP*, pulmonary artery occlusive pressure; *RVEDP*, right ventricular end-diastolic pressure; *RVEDV*, right ventricular end-diastolic volume; *LVEDV*, left ventricular end-diastolic volume.

TABLE 16-8 Potential Clinical Diagnosis Via the Use of Hemodynamic Values: Interpretation of Pulmonary Artery Catheter Data

CVP	PADP	PAOP	Interpretation
Low	Low	Low	Hypovolemia, transducer not at phlebostatic axis*
Normal or high	High	High	LV failure
High	Normal or low	Normal or low	RV failure, TR, or TS
High	High	Normal or low	Pulmonary embolism
High	High	Normal	Pulmonary HTN
High	High	High	Cardiac tamponade, ventricular interdependence, transducer not at phlebostatic axis*
Normal	Normal or high	High	LV myocardial ischemia or MR
Low	High	Normal	ARDS†

*Phlebostatic axis is the fourth intercostal space, midanteroposterior level (not midaxillary line); for the right lateral decubitus position, fourth intercostal space midsternum; for the left lateral decubitus position, fourth intercostal space at the left parasternal border.
†ARDS patients commonly require initial fluid administration for hemodynamic stability.
ARDS, Acute respiratory distress syndrome; *CVP*, central venous pressure; *HTN*, hypertension; *LV*, left ventricular; *MR*, mitral regurgitation; *PADP*, pulmonary artery diastolic pressure; *PAOP*, pulmonary artery occlusive pressure; *RV*, right ventricular; *TR*, tricuspid regurgitation; *TS*, tricuspid stenosis.

Other Hemodynamic Indexes

Some authors encourage the use of calculated indexes to optimize the care of critical care patients. These indexes include the pulmonary vascular resistance index (PVRI), systemic vascular resistance index (SVRI), and cardiac index (CI). The potential advantages and limitations of each index are reviewed below.

The PVRI (PVR calculated with the CI instead of the cardiac output [CO]) is equal to the difference in pressure across the pulmonary circuit (mean PAP − PAOP) divided by flow (CI) times 80. This formula is taken from Ohm's law (with the variables mathematically manipulated) for electric currents (R [Resistance] = V [Voltage] = I [Current]). A normal value is considered to be 45 to 225 dynes/sec/cm^5/m^2. Two limitations of extrapolating physiologic resistance from Ohm's law are (1) blood flow is pulsatile and not flowing continuously through a set of rigid pipes, and (2) resistance is not uniform throughout the pulmonary circuit. The electrical counterpart describes resistance not in alternating currents, but direct currents.[50]

When PVR is used clinically, it should be viewed as a gross *estimate* of RV afterload; similarly, SVR is associated with LV afterload. In the intact heart *afterload* is defined as systolic wall stress or the impedance the ventricle must overcome to eject its stroke volume. It is important to understand that vascular resistance is not synonymous with afterload but is used as an extension of the concept. Pulmonary vascular resistance, like SVR, can affect afterload, but neither formula accounts for changes in ventricular wall thickness or radius, which are components of afterload.

Systemic vascular resistance index is calculated as the difference between systemic input pressure (mean arterial pressure) minus the output pressure (right atrial pressure or CVP), divided by the CI times 80. The normal range is 1760 to 2600 dynes/sec/cm^5/m^2. Systemic vascular resistance is commonly used to offer some guidance in the use of vasoconstrictors (e.g., phenylephrine infusion) or afterload reduction (e.g., intravenous nitroglycerin or sodium nitroprusside). The limitations described previously for PVR also hold true for SVR, although perhaps to a lesser extent, because the systemic vasculature has lower compliance. In general, supporting afterload via vasoconstrictors should be deferred until maximization of preload or the use of positive inotropes has proven to be ineffective.

Determination of CO assists critical care specialists in providing rational hemodynamic therapy, evaluating the response to therapy, and determining the adequacy of tissue perfusion, which is linked to maintenance of arterial blood pressure, the delivery of oxygen, and removal of wastes. It also permits the calculation of other hemodynamic indices (e.g., PVR and SVR). A "normal" CO value can be qualified by taking into account age differences, metabolic activity (declines with anesthesia and increases with hyperthermia), and patient size. This last factor may be adjusted for by converting a CO to a CI, which attempts to normalize CO for the large number of values found in the general population. However, CI adjusts only for the variables of height and weight. It does not address the lack of uniformity of predicted basal oxygen consumption and metabolic rates resulting from differences in sex and age. In addition, the relationship between body surface area (BSA) and blood flow is indistinct.[51] CI is calculated by dividing CO by BSA. The plotting of height and weight on a body surface chart estimates the BSA in square meters (Figure 16-20). Commonly quoted "normal" values are 5 to 6 L/min for CO and 2.8 to 3.6 L/min/m^2 for CI.

The most commonly used technique for determining CO is thermodilution, whereby an analog computer calculates the CO by using the modified Stewart-Hamilton equation. This method

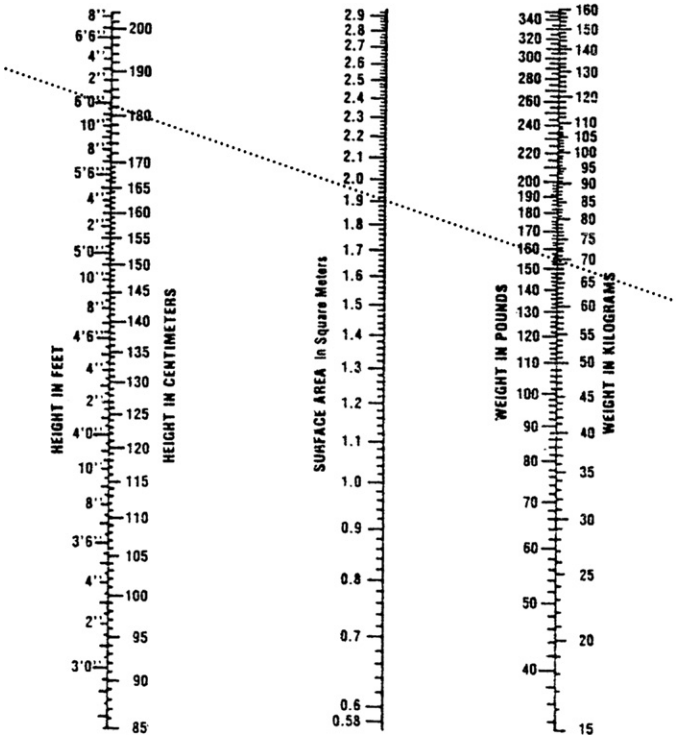

FIGURE **16-20** Chart used to calculate body surface area. In this example, a height of 6 feet and a weight of 155 lb translates into a surface area of approximately 1.9 m^2.

was first used by Fegler in 1954.[52] It entails the injection of a known quantity of an indicator solution (most commonly 5% dextrose in water, although 0.9% normal saline has a similar density factor) through the proximal port of a thermodilution PAC.[53]

The injected solution is considered a thermal indicator because it is cold relative to body temperature. It rapidly mixes with the incoming blood and is carried through the RV until it is detected by the thermistor near the end of the catheter in the PA. The computer plots a time-temperature curve, with the area under the curve being inversely proportional to the CO; therefore larger curves are not desired. Variables that can influence recorded values include the computation constant (which varies with catheter size, injectate volume, and temperature), temperature of the injectate (desired range of 0° to 24° C), volume of injection,[54] speed of injection (should be done in 4 seconds or less),[55] and the timing of injection (it should be consistent, i.e., the same time during each respiratory cycle).[56] Iced injectates have not been shown to offer any significant advantage over room-temperature injectates.[54] In fact, cold indicator solutions injected rapidly into the right atrium have been shown to produce arrhythmias[57] including sinus bradycardia.[58] Research that has examined the impact of valvular or septal defects on thermodilution CO (TDCO) values has produced conflicting results.[59-61] A list of variables that can skew CO measurements is provided in Table 16-9.

The accuracy for TDCO (including when performed in patients in the lateral position) is ±10%, and the reliability is ±5%.[62] These values are lower in the pediatric population,[63] in patients who have low CO,[64] and for measurements taken in the operating room.[65] Anesthetists should be careful not to overinterpret small changes (e.g., 5% to 10%) and should never express values beyond one decimal point. The common practice of averaging three CO output values has also been shown to improve accuracy.[66]

TABLE 16-9 Variables That May Influence Thermodilution CO Values

Overestimates	Underestimates	Unpredictable
Low injectate volume	Excessive injectate volume	Right-to-left ventricular septal defect
Injectate that is too warm	Injectate solutions that are too cold	Left-to-right ventricular septal defect
Thrombus on the thermistor of the PAC		Tricuspid regurgitation
Partially wedged PAC		

CO, Cardiac output; *PAC*, pulmonary artery catheter.

A further advancement in CO technology has been achieved via the placement of thermal filaments within the right ventricular portion of the PAC and near the tip of the thermistor (Vigilance system [Edwards Life-Sciences Corporation], OptiQue system [Abbott Laboratories]). A sophisticated computer algorithm permits for analysis of a thermal signal created by small quantities of heat being emitted from the PAC—a pulsed warm thermodilution continuous cardiac output (TDCCO) technique. This heat signal is eventually transmitted by the blood to the distal thermistor, which permits for continuous CO (CCO) assessment.[67] An adequate signal-to-noise ratio is necessary to produce accurate and *reliable* CCO measurements. Research has shown a low ratio (derived from a core body temperature greater than 38.5° C) can result in inaccurate CCO values.[68] One advantage of a CCO catheter is the elimination of the time-consuming administration of a thermal injectate through the proximal port of the PAC. It also reduces the number of discrepancies in thermodilution CO values that can occur with inconsistent injectate administration relative to the respiratory cycle.

A drawback to the CCO device is the hysteresis in recording hemodynamic information. Although the monitor displays updated CO figures every 30 seconds, they nonetheless do not represent real-time data. Instead, the CCO values depict the average CO from the prior 3 to 6 minutes.[69] This can be a significant limitation in patients who develop acute hemodynamic changes occurring in response to hemorrhage and resuscitation.[70] In this setting, a standard bolus thermodilution technique is preferable.

Manufacturers of TDCCO monitors have attempted to circumvent this limitation by developing "Fast-Filter" and "Urgent" modes to supplement the "Normal" mode of data processing. One investigation found a significant decline in the precision of CO measurements when the Fast-Filter and Urgent modes were used.[71] The reliability and accuracy of the device with intensive care and surgical patients have been established with recordings taken in the supine position[68,72] and with the backrest elevated up to 45 degrees.[73] Nevertheless, some investigators have found the TDCCO technique to be less precise than bolus thermodilution.[74-76]

Other investigators have examined a variation of the TDCCO PAC, specifically a PAC (truCATH) that measures the amount of energy required to maintain a fixed blood temperature gradient between two distal thermistors. Researchers have found the truCATH PAC and TruCCOMS monitor to overestimate low CO and underestimate high CO and suggested that an improvement in the calibration scheme may obviate this problem.[77,78] Although the truCATH provides ultrafast data, it demonstrates problems with reliability.

In spite of reports in the literature of a positive clinical outcome based on the use of TDCCO,[33,79] future studies will be required to establish whether CCO measurements (as well as other monitoring modalities such as Doppler techniques[80]) reduce the length of hospitalization and improve morbidity and mortality rates.[81]

Mixed Venous and Central Venous Oxygen Saturation

Since its introduction in 1981, SvO_2 has been described as a means to indirectly monitor oxygen delivery. This purported usefulness is based on the knowledge that SvO_2 is determined by pulmonary function, cardiac function, oxygen delivery, tissue perfusion, oxygen consumption, and hemoglobin concentration. During the course of an anesthetic (excluding cases of major trauma or hemorrhagic shock), it is not unusual for pulmonary function, hemoglobin content, and oxygen consumption to remain relatively stable. Therefore proponents of SvO_2 monitoring state that it is reasonable to assume that a decrease in SvO_2 reflects a change in oxygen delivery, presumably via a reduction in CO.[82,83] In contrast, some researchers have found a poor correlation between SvO_2 and CO.[84,85]

Continuous mixed venous oximetry is measured with the use of fiberoptic reflectance spectrophotometry through two fiberoptics housed in the PAC. One fiberoptic transmits light-emitting diodes (narrow wavebands of light) to the distal catheter. The extent of light absorption and reflection is a function of the quantity of oxyhemoglobin and deoxyhemoglobin present in the PA.[86] The receiving fiberoptic transports the reflected light to a microprocessor that interprets the signal and displays an SvO_2 value; the normal range of SvO_2 is 65% to 77%. Factors that increase SvO_2 values include left-to-right shunts, hypothermia, sepsis, cyanide toxicity, a wedged PAC, and an increase in CO. SvO_2 decreases with hyperthermia, shivering, seizures, reduced pulmonary transport of oxygen, hemorrhage, and decreased CO. Sustained low values (e.g., 50%) merit investigation followed by appropriate intervention(s). It has also been demonstrated that some SvO_2 monitoring systems adapt well to acute changes in hematocrit.[87] In addition, research with two-wavelength and three-wavelength SvO_2 oximetry catheters has shown the systems to be comparable in accuracy.[88]

Central venous oxygen saturation ($ScvO_2$) monitoring has been advocated as a surrogate for SvO_2 when a less invasive form of hemodynamic monitoring is indicated. Modified central venous catheters (CVC) that contain a fiberoptic lumen can measure $ScvO_2$ when positioned at the junction of the superior vena cava and right atrium. A major difference between SvO_2 and $ScvO_2$ measurements is the latter is considered a regional indicator of venous oxygen saturation; it measures venous O_2 saturation from the upper body and head. In contrast, SvO_2 measurements depend on blood flow from the superior vena cava, inferior vena cava, and coronary sinus (which has an O_2 content of approximately 7 mL/dL [venous O_2 saturation of 35%]). Also, the mixed venous O_2 content is greater in the inferior vena cava than the superior vena cava.[89,90] The net effect of these differences is that under normal conditions (e.g., unanesthetized subjects),[90] the $ScvO_2$ is about 2% to 3% less than the SvO_2.[89-92] However, the literature also reports the opposite relationship.[93]

From a monitoring perspective, research indicates that the use of $ScvO_2$ as a substitute for SvO_2 is both advocated[84,93-95] and discouraged.[91,96-98] Numerous clinical investigations in different practice settings with patients having diverse pathologic states have been conducted. In spite of the diverse opinions, some professional healthcare societies have established guidelines that recommend $ScvO_2$ be used as a clinical tool to guide therapy for improving morbidity and mortality. For example, the 2008 surviving sepsis campaign—international guidelines for management of severe sepsis, strongly suggested using a $ScvO_2$ goal of 70% or more (or SvO_2 65% or more) in the first 6 hours of resuscitation. Concurrent hemodynamic/clinical recommendations included achieving a CVP 8 to 12 mmHg, MAP (mean arterial blood pressure) 65 mmHg or greater, urine output 0.5 mL/kg/hr or greater, and intravenous antibiotics within the first hour of recognizing severe sepsis and septic shock.[94]

In conclusion, the cost-benefit ratio of using PACs that provide TDCO, TDCCO, SvO_2 measurements, or even CVCs with $ScvO_2$ monitoring capabilities remains controversial. As with any physiologic monitor, the potential to promote health or cause harm is determined by the clinician's ability to interpret and apply data.[99] A similar analogy can be made for computerized ST-segment analysis whereby numerous variables unaccounted for in interpretation of ST-segment shifts can potentially lead to iatrogenic injury. Therapeutic strategies should be guided by a knowledge of the patient's underlying pathophysiology and limitations of the respective hemodynamic monitoring device.

ARTERIAL PRESSURE MONITORING

As with ECG monitoring, professional societies have designated the routine assessment of arterial blood pressure (BP) to be essential for the safe conduct of any anesthetic; at minimum, BP should be recorded at least once every 5 minutes.[1] This frequency of assessment should be increased for patients noted to have any systemic disease that limits physiologic reserve, such as coronary artery disease (CAD) or valvular heart defects (e.g., aortic stenosis). This author advocates BP assessment at 1-minute intervals during the induction period of most anesthetics, the rationale being that many commonly administered induction agents are associated with cardiac depressant effects. The concomitant disruption or gross activation of homeostatic reflexes can lead to substantive changes in hemodynamics—even in relatively healthy patients. It is also known that the hemodynamic response to many drugs used during induction of anesthesia can be unpredictable, owing to differences in pharmacokinetics and pharmacodynamics among patients.

BP monitoring can be accomplished through both noninvasive and invasive techniques. Each recording modality will be reviewed with an emphasis on clinical relevance. Other resources provide a comprehensive description of the theoretic underpinnings for the calculation of noninvasive and invasive arterial BP data. In today's modern OR environment, noninvasive blood pressure (NIBP) monitoring is most often recorded by automated BP cuffs that can be configured to measure systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial blood pressure (MAP) in a standard mode, stat mode, at varied frequencies of assessment, and adjusted for patient age and habitus. The literature recommends BP cuffs have a bladder dimension of approximately 40% of the circumference of the extremity.[100] Bladders not properly sized and cuffs not applied firmly to the extremity can lead to inaccurate recordings. For example, cuffs that are applied loosely to the extremity, positioned below the level of the heart, or are too small can produce arterial blood pressure values that are falsely elevated.[101]

The physics associated with auscultation of BP relates to the audible discernment of Korotkoff sounds through a stethoscope. These sounds are produced by turbulent blood flow within an artery during cuff deflation. A second mechanism for BP assessment is via an oscillometric technique (Figure 16-21). NIBP devices have inflation and deflation cycles controlled by

a microprocessor. During deflation of the cuff, oscillations are sampled over the span of several cardiac cycles. Any oscillations sensed by the pressure transducer are then processed numerically. If none are sensed, a stepwise reduction in cuff pressure followed by sustained measurement for oscillations occurs. This process repeats until SBP, DBP, and MAP are derived. MAP can also be estimated by taking the sum of the SBP and DBP—the latter multiplied by two, then dividing this figure by three. Example: a BP of 120/80 has a MAP of (120 + 80 + 80) ÷ 3 = 93 mmHg). This formula accounts for diastole comprising approximately two thirds of a normal cardiac cycle.

Generally speaking, the benefits outweigh the risks of frequent NIBP recordings taken during an anesthetic. Nevertheless, injury and harm can occur with automatic NIBP measurements and may include damage to peripheral nerves (e.g., ulnar), development of a compartment syndrome, or interference with delivery of drugs through an intravenous (IV) line. For example, propofol sequestered in a forearm during BP-cuff inflation can cause intense pain. The latter can be avoided by routinely placing the BP cuff on the extremity *without* the peripheral IV. In circumstances in which the scheduled surgery involves an upper extremity, the BP cuff and IV can be placed on the contralateral arm (brachium or antebrachium), with the caveat that the NIBP be configured so BP measurements are recorded in the manual mode to prevent unexpected disruption of the delivery of IV induction drugs. Alternatively, a lower extremity (thigh or calf) can be used for BP measurements.

In morbidly obese patients, it is not unusual to have to relocate a BP cuff from the upper arm because of the cone shape of the extremity. An alternative BP monitoring site is the forearm. However, NIBP measurements taken in the forearm with the patient in supine or sitting position or the head of the bed elevated 45 degrees can *overestimate* the more proximal brachial BP.[102,103] Formulas have been proposed to correct for such discrepancies. For example, in an obese patient with a diastolic forearm pressure of 80 mmHg and arm circumference between 32 and 44 cm, the adjusted DBP would equal 72.4 mmHg. This is derived from the following equation:

$$\text{Brachial DBP} = 25.2 + 0.59 \times \text{Forearm DBP}$$

This formula was proposed relative to 129 subjects with an average body mass index of 40 ± 7 kg/m^2.[102] Discrepancies in BP measurements have also been noted between upper and lower extremities and between arms. In study participants up to 16 years of age, SBP has been shown to be *greater* in the thigh and calf than in the arm. In contrast, DBP and MAP are *lower* in the calf and thigh than in the arm.[104] Patients most likely to exhibit inter-arm BP differences are those who are obese and have a higher HR and SBP.[105] Concerns about accuracy also arise when measuring BP noninvasively versus invasively. One group of investigators found NIBP taken in the upper arm in patients with septic shock to correlate poorly with arterial-line pressure measurements, specifically causing an overestimation of MAP with the noninvasive technique.[106]

It is apparent that in the demographics of the population of the United States, a substantive change has occurred in recent years in the number of adults and children who are classified as obese. Consistent with this change are the findings that mean mid-arm circumference has increased across the country, with the greatest increase occurring in 20- to 39-year-olds. This change should cause anesthesia providers to be more attentive to the daily task of selecting properly sized BP cuffs. In fact, research has shown that up to 39% of all hypertensive patients and 47% of self-reported diabetic patients should not have their BP measured with the standard adult-size cuff.[107] Inattentiveness to this basic and essential monitoring need could cause the anesthetist to process inaccurate hemodynamic data (e.g., overestimated BP recordings) and ultimately contribute to a poor surgical outcome.

Direct measurement of arterial BP is considered by many the gold standard for recording BP. Many anatomic locations can be used for direct BP measurement, with the most common being the radial artery. Other less commonly used arteries are the ulnar, brachial, axillary, femoral, and dorsalis pedis. Risks associated with placement of an intraarterial catheter include infection (localized and systemic), thrombus formation, hematoma, vasospasm, embolization, injury to adjacent nerves and veins, ischemia to extremities or digits, loss of a limb secondary to poor collateral circulation, iatrogenic injuries (e.g., air embolization, intraarterial injection of drugs meant to be administered intravenously), and acute blood loss due to an unexpected disruption of the transducing system (e.g., cracked or disconnected stopcock). A displaced transducer (no longer level with the phlebostatic axis) can cause an "increase" in arterial blood pressure if positioned substantially below the level of the heart. Assessment of an abnormal BP recording should include an understanding of problems inherent to a fluid-pressure monitoring system. To mitigate the ongoing risks of direct arterial BP monitoring, constant vigilance on the part of the anesthetist is paramount.

Monitoring BP directly offers several distinct advantages, including beat-to-beat assessment of BP, limited hysteresis in measured values, and easy access for arterial sampling of blood for any number of laboratory tests (e.g., arterial blood gases, serum

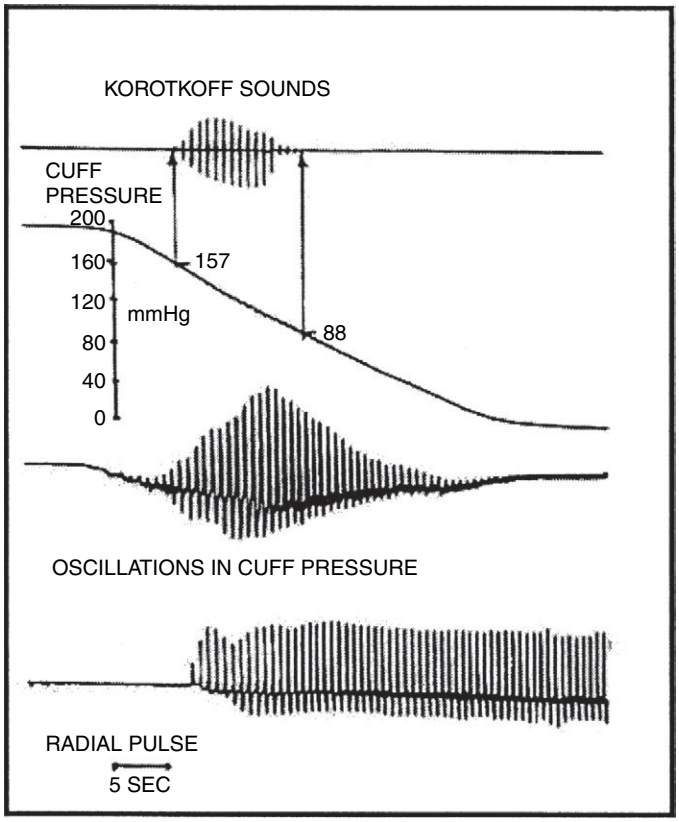

FIGURE **16-21** Arterial blood pressure, comparing Korotkoff sounds, oscillations with a blood pressure (BP) cuff, and radial artery palpation. Note correlation between onset of the first Korotkoff sound, onset of oscillations in the cuff pressure, and radial pulse wave. (From Saidman LJ, Smith NT, eds. *Monitoring in Anesthesia.* New York: Wiley & Sons; 1978.)

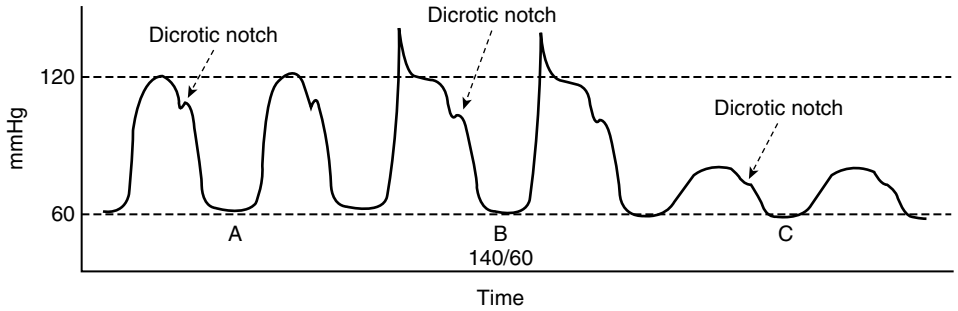

FIGURE **16-22** Radial arterial pressure waveforms. *(A)* normal morphology, *(B)* overshoot, *(C)* dampened. With waveform B, the overshoot should be ignored regarding the displayed systolic blood pressure.

electrolytes, glucose, hemoglobin levels). Indications for direct arterial BP monitoring include surgical procedures in which there is potential for acute and/or gross changes in hemodynamics. This would include operations such as repair of aortic aneurysms, carotid endarterectomy, and craniotomies. Even with lower-risk surgical procedures, direct arterial BP monitoring may be indicated, particularly if preoperative BP is poorly controlled (labile). Patients with comorbidities may be at substantial risk for a stroke or heart attack during periods of acute stress (e.g., laryngoscopy or emergence from an anesthetic) if BP is not directly monitored.

Risks associated with placement of a radial artery catheter can be minimized if precautionary measures are taken. This would include positioning of the hand and wrist on an armboard. A roll should be placed beneath the wrist, and the fingers and thumb should be taped securely across the board. This position keeps the hand from interfering with manipulation and placement of the needle-catheter system; it also facilitates palpation of the radial artery. Commonly, a 20-gauge nontapered catheter is used (a 22-gauge is optional) to penetrate an area of skin that has been prepped with antiseptic solution and infiltrated with local anesthetic. The needle, bevel pointing upward, is directed at a 45-degree angle toward the palpated pulse. If bone is encountered with the tip of the needle during advancement, the complete catheter system (catheter and needle) is slowly withdrawn while observing for the free flow of arterial blood; sometimes the artery can be pierced without a "flash back" (unintentional transfixion-withdrawal method). If during catheter withdrawal no blood is seen, the needle system is directed slightly laterally (in either direction) and readvanced. Once arterial blood is seen in the lumen of the catheter, the angle of the needle is reduced to approximately 30 degrees, then advanced slightly (a few millimeters). The catheter is subsequently threaded off the needle. "Fatigue" at a puncture site may occur, at which time a new artery may be chosen to cannulate or a "fresh set of hands" (perhaps another anesthesia provider or member of the surgical team) used to repeat the attempt at arterial puncture. After verifying correct placement of the catheter within the lumen of the artery (free flow of blood through the rigid tubing when vented to air), it is important to securely fasten the arterial catheter to the skin, preferably with suture and a sterile dressing applied on top of the puncture site.

The transducing system should be zeroed to atmospheric pressure (with the stopcock vented to air) and referenced at the level of the left atrium. In patients with poor vascular compliance, the arterial tracing can produce an "overshoot" or "ringing" phenomenon. If not recognized, BP recordings will overestimate SBP and MAP values. In contrast, a dampened waveform, which can develop with a flexed wrist or low pressure in the continuous-flush device, can lead to an underestimation of BP recordings (Figure 16-22). Direct arterial pressure measurements, although very accurate in many clinical circumstances, can still produce BP recordings that are significantly skewed and lead to inappropriate interventions (e.g., preload augmentation, indiscriminate use of vasoactive drugs).

TRANSESOPHAGEAL ECHOCARDIOGRAPHY MONITORING

Transesophageal echocardiography (TEE) has been established as a safe, noninvasive diagnostic tool for monitoring numerous cardiac parameters to guide medical and nursing care. Systolic wall motion abnormalities (SWMA), vascular aneurysms, calculation of ejection fraction, ventricular preload, and measuring blood flow within heart chambers and across valves are a few of the utilities of ultrasound imaging applied during TEE. Guidelines for indications and training proficiency have been advocated by medical professional societies.[108,109]

Sound waves used to define anatomic structures in the human body were first described by Dussik and colleagues in 1947. These investigators attempted to outline the cerebral ventricles by driving sound waves across the skull.[110] In 1971, C.D. Side and R.G. Gosling were the first to report the assessment of cardiac function via transesophageal techniques.[111] Forty years later, substantial advancements in the medical application of ultrasound have occurred, leading in some circumstances to an improvement in surgical outcomes.[112] Fundamental to the interpretation of data obtained by TEE is an understanding of the physics of ultrasound. Ultrasound waves are inaudible to the human ear, having a frequency greater than 20,000 Hz. Piezoelectric crystals are known to produce ultrasound by vibrating when exposed to an electric current. The opposite also occurs, in that they produce voltage in response to an ultrasound echo or when pressed (mechanical stress) or released. The electric current produced has been shown to be of sufficient magnitude to temporarily illuminate a small bulb. Thus they function as both generators and receivers of ultrasound waves and electric currents.

Within the esophagus, ultrasound waves emitted by piezoelectric elements are absorbed, reflected, or scattered. When reflected by an organ (e.g., heart), the ultrasound echo produced is received by the piezoelectric elements housed within the TEE probe. These elements then generate an electrical impulse that is processed, amplified, and subsequently displayed as an image on the echograph machine. Manufacturers can place as many as 32 linearly arranged elements within a probe (Figure 16-23). The frequency of the piezoelectric crystals in TEE probes ranges from 3.7 to 7 MHz. This frequency range allows for greater detail in displayed images. Unfortunately, the tradeoff for clearer images is lower tissue penetration. Thus smaller frequency values (e.g., 2.5 MHz) are required in transthoracic echocardiographic (TTE) probes because of greater distances between elements and distal anatomic structures.

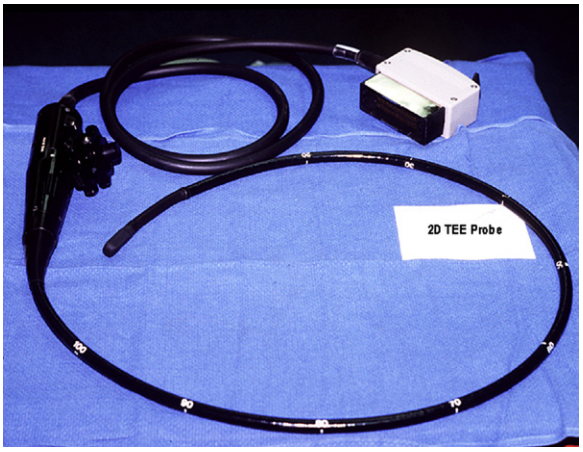

FIGURE **16-23** A 170-cm transesophageal echocardiography probe with cm markings is displayed. Examination depth is approximately 35 to 40 cm from teeth. The positioning-holding mechanisms are located on control knobs, allowing for manipulation of the probe in the anterior, posterior, and lateral planes. *2-D TEE*, Two-dimensional transesophageal echocardiography.

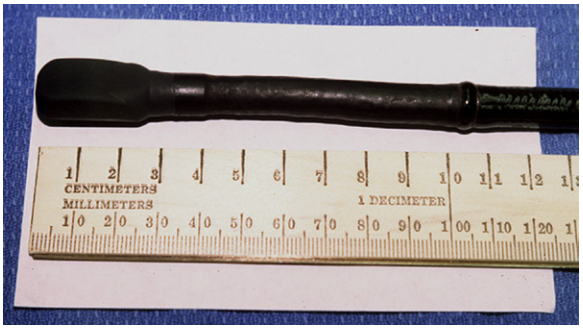

FIGURE **16-24** Transesophageal echocardiography probe. Distal tip contains thermistor and piezoelectric elements.

Clinically, three primary ultrasound imaging techniques are used: the M-mode, 2-dimensional (2-D) imaging, and the Doppler exam. The M-mode provides high picture resolution with 1000 images per second. It is commonly referenced as being unidimensional and produces a well-focused, narrow ultrasound beam. It is sometimes referred to as an *ice-pick view*. With the 2-D scan, the ultrasound beam is electronically steered across a target field. The intermittent pulses of ultrasound are produced by varying the firing sequence (phasing) of individual piezoelectric crystals. The monitor subsequently displays an image that is somewhat triangular or appears as a "slice" of pie. This produces excellent spatial orientation; however, at 30 images per second, the pictures are less well defined. The Doppler exam incorporates the concept of frequency shift, which was first described in 1842 by Austrian physicist Christian Doppler. The clinical application of this concept involves viewing red blood cells (RBCs) as moving reflectors of ultrasound. As ultrasound reflects off the moving RBCs, echos are produced, which are then recorded by the TEE transducer. With the flow of RBCs toward the TEE probe, the distance between the sound source and its reception is changing. This phenomenon is referred to as a *frequency shift*. It is analogous to the change in pitch of a train whistle as the locomotive approaches the station; sound waves are compressed, and the pitch increases (frequency shift). In contrast to RBCs, body fluids (plasma) only minimally reflect ultrasound. Spectral and color-flow Doppler exams performed with echographs incorporate this concept by assigning different colors to RBCs that move toward and away from the source of ultrasound. This permits easy visualization of retrograde flow of blood across incompetent heart valves, as may occur with mitral regurgitation (MR). For example, the retrograde flow of blood from the left ventricle into the left atria during MR is seen distinctly as a mosaic pattern of color. Doppler exams are recognized as being beneficial in determining the etiology of regurgitation and the adequacy of valve repair, as well as influencing surgical management, such as the use or nonuse of cardiopulmonary bypass.[109,112]

Fundamental elements of the TEE exam include positioning the TEE probe in the esophagus, either under sedation or after induction of the anesthetic (Figure 16-24). During the examination, cardiac anatomy can be assessed, myocardial ischemia diagnosed via the presence of SWMA, and blood flow through heart chambers and across valves seen. By convention, the posterior structures are displayed at the top of the screen (apex of the sector) and anterior structures at the bottom. The first image displayed in a standard exam is the short-axis view of the aortic valve. At a depth of approximately 35 to 40 cm from the teeth, the aortic valve leaflets and coronary arteries are seen. Rotation and angulation of the probe can allow a long-axis view of the right and left atria, tricuspid and mitral valves, pulmonic and aortic valves, and right and left ventricles. This view is useful for assessing stenotic valves, identifying masses within the atria or ventricles, and observing the overall size of each heart chamber. A short-axis view of the left ventricle can be obtained with further advancement of the probe and angling of the tip. This position is also referred to as the *standard monitoring view*, which allows the echocardiographer to assess for SWMA. Normal ventricular wall motion (which is not entirely uniform) thickens during systole, and the endocardial surface moves inward. Approximately 87% of the normal stroke volume is derived from shortening in the short axis of the ventricle—with little contribution from the long axis.

Abnormal wall motion can be described by three terms: hypokinesia, akinesia, and dyskinesia. *Hypokinesia* represents contraction that is less vigorous than normal; wall thickening is decreased. *Akinesia* depicts the absence of wall motion and can be associated with myocardial infarction. *Dyskinesia* correlates with paradoxical movement (i.e., outward motion during systole) and is a hallmark of myocardial infarction and ventricular aneurysm (Figure 16-25). Not all wall motion abnormalities are diagnostic of an imbalance between myocardial oxygen supply and demand. Abnormal loading conditions, asynchronous ventricular depolarization (e.g., left bundle branch block), echo dropout due to haphazard reflection of ultrasound off myocardial walls in lateral fields of the sector arc, or improper use of the gain controls of the TEE probe can lead to an erroneous diagnosis of SWMA. Also, the duration of SWMA can persist well after coronary reperfusion has been restored (e.g., 6 hours), indicating a stunned myocardium.[113] In canine research, a 50% decline in coronary blood flow has been shown to serve as a threshold for hypokinesia. In contrast, a 75% reduction in coronary blood flow commonly produces ST-segment deviation. Thus there is greater hysteresis and less sensitivity with ischemia-induced ECG changes than with ischemia-induced SWMA.[114,115] This finding is consistent with classic research done by Tennant and Wiggers in 1935.[116]

To summarize, the best single view for routine monitoring for SWMA (myocardial ischemia) is the short axis at the midpapillary muscle level (see Figure 16-25), followed by the apical segment in the same axis. The midpapillary muscle level includes segments of the myocardium perfused by all three coronary arteries. This level is created by dividing the long axis of the left ventricle into

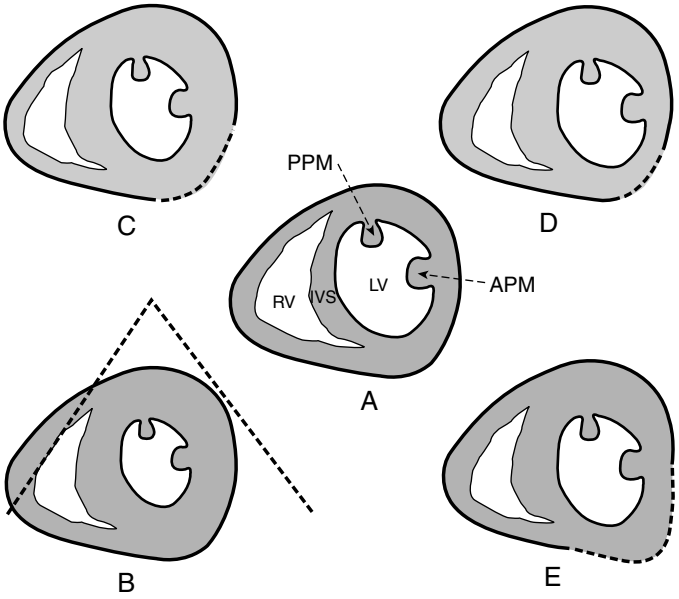

FIGURE **16-25** Midpapillary muscle level short-axis view of the heart **(A)** during diastole, **(B)** during systole with normal wall thickening and inward movement of endocardial surface, **(C)** systole with area of hypokinesia (decreased wall thickening), **(D)** systole with an area of akinesia (no change in wall thickness), and **(E)** systole with an area of dyskinesia (paradoxical movement). *APM*, Anterior papillary muscle; *IVS*, interventricular septum; *LV*, left ventricle; *PPM*, posterior papillary muscle *RV*, right ventricle.

three parts (i.e., basal, mid-, and apical regions). The mid-region extends from the tips to the bases of the papillary muscles. Interesting is the finding that the skills required of anesthesiologists, residents, and CRNAs (compared with trained observers) for recognizing gross SWMA can be acquired with little training; the study group successfully identified 95% of regional wall motion abnormalities.[117]

Newer imaging techniques introduced with TEE include contrast echocardiography, selected three-dimensional techniques, parametric imaging modes, and harmonic imaging modalities. Continued research with these echocardiographic diagnostic tools will help elucidate what patient populations may benefit most from their application. Recent investigations have shown that real-time, three-dimensional (3-D) echocardiography is a feasible way to estimate the area of the aortic valve orifice in patients with stenotic lesions and to evaluate patients with suspected CAD for myocardial wall motion and perfusion abnormalities.[118,119] Also of interest was porcine research that showed intracardiac transvenous echocardiography (ICE) to be superior to precordial Doppler and TEE techniques in diagnosing venous air embolism and retrieving as little as 0.05 to 1 mL of air.[120]

SUMMARY

With continued advancements in technology and improved clinical databases derived from research, future monitoring techniques offer promise for continued improvement in anesthesia care. The development of specialized task forces comprising multiple professional societies also contributes substantively to professional practice. Understandably, anesthesia providers should continue to maintain a healthy skepticism of reported advancements in monitoring modalities. The decision to change practice routines should occur only after critiquing the reported merits of any research findings. Ultimately, this clinical paradigm will allow patients to benefit from medical and nursing care derived from evidence-based practice.

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Clinical Monitoring II

Respiratory and Metabolic Systems

◆ *Gregory Bozimowski*

CHAPTER 17

"Every breath you take, every move you make…I'll be watching you."

(Sting, 1983)[1]

The lyrics to the song, "Every Breath You Take" were written decades ago and refer to a stalking, obsession-based relationship and yet, when considered in an anesthesia monitoring context, they succinctly define the contract between the nurse anesthetist and the patient undergoing anesthesia care. Clinical monitoring in the perioperative setting is the process of observing physiologic responses to surgery and anesthesia. It is the essence of what the Certified Registered Nurse Anesthetist (CRNA) does to ensure an optimal, safe outcome.

It is important to note that the modalities chosen to obtain physiologic feedback may or may not lead to a reduction in patient morbidity and mortality.[2] Research provides rationale to support the standardization of minimal monitoring modalities. Standards are available to the anesthesia provider from both the American Association of Nurse Anesthetists (AANA) and the American Society of Anesthesiologists (ASA).[3,4] It is a matter of clinical judgment by the anesthetist that determines what modalities beyond those minimally required will provide useful information when added to the anesthetic plan of care. It is through this evidence-based approach that best practices are developed.

It is important to emphasize that despite advancements in technology, human vigilance must be maintained and considered primary in assessing patient responses to anesthesia. Human error is always possible and often associated with adverse outcomes. Monitoring alone cannot prevent adverse outcomes, but a timely response to warnings can have a positive impact.[5] It cannot be emphasized enough that reliance on technology must never be allowed to lull the clinician into complacency. Although accuracy and reliability of monitors continue to improve, the potential for machine malfunction and artifact is ever present. Timely human response to intraoperative events remains the key to predicting, avoiding, and managing untoward responses to anesthesia and surgery. The basic human senses of sight, hearing, touch, and even smell remain the primary tools in clinical monitoring. The patient is the primary source of assessment data.

This chapter reviews current monitoring standards as outlined by the AANA. In addition, a practical systems approach to monitoring is presented as it relates to the avoidance of critical incidents. Respiratory monitoring is reviewed as it relates to the ongoing assessment of airway and breathing using not only the human senses but also technologic tools used by nurse anesthetists. The modalities to be discussed in this chapter include the precordial stethoscope, carbon dioxide detection devices, and pulse oximetry. Thermoregulation is significantly altered under anesthesia, so temperature monitoring modalities are reviewed in this chapter. Finally, implications for the education of nurse anesthetists and the future of clinical monitoring are visited.

MONITORING STANDARDS

Monitoring standards are published and reviewed by anesthesia professional associations so that minimal standards in the provision and monitoring of care can be recommended. Such standards are intended to provide guidance to anesthesia providers and healthcare facilities in evaluating quality care and developing and improving the safety of practice while educating the public regarding patient rights and expectations. Standard V of the AANA *Scope and Standards for Nurse Anesthesia Practice* outlines specific monitoring requirements necessary for compliance (Table 17-1).[4] The standards acknowledge the importance of vigilant monitoring as the basis of safety in anesthesia practice. In addition, the standards point out that the CRNA must constantly be in attendance of the patient until the responsibility for care can be safely transferred to another qualified healthcare provider. They further state that these are intended to be minimum requirements and should be exceeded as deemed necessary in the judgment of the anesthetist. In most cases, when certain monitoring modalities are not used, they must be at least immediately available. The AANA interpretation specifically indicates that alarm limit parameters and audible warning systems should be used, and a specific statement is made recommending the use of variable pitch alarms. The value of variable pitch commonly used in pulse oximetry equipment has been widely appreciated for its ability to provide information regarding subtle changes in oxygen saturation using the sense of hearing, prior to visualizing the monitor. Alarms are designed to protect the patient by alerting the practitioner that the individual is at increased risk and needs immediate assistance.

An area of concern related to electronic monitoring devices is a phenomenon referred to as *alarm fatigue*. Alarm fatigue can be defined as a type of human error occurring when a practitioner is desensitized to alarms or alerts.[5,6] The ideal alarm would be easy to localize and recognize. It would be evident despite other noises and alarms, yet would allow for effective communication between care providers. The ideal monitoring device would also elicit a minimal number of false alarms. Alarms in many medical devices fall short of the ideal and as a result are subject to being ignored or even disabled by the practitioner—a very dangerous practice. Biomedical specialists continue to develop and perfect alarms to improve their usefulness in alerting the clinician to significant changes in patient status.[7]

The ever changing and developing technologic capabilities warrant that these standards also allow for consideration of new monitoring modalities as they are introduced. It is important to note that the type of anesthetic given may influence the specific monitoring needed but should not be a factor in considering the level of vigilance or accessibility of advanced monitoring and interventional equipment.

TABLE 17-1 Scope and Standards for Nurse Anesthesia Practice

Standard V	
Monitor the patient's physiologic condition as appropriate for the type of anesthesia and specific patient needs	
Parameter	**Modifier**
Monitor ventilation continuously	Verify intubation of the trachea by auscultation, chest excursion, and confirmation of carbon dioxide in the expired gas; continuously monitor end-tidal carbon dioxide during controlled or assisted ventilation including any anesthesia or sedation technique requiring artificial airway support; use spirometry and ventilatory pressure monitors as indicated
Monitor oxygenation continuously	By clinical observation, pulse oximetry, and if indicated, arterial blood gas analysis
Monitor cardiovascular status continuously	Via electrocardiogram and heart sounds; record blood pressure and heart rate at least every 5 minutes
Monitor body temperature continuously	On all pediatric patients receiving general anesthesia and when indicated, on all other patients
Monitor neuromuscular function and status	When neuromuscular blocking agents are administered
Monitor and assess the patient positioning	Assess and institute protective measures

Adapted from the American Association of Nurse Anesthetists. *Scope and Standards for Nurse Anesthesia Practice*; 2010. Available at http://www.aana.com.

TABLE 17-2 Crisis Management Algorithm

Algorithm	**Descriptor**
C—Circulation, Color	Determine adequacy of circulation, check pulse, blood pressure; ECG notes oxygenation through assessment and oximetry
O—Oxygen, Oxygen analyzer	Check oxygen delivery system, hypoxic guard
V—Ventilation, Vaporizer	Ventilate by hand to assess breathing circuit and airway patency, assess chest excursion and auscultation; assess $ETco_2$; check vaporizer function
E—Endotracheal tube	Systematic assessment of ETT if used, including patency, seal, etc
R—Review monitors, Review equipment	Review all monitors in use, assure appropriate calibration and maintenance, review any and all equipment in contact with the patient
A—Airway	Check patency of the unintubated airway, assess for laryngospasm, foreign body, etc
B—Breathing	Assess pattern, rate, and depth of respirations; examine, auscultate, and review $ETco_2$ and pulse oximeter monitors
C—Circulation	Repeat assessment of circulation
D—Drugs	Review drugs given; consider needed pharmacologic intervention; consider possibility of medication administration error

Adapted from Runciman WB, Merry AF. Crises in clinical care: an approach to management. *Qual Safe Health Care*. 2005; 14(3):156-163.
ECG, Electrocardiogram; *$ETco_2$*, end-tidal carbon dioxide concentration; *ETT*, endotracheal tube.

SYSTEMATIC APPROACH TO MONITORING

A systematic, evidence-based process shown to be effective in reducing anesthetic morbidity and mortality should be the goal when planning appropriate monitoring to be used. As monitoring standards guide practice by prescribing minimums to be adhered to, other processes can be helpful in defining how monitoring should occur and which modalities should be used. In the spirit of learning from previous errors or untoward events, closed-claim studies can provide valuable insight into monitoring techniques and habits that could be useful in preventing future anesthesia mishaps. Incident monitoring systems and practices can be used to collect data for practitioners to use to develop safer processes as in the often referenced analogies made to the aviation industry.[8] In a manner of speaking, clinical monitoring can be thought of as a means to avoid critical incidents.

The act of administering anesthesia results in a physiologic response to the pharmacodynamics and pharmacokinetics of each substance given. The insult of the surgical or diagnostic procedure performed also results in a physiologic response. As such, observation of the human systems response is the monitoring of the pharmacology of the agents used and the physiology of the human system. As the science and process for quality assurance and improvement have evolved, much has been learned and written about the value of a systematic approach to the analysis of critical incidents and crisis management. The concepts used in quality assurance management are therefore easily applied to anesthesia monitoring because a primary function of the nurse anesthetist is to prevent or respond to critical incidents. A systematic approach to clinical monitoring provides a means of ensuring timely responses to physiologic changes presented by the patient.

Many algorithms and protocols have been written to guide the practitioner through the monitoring process and ensure thorough, vigilant observation. Simple, systematic approaches to crisis management are often focused on or derived from the common algorithm "ABC," representing airway, breathing, and circulation. In an anesthesia context, additional foci for monitoring can include color (i.e., cyanosis), oxygen and oxygen analyzers, ventilation, vaporizer or pump settings and status, endotracheal tube patency and placement, monitors and equipment, and drug effects, thereby expanding the crises response algorithm to COVERABCD (Table 17-2).[9] There is an enormous value in developing a systematic approach to monitoring. The habit sometimes referred to as "sweeping" the anesthesia field to visualize the patient, with the eyes following a path to the anesthesia machine via the airway and breathing circuit and progressing to the monitoring modalities used, has long been taught as a means of increasing vigilance and attention to detail.

Review of critical incidents has provided insight into how clinicians can enhance safety and prevent mishaps through their use of monitors with alarms. Closed-claims review of various databases supports the notion that vigilance remains a key point, and respiratory events are of particular concern.[10] It has been suggested that in cases in which anesthesia is provided outside of the operating room, (e.g., a rapidly growing practice in which monitoring may not be as focused as in a standard anesthetizing area), the number and severity of liability claims may be increased.[11] The well

known mantra of the ABCs—observing the Airway, Breathing (respiration), and Circulation—remains foremost and critical in anesthesia clinical monitoring. Monitoring drug effects completes the basic monitoring approach. The monitoring of cardiovascular circulation is addressed in Chapter 16. The monitoring of the neurologic system can be found in Chapter 18.

Airway Monitoring

Monitoring the airway includes the observance of gas exchange from the upper to lower airways. Assessment of airway patency is performed in very subtle yet essential ways. Ventilatory movement of the chest must be observed and the presence of any sign of airway obstruction such as retractions, or seesaw motion of the chest and abdomen, is noted. Seeing the presence of condensation in an airway device or clear mask can serve to indicate the presence of gas exchange. The sense of touch can be used to perceive subtle movement of air exchange felt on the hand of the anesthetist. The sense of smell can be the first aid in detecting a disconnected circuit or airway device when volatile agents are being used. Listening for the presence of abnormal airway sounds such as stridor is crucial in noting airway obstruction. The precordial stethoscope is a valuable tool in auscultating the presence or absence of airway exchange during all phases of the anesthetic, regardless of the type administered. Ensuring adequacy of ventilation, whether an endotracheal tube or laryngeal mask airway is in use, must include verification of placement by assessing breath sounds and chest expansion, as well as verification of the presence of carbon dioxide (CO_2) in the expired gas.[3] While failure to successfully intubate is problematic, failure to recognize misplacement is catastrophic.

Respiratory Monitoring: Ventilation

Monitoring respiratory parameters is aimed at evaluating both ventilation and oxygenation. The patient must be observed for adequate minute ventilation throughout the anesthetic course. At the most basic level, this is accomplished through visualization of chest excursion and auscultation of breath sounds. The value of the precordial or esophageal stethoscope is twofold: it provides continuous assurance that ventilation is occurring and can be used to detect changes in breath sounds. Assessing the respiratory rate and tidal volume (rate alone is not adequate to determine adequacy of ventilation) is crucial to ensuring adequacy of minute ventilation, as well as interpreting patient response to pharmacologic agents and surgical stimuli.

Skin and nail bed color should be observed as part of the whole patient-assessment picture; however, skin color changes alone are not a reliable measure of whether ventilation and oxygenation are adequate. Cyanosis is a late sign of anemia or hypoxia and can be difficult to assess accurately, given such variables as differences in lighting during certain procedures and lack of controls in comparisons of patients' coloring throughout the perioperative period to name a few. Besides physical assessment skills, monitoring the adequacy of ventilation must be done throughout the perioperative period, using multiple parameters. Several themes are evident that relate to safety and vigilance in monitoring when reviewing closed-claims studies for anesthesia incidents. The most prominent of these is the value of certain specific monitors and their alarms. These include pulse oximetry, end-tidal carbon dioxide measurement, oxygen analyzers, and disconnect alarms. Of equal importance is the users' ability to assure the proper function of these prior to administering an anesthetic.[10]

Carbon Dioxide Monitoring

The measurement of arterial blood gases to determine level of carbon dioxide provides direct measurement of ventilation and metabolic status, and the necessity of this action may be indicated at times. The means of measuring the carbon dioxide tension in the blood (Pa_{CO_2}) is based on hydrogen ion concentration because CO_2 reacts with water to produce hydrogen ions through a reversible reaction. This reaction yields carbonic acid, which dissociates to yield hydrogen and bicarbonate ions,[12] as shown in the following equation:

$$CO_2 + H_2O \leftrightarrow H_2CO_3^- \leftrightarrow H^+ + HCO_3^-$$

The production of carbonic acid also allows for the qualitative—and to a limited extent, quantitative—detection of the presence of carbon dioxide through the use of disposable end-tidal carbon dioxide (ET_{CO_2}) detector devices. These colorimetric devices react to changes in pH and display it as a color change. They are widely used in emergency settings to verify proper placement of an endotracheal tube.[13] Although these devices are sensitive enough to detect carbon dioxide quickly, a minimum of six breaths has been suggested to avoid misinterpretation. False positives may result from the detection of CO_2 from air forced into the stomach during mask ventilation or the presence of carbonated beverages or antacids in the stomach.[14]

The means to measure CO_2 level must be based on the patient's condition, the type of anesthetic administered, and the complexity of the surgical procedure. The continuous measurement of carbon dioxide in expired gas provides a practical, noninvasive, and accurate reflection of arterial blood carbon dioxide and is the most common means of monitoring carbon dioxide levels in the anesthesia setting. It is also a monitoring standard of care during general anesthesia, for the patient being ventilated or whose ventilations are being assisted. In addition, the ASA monitoring standards state that "during moderate or deep sedation the adequacy of ventilation shall be evaluated by continual observation of qualitative clinical signs and monitoring for the presence of exhaled carbon dioxide unless precluded or invalidated by the nature of the patient, procedure, or equipment."[3] Accuracy of ET_{CO_2} as a correlation with arterial carbon dioxide has been well documented. End-tidal CO_2 is said to be approximately 2 to 5 torr lower than arterial CO_2 in patients who have no cardiac or pulmonary abnormalities.[14] *Capnometry* is a term that encompasses all means of measuring carbon dioxide, whereas *capnography* refers to the recording of the measurement. The term *capnogram* is used to describe a continuous display of carbon dioxide during the phases of ventilation. The continuous measurement of ET_{CO_2} is accomplished through the use of infrared analysis. When a gas mixture containing more than one substance, (e.g., an exhaled gas sample) is analyzed, a quantitative measurement can be made to determine the proportional contents. Each gas in the mixture absorbs infrared radiation at a different wavelength. The amount of CO_2 is measured by detecting its absorbance at specific wavelengths and filtering the absorbance related to other component gases. Older monitors had difficulty distinguishing between nitrous oxide and CO_2, but this fault is corrected in current models.[12]

Sampling of ET_{CO_2} can be accomplished through either a nondiverting (also known as *mainstream*) or diverting (also known as *sidestream*) monitor. A nondiverting monitor measures gas directly within the breathing system. Gas passes through a wide-chambered sensor that fits over a connector between the anesthesia circuit and mask adapter. The sensor is connected to the monitor by a cable. Nondiverting monitors offer several advantages. They have

minimal sampling-time delays, use few disposable items, and do not require scavenging because gas is not removed from the system. Disadvantages include the inability to measure gases other than CO_2 and nitrous oxide, an increase in circuit deadspace by the adapter, and greater risk of interference by condensation and secretions. Also, because the sensor and cable are attached in proximity to the patient, the added weight may cause traction on the tube, increase the risk of circuit disconnect, and make sampling in a nonintubated patient difficult.

The other more commonly used CO_2 monitor type is the diverting monitor. The diverting monitor extracts gas from sample tubing attached near the patient end of the circuit and pumps it to the monitor. Disadvantages include the need for scavenging of sampled gases because they are removed from the circuit and some risk of contamination by condensation or secretions exists. Advantages of the diverting system include minimal increase in deadspace and versatility in gas analysis because the sample can also be sent to anesthetic agent monitors. In addition, the small, lightweight tubing can be adapted to sample awake, spontaneously breathing patients through the mouth, nares, or simple mask.[14]

It has become common to adapt the sampling line of a diverting $ETCO_2$ monitor to trace a capnogram in awake or sedated, spontaneously breathing patients receiving O_2 via simple mask or nasal cannula. Nasal cannula tubing already equipped with a sampling line is commercially available. It has been shown that sampling $ETCO_2$ in the spontaneously breathing patient's hypopharynx is reliable and accurate and that the exact position and use of supplemental O_2 flow will not affect reliability.[15] The use of $ETCO_2$ monitoring as a warning of hypoventilation or excess sedation has gained attention outside of the anesthesia setting. For example, $ETCO_2$ monitoring has been shown to be a more sensitive indicator of hypoventilation than clinical observation or pulse oximetry when used during sedation in the emergency department setting.[16] Other studies note the value of $ETCO_2$ monitoring during sedation as well and note the advantage over pulse oximetry alone in detecting hypoventilation in patients receiving supplemental O_2. It has been suggested that like pulse oximetry, $ETCO_2$ monitoring should be considered a standard of care for patients receiving sedation outside the operating room.[17]

End-Tidal Carbon Dioxide Capnography. Capnography can record CO_2 as a component of expired lung volume or as a measure of CO_2 alone throughout the phases of respiration plotted against time. Time capnography is most commonly used in the perioperative setting. Basic interpretation of the $ETCO_2$ capnogram is a necessary skill. The capnogram can differentiate between normal and abnormal patterns of ventilation that result from patient pathologies, anesthesia system problems, or unexpected patient responses during anesthesia.

The normal time capnogram can be recorded at varying speeds. A fast speed setting of approximately 12.5 mm/second allows interpretation of individual respiratory components and short-term changes, whereas a slow speed of approximately 25 mm/minute displays long-term changes.[18] Although no standard descriptions exist for the components of the capnogram, it is typically described as encompassing four basic phases (Figure 17-1). These phases are often displayed in a classic waveform shape best recorded during mechanical ventilation in an intubated patient. It is important to note that the basic shape of the wave form will vary depending on the mode of airway management used (endotracheal tube, laryngeal mask airway, simple mask, nasal cannula, etc.) as well as in comparison to the spontaneously breathing patient.

Although the shapes may vary, the represented phases apply universally. The first phase is the end of inspiration and very

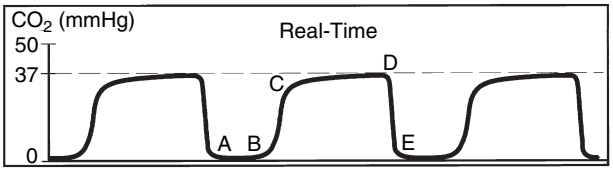

FIGURE **17-1** The four phases of a normal capnogram. *A-B* represents baseline; *B-C* represents expiratory upstroke; *C-D* represents expiratory plateau; *D* represents end-tidal concentration; and *D-E* represents descent to original baseline. (Courtesy Novametrix Medical Systems, Wallingford, Conn.)

beginning of expiration. Gas sampled at this point identifies the baseline. This sample comes from the anatomic deadspace and contains no CO_2. This portion in a normal capnogram should approximate zero. The second phase is the expiratory upstroke. Gas sampled represents a mix of deadspace and alveolar gas and thus records measurable CO_2. This phase represents the rapid passing of initial expired gas through the upper airways. The third phase represents the plateau and records alveolar emptying of CO_2. In the normal pulmonary measurement, the plateau is very nearly flat. This phase represents the longest duration of the measurement. $ETCO_2$ is measured at the end of the plateau just prior to the beginning of phase four. The fourth phase is displayed as the rapid decrease in CO_2 concentration of sampled gas as a result of inspiration of air or O_2. This downstroke returns the recorded CO_2 measurement to or very near to zero. Variations in the capnograph tracing can be very subtle and represent specific alterations in the ventilatory process. Some common deviations are worth noting. In the process of evaluating the capnogram, the anesthetist should note the respiratory rate, whether ventilation is spontaneous or mechanical, the value of measured end-expired CO_2, the shape of the recorded waveform, and the presence of additional respiratory efforts. Deviations from what is normally a close approximation of arterial CO_2 can occur. End-tidal CO_2 measurements may be inaccurate in the presence of significant ventilation and perfusion mismatching. When ventilation-to-perfusion ratio is large, the resultant increase in deadspace causes a low concentration of $ETCO_2$ overall.[19] In addition, small tidal volumes—reflecting inadequate alveolar ventilation—may produce $ETCO_2$ recordings that significantly underestimate arterial CO_2 levels. Some controversy exists as to the relative accuracy of capnography during laparoscopic procedures.[20]

After esophageal intubation, an initial, slight upstroke of carbon dioxide may be seen in those rare circumstances when carbon dioxide may be sampled from the stomach as mentioned previously in reference to disposable $ETCO_2$ detector devices. These CO_2 measurements are the result of excess air blown into the stomach during overzealous ventilation or a partially obstructed airway. Such a waveform will display for a very brief period and be followed by a measurement of zero. A waveform that fails to return to baseline during phases one and four indicates that rebreathing of carbon dioxide is occurring. This can be the result of inadequate fresh gas flow in the nonrebreathing system or a depleted or ineffective carbon dioxide absorber (Figure 17-2). Although this may be detected over time, it can be difficult to distinguish.

Sloping of the plateau phase represents a progressive prolongation of expiration. It is typically the result of either an obstruction of expired gas flow at some point along the airway or ventilation-perfusion mismatch (Figure 17-3). It also can be indicative of chronic obstructive lung disease because CO_2 is exhaled more slowly from diseased portions of the lungs (with more significant airway narrowing) than from areas with less severe narrowing.

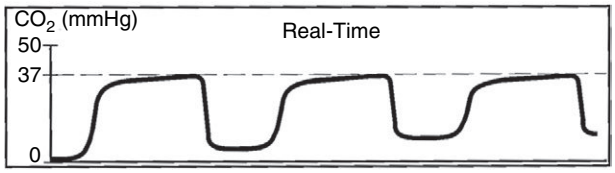

FIGURE **17-2** Elevation of the baseline indicates rebreathing. (Courtesy Novametrix Medical Systems, Wallingford, Conn.)

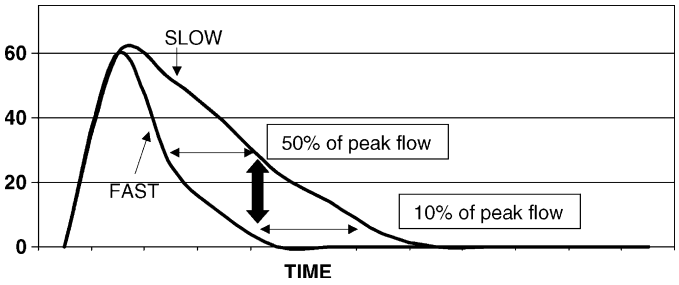

FIGURE **17-3** Inspiratory flow waveform demonstrating the effect of impedance on decay of flow. In a patient with stiff lungs (e.g., ARDS) and a fast time constant, flow decay is rapid. In the patient with normal compliance and high airway resistance (e.g., COPD), the flow decay is prolonged. In these two breaths with the same peak flow, 10% of the fast-time constant is equivalent to 50% of the slow-time constant. (From Branson RD. Functional principles of positive pressure ventilators: implications for patient-ventilator interaction. *Respir Care Clin N Am*. 11(2):2005; 119-145.)

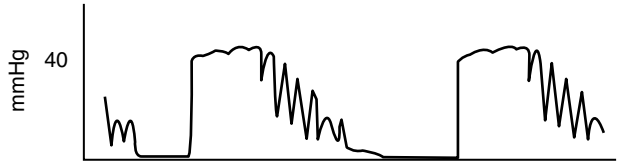

FIGURE **17-4** Cardiac oscillations occur as a result of contractions of the heart and great vessels. (From Miller RD. *Miller's Anesthesia*. 7th ed. Philadelphia: Churchill Livingstone; 2010.)

Plateau-phase sloping also can occur with kinking of the endotracheal tube (ETT) or any aspect of the circuit tubing. Changes in the waveform from baseline normal should always be evaluated to determine the cause and necessary interventions.

Regular, saw-tooth waves within the expiratory phase at a rate equal to the heart are likely the result of cardiac oscillations (Figure 17-4). This is the result of the contraction of the heart and great vessels forcing gas in and out of the lungs. This is a common occurrence in pediatric patients owing to the relative size of the heart to the thorax.

During mechanical ventilation in an anesthetized and/or paralyzed patient, spontaneous respiratory effort may be seen if the anesthetic depth is insufficient to prevent respiration or when inadequate muscle relaxation is present. The resultant capnogram is often referred to as *curare cleft* (Figure 17-5). This irregular asynchronous waveform may occur within the mechanically ventilated wave or separate from it. Causes of increased or decreased end-tidal carbon dioxide levels are noted in Box 17-1.

Transcutaneous Carbon Dioxide Monitoring. As previously stated, accurate analysis of carbon dioxide reflects adequacy of ventilation. Transcutaneous CO_2 monitoring does not provide immediate, breath by breath verification of endotracheal tube placement, so its use is not common in the anesthesia care realm. Nonetheless, it is a reliable, noninvasive means of CO_2 measurement and can

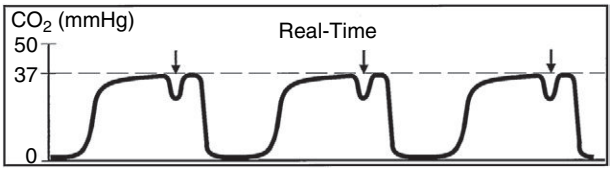

FIGURE **17-5** Clefts displayed as a spontaneous inspiration asynchronous with controlled ventilation. (Courtesy Novametrix Medical Systems, Wallingford, Conn.)

BOX 17-1

Causes of High and Low End-Tidal Carbon Dioxide

Increased PetCO2

Increased CO_2 delivery/production

Malignant hyperthermia, fever, sepsis, seizures, increased metabolic rate or skeletal muscle activity, bicarbonate administration/medication side effect, laparoscopic surgery, clamp/tourniquet release

Hypoventilation

COPD, neuromuscular paralysis or dysfunction, CNS depression, metabolic alkalosis (if spontaneously breathing), medication side effect

Equipment problems

CO_2 absorbent exhaustion, ventilator leak, rebreathing, malfunctioning inspiratory or expiratory valve

Decreased PetCO2

Decreased CO_2 delivery/production

Hypothermia, hypometabolism, pulmonary hypoperfusion, low cardiac output or arrest, pulmonary artery embolism, hemorrhage, hypotension, hypovolemia, V/Q mismatch or shunt, auto-PEEP, medication side effect

Hyperventilation

Pain/anxiety, awareness/"light" anesthesia, metabolic acidosis (if spontaneously breathing), medication side effect

Equipment problems

Ventilator disconnection, esophageal intubation, bronchial intubation, complete airway obstruction or apnea, sample line problems (kinks), endotracheal tube or laryngeal mask airway leaks

PetCO2, End-tidal carbon dioxide; CO_2, carbon dioxide; *COPD*, chronic obstructive pulmonary disease; *CNS*, central nervous system; *V/Q*, ventilation perfusion.
Adapted from Newmark JL, Sandberg WS. Noninvasive physiologic monitors. In Sandberg WS, et al, eds. *The MGH Textbook of Anesthetic Equipment*. Philadelphia: Saunders; 2011:137.

be useful in detecting hypoventilation. Transcutaneous CO_2 measurement is a noninvasive measure of Pa_{CO_2}. It can either estimate Pa_{CO_2} or determine trends in the measurement. Transcutaneous CO_2 monitoring can be accomplished using the same technology that is commonly used for measurement of oxygen saturation through pulse oximetry. The electrode used provides a measurement of CO_2 through measurement of H^+ ion change. Progress in the technical aspects of developing these monitors is beginning to be noted amongst researchers and clinicians.[21] Transcutaneous CO_2 monitors have gained notice for their value in analyzing analysis during circumstances in which ET_{CO_2} measurement may be inaccurate, as in the case of ventilation-perfusion mismatching. In

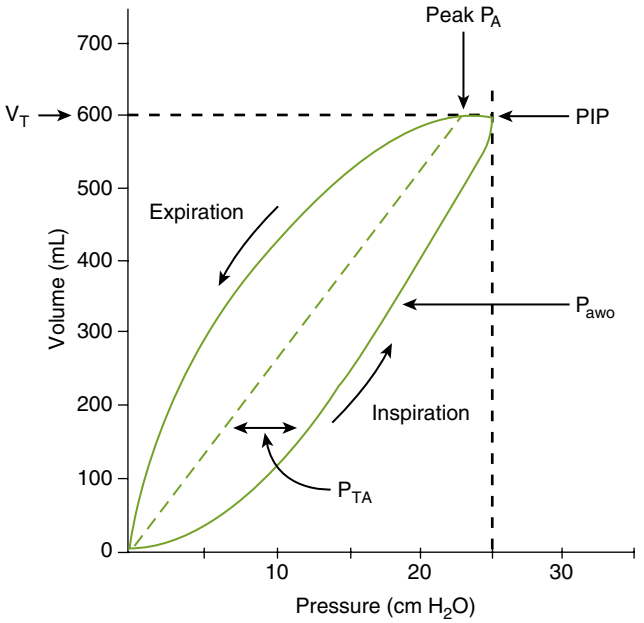

FIGURE **17-6** P-V loop showing the peak inspiratory pressure (PIP), pressure at the airway opening (Pawo), alveolar pressure (P_A), and transairway pressure (P_{TA}). (From Pilbeam SP, Cairo JM. *Mechanical Ventilation*. 4th ed. St. Louis: Mosby; 2006.)

such cases as severe obesity, which may affect ventilation-perfusion ratios as a result of reduced functional residual capacity, transcutaneous CO_2 monitoring may provide a more accurate estimate of arterial carbon dioxide than $ETCO_2$.[22] Transcutaneous carbon dioxide measurement may prove beneficial during one-lung anesthesia for thoracic surgery because it has been shown to provide a close correlation with arterial CO_2.[19] An added benefit of transcutaneous CO_2 measurement may be seen in monitoring the awake patient at risk of hypoventilation in whom $ETCO_2$ monitoring is impractical.

Flow, Volume, and Pressure Monitoring of Ventilation

Many modern anesthesia machines offer the ability to monitor spirometry loops. Observation of spirometry loops can provide rapid evaluation of changes in lung compliance and resistance. A spirometry loop is a graphic representation of a dynamic relationship between two respiratory variables: *flow and volume* or *pressure and volume*. Pressure-volume loops provide insight into lung compliance and show volume on a vertical axis and airway pressure on the horizontal axis (Figure 17-6). Flow-volume loops provide information on pulmonary resistance and show flow on the vertical axis and volume on the horizontal axis (Figure 17-7).

The forces that oppose lung expansion determine the compliance of the lung. In states of high compliance, minimal force is needed for expansion, and conversely, when compliance is low, higher force (pressure) is needed for lung expansion. Compliance is shown by a pressure-volume loop in Figure 17-6. The more upright, solid loop shows increased compliance in that greater volumes are achieved at lower pressures, as compared to the dotted loop showing decreased compliance, in that more pressure is needed to deliver the same tidal volume. Decreases in compliance will also show on a flow-volume loop as an increase in flow during exhalation and will have a higher peak and steep slope.[14] Decreases in compliance can occur as a result of pulmonary embolism, bronchoconstriction, pneumothorax, insufflation of the abdomen for laparoscopic surgery, or even inadequate muscle relaxation, to name a few causes. Compliance may be increased in emphysema, positive end-expiratory pressure (PEEP), or simply by resolving those factors that decrease compliance.[23]

Changes in resistance can also be detected by loop spirometry. An increase in resistance may occur when an endotracheal tube is kinked or blocked, when there is an airway obstruction, and when bronchoconstriction is seen. Mild bronchospasm may cause slight changes in the flow-volume loop, but as the spasm progresses, a decreased flow throughout exhalation can be seen. In a pressure-volume loop, increased resistance manifests as an increased pressure needed to deliver the same volume as that prior to the added resistance.[4]

Respiratory Monitoring: Oxygenation

While it may be a statement of the obvious, ensuring adequate oxygen delivery to the tissues is of paramount importance in the safe delivery of anesthesia. Monitoring of oxygenation follows the continuum of oxygen delivery from the source to the patient until distribution within the body. The anesthetist must evaluate the adequacy of the gas machine's delivery of O_2 and the efficiency of its delivery to the alveoli during ventilation. The anesthetist must be aware that oxygenation monitoring by itself only constitutes a part of the whole picture when considering the respiratory process. Hypoventilation, hypercapnia, and impending respiratory arrest can occur despite adequate oxygenation, particularly during the administration of supplemental O_2.[24]

Like ventilation monitoring, the means to ensure oxygenation uses multiple senses and technologies. Monitoring oxygenation starts with O_2 delivery analysis and is covered in depth elsewhere in the text. It is crucial to note that ensuring delivery of O_2 from the source does not ensure adequate uptake and distribution of O_2 on the part of the patient.

To assess the major aspects of acid-base balance and respiratory function including oxygenation, arterial blood gas (ABG) analysis is most helpful. Although the need for frequent sampling and analysis of ABG is dictated by the patient's physiologic status or surgical procedure, noninvasive, continuous monitoring of oxygenation through clinical observation and pulse oximetry is the standard of care[4] (see Table 17-1). Clinical observation parameters also include an assessment of skin color and temperature, nail-bed perfusion signs, assessment of depth and rate of respirations, auscultation of breath sounds, and assessment of upper airway patency.

Pulse Oximetry

The use of pulse oximetry has become commonplace in many healthcare settings, both inside and outside of critical care areas, and has proven valuable in detecting hypoxemia. Pulse oximetry measures heart rate and percent of oxygen saturation (SaO_2) of hemoglobin (Hgb) continuously and noninvasively. The technology involved in providing the transcutaneous measurement uses a spectrophotometer to determine SaO_2. Oxygenated Hgb absorbs infrared light at a different wavelength than unoxygenated Hgb. A light signal is emitted from one diode and transmitted through tissue, most commonly a finger, to an oppositely placed photosensitive diode that measures the amount of unabsorbed red light. Pulse oximeters can distinguish arterial from venous blood by measuring the change in transmitted light during pulsatile flow. The pulse oximeter converts the detected light to a plethysmographic signal that measures the drop in light intensity with each beat.[22,25,26]

Oxygen Saturation Physiology. To understand the measurement and significance of monitoring oxygen saturation via pulse oximetry, it is important to understand the physiology of oxygen

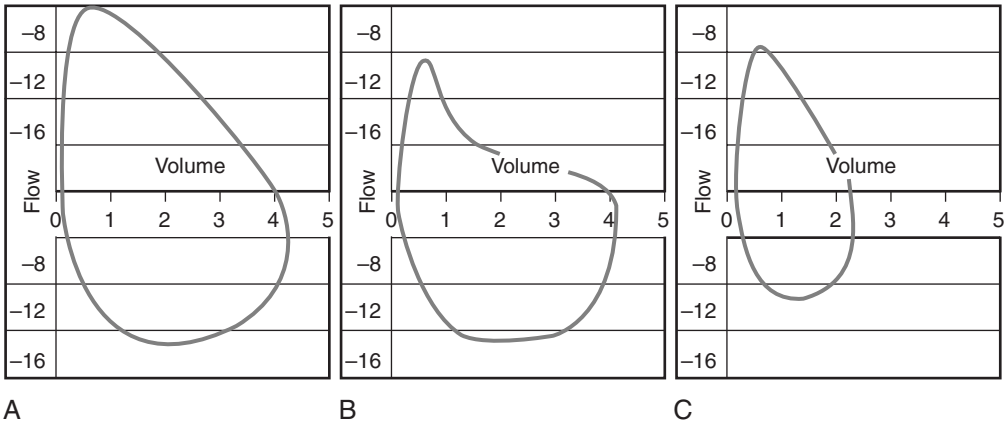

FIGURE **17-7** Flow-volume loop showing curves for normal (A), obstructive (B), and restrictive (C) lung disease. (From Rakel RE, Rakel DP. *Textbook of Family Medicine*. 8th ed. Philadelphia: Saunders; 2011.)

transport and the factors that influence its binding to and release from Hgb. This is expressed in the following equation.

$$Hgb + O_2 \leftrightarrow HgbO_2$$

The reversibility of the reaction allows for the release of O_2 to the tissues. Oxygen is transported throughout the body either physically dissolved in the blood or chemically combined with Hgb. The vast majority is carried bound to Hgb. As a result, the oxygen-carrying capacity is mainly dependent on the amount of Hgb. If varying concentrations of O_2 are added to a volume of blood, after allowing the mixture to equilibrate, the oxygen tension (P_{O_2}) of the gas can be measured. Because it is known that 0.003 mL of O_2 will dissolve in 100 mL of blood (at a P_{O_2} of 100 mmHg), the remaining O_2 bound to Hgb can be determined. In short, the P_{O_2} of the plasma determines the amount of O_2 that binds to Hgb. Like oxygen-carrying capacity, this is expressed in milliliters (mL) per 100 mL of blood.[27,28]

The proportion of Hgb bound to O_2 is expressed as percent saturation and excludes that amount dissolved in the blood. The relationship between oxygen tension and percent of oxygen saturation is illustrated in the oxyhemoglobin dissociation curve (Figure 17-8). It shows how the availability of O_2 (P_{O_2} in plasma) can affect the reversible reaction between O_2 and Hgb. The curve demonstrates that the amount of O_2 carried by Hgb (percent saturated) increases rapidly to a P_{O_2} of approximately 50 and slows thereafter, as displayed by a flattening of the curve. As blood travels to the systemic capillaries, the oxygenated Hgb releases O_2 to tissue with lower oxygen tension. In the 10 to 40 mmHg range, the curve is very steep. This demonstrates that small decreases in P_{O_2} can result in significant dissociation of O_2 for use by the tissue. For example, at a P_{O_2} of 40 mmHg, Hgb is approximately 75% saturated with O_2, whereas at 20 mmHg, only 32% is saturated. This relationship can be altered by a variety of physiologic changes. The result is a shift in the curve either to the *right*, indicating a more ready release of O_2 from Hgb at the tissue level, or to the *left*, indicating a greater attachment of O_2 to Hgb, thereby decreasing release to tissues (Table 17-3).[27,29]

Clinical Use of Pulse Oximetry. Although many studies regarding the use of pulse oximetry show conflicting impact on outcome, it should be intuitive that early detection and warning of hypoxemia, followed by appropriate interventions, will improve care. Pederson and colleagues[30] reviewed more than 21,000 perioperative patients and reported that the incidence of hypoxemia ranged from 1.5 to 3 times less in patients monitored

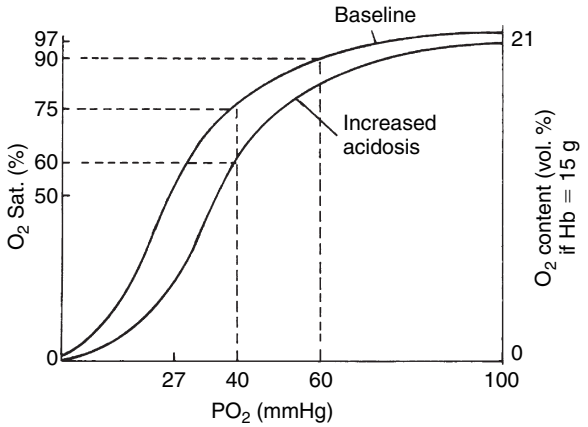

FIGURE **17-8** Oxyhemoglobin dissociation curve. (From Roberts JR, et al. *Clinical Procedures in Emergency Medicine*. 5th ed. Philadelphia: Saunders; 2009.)

TABLE 17-3 Factors Influencing the Oxyhemoglobin Dissociation Curve

Curve Shift to the Right	Curve Shift to the Left
Elevated CO_2	Decreased CO_2
Elevated temperature	Decreased temperature
Elevated levels of 2, 3-DPG	Decreased levels of 2, 3-DPG
Decreased pH, acidosis (elevated H^+ ions)	Elevated pH, alkalosis (decreased H^+ ions)

Adapted from Levitzky MG. *Pulmonary Physiology*. 7th ed. New York: McGraw-Hill; 2007.
2,3-DPG, 2,3-Diphosphoglycerate; *H^+*, hydrogen.

with pulse oximetry. Perhaps one of the greatest benefits of pulse oximetry is in its simplicity. The pulse oximeter is calibrated by the manufacturer and needs little or no further maintenance. It is basic to apply, and ongoing product development has made the device quite portable and durable. Its efficiency in measuring O_2 saturation has been shown to be accurate within 2% when oxygen saturation is between 80% to 100% and approximately 5% when saturation falls below 80%.[5]

Despite the qualities of pulse oximetry, it is essential to understand the optimal use and limitations. Pulse oximeters can use a

variety of sensor types applied to the body. The finger probe is the most commonly used and is available as a reusable clip-on device or disposable stick-on probe. The finger probe is often used successfully on the toe as well, particularly in the pediatric population. One common problem with pulse oximeter monitoring is motion artifact.[31] Although monitors have been improved since their development, motion artifact can still be problematic. Using alternative sites can be helpful. Forehead, ear, or nose probes can be used with comparable accuracy and reliability.[14,32] The site of application of the pulse oximeter probe should be assessed at reasonable intervals during particularly long periods of use and changed as needed to avoid skin irritation or ischemia because prolonged application of a clip-on probe could potentially compromise perfusion. Another common problem associated with inaccurate measurement or sensor difficulties with pulse oximeter monitoring is the vasoconstriction state that results from cold temperatures or inadequate circulation. During such circumstances, measurement may be improved by using oximeter sites closer to the central circulation and away from the periphery, such as the forehead, nose, or ear.[32-34] Much discussion has surrounded whether the presence of nail polish affects pulse oximeter measurement. Some authors have noted that the presence of nail polish, particularly certain colors, will cause artifact and/or inaccurate measurements. More recent studies suggest that improved monitor sensitivity has virtually eliminated any effect nail polish might once have had on pulse oximetry readings.[35,36] A less commonly occurring but still problematic issue is the presence of abnormal hemoglobin. For example, methemoglobin absorbs light equally to oxyhemoglobin. As a result, pulse oximeter measurements are falsely underestimated when oxygen saturation is above 85% and overestimated when oxygen saturation is below 85%. Likewise, abnormally high levels of carboxyhemoglobin can cause the oximeter to overestimate oxygen saturation. Sickle cell anemia and other rarer forms of anemia may also impact the accuracy of pulse oximeter measurements. Injectable dyes for diagnostic use, such as methylene blue or indigo carmine, will result in a significant, but transient, decrease in the measured oxygen saturation by pulse oximetry.[14] This is because the presence of the dye alters the absorption of infrared light. Technology available on some pulse oximeters enables the monitor to distinguish between normal Hgb and carboxyhemoglobin or methemoglobin. In fact, oximetry principles in these monitors can quantitatively measure amounts of these variant forms of hemoglobin.[37]

The versatility and accuracy of pulse oximeters has sparked their use for other diagnostic purposes such as assisting in the measurement of systolic blood pressure by inflating a cuff and noting the point at which the pulse oximeter wave form is obliterated. The pulse oximeter may be useful in assisting in the location of a vessel by occluding the anatomy distal to the probe until that point is reached at which the waveform is lost.[14] Because of their sensitivity to changes in vascular supply, pulse oximeters have been used to determine the presence of vascular disease, such as in diabetic patients.[38] Changes in sympathetic tone are perceived by pulse oximetry. Vessels of the arm are subject to changes in autonomic tone and pulse oximetry has demonstrated an ability to detect the subtle changes in blood flow that occur during regional anesthesia, thereby indirectly indicating the degree of regional blockade. Research suggests that circulation to the earlobe is not greatly affected by changes in sympathetic tone but rather by changes in pulse pressure. As a result, pulse oximetry measured at the earlobe may be a sensitive indicator of systemic circulation and possibly stroke volume.[33] The degree and sensitivity to which individual monitors perform under circumstances of hypothermia or circulatory changes may vary by manufacturer.[39]

The practice of closely monitoring respiration (ventilation and oxygenation) through the measurement of carbon dioxide and oxygen saturation during the anesthetic period has proved to be priceless in ensuring safe care. As technology has advanced to allow reliable, affordable, noninvasive measurement, this practice is being adopted in other settings. Combined sensors that measure both carbon dioxide and oxygen saturation are available and may prove valuable in managing patients at risk for respiratory complications such as during the postoperative period or whenever potent opiates are administered.[24,40,41]

Temperature Monitoring

The standards of care from both the AANA and the ASA support the notion that the ability to monitor the patients' body temperature is essential.[3,4] Temperature monitoring alerts the anesthetist to hyperthermia, and as is more commonly the case, hypothermia. Despite clinical standards and the known physiology, hypothermia is an occurrence that is often underestimated in significance. The American Society of Perianesthesia Nurses (ASPN) defines hypothermia as a core temperature of less than 36° C (96.8° F). It has been reported that approximately 70% of postoperative patients experience some degree of hypothermia while other estimates reach as much as 90% of surgical patients experience some adverse effect of hypothermia.[42,43] Risks of hypothermia include wound infection and delayed healing, increased O_2 consumption through shivering, increased risk of cardiovascular incidents and myocardial infarction, and increased rate of sickling in sickle cell patients.[5,43,44] In addition, hypothermic patients have been shown to have a prolonged stay in the postanesthesia care unit, thus increasing the cost of care during the perioperative period.[42,45]

Appropriate and aggressive means of maintaining normothermia intraoperatively should be instituted, and a keystone to implementation of these interventions is temperature monitoring. National quality improvement initiatives supported by the Centers for Medicare and Medicaid Services have partnered with healthcare organizations and accrediting bodies to promote best practices aimed at improving surgical care. These initiatives have identified essential factors in preventing postoperative complications. Not the least of these identified areas of care is centered on maintenance of normothermia.[45] An understanding of the potential causes of variations in core body temperature is valuable in appreciating the importance of temperature monitoring.

Thermoregulation

Body temperature is tightly regulated through a process termed *thermoregulation*. Thermoregulation occurs through a three-phase process: afferent thermal sensing, central regulation or control, and efferent responses. Peripheral sensors send thermal information via tracts in the anterior spinal cord, such as the spinothalamic tract, to various regions of the brain including the hypothalamus. Behavioral responses to changes in temperature (i.e., layering clothing, seeking warmth) are the most important aspect of thermoregulation in persons who are awake; however, anesthesia prevents patients from responding accordingly. As a result, they must rely on autonomic efferent responses such as shivering, vasoconstriction, and sweating. General anesthetics do not have significant effects on sweating but do reduce shivering and vasoconstriction thresholds. Neuraxial anesthesia also affects thermoregulatory control, resulting in hypothermia.[46]

Normothermia can be defined as a body temperature of 37° C. It is important to note that there is typically a variance between

TABLE 17-4 Comparisons of Body Temperature Monitoring Sites

Monitoring Site	Advantages	Disadvantages
Bladder	Reflects core temperature Correlates accurately with other core sites	Invasive—requires urinary catheter placement Risk of UTI
Pulmonary artery	Reflects core temperature Correlates accurately with other core sites	Invasive—requires PA catheter Not reliable during open chest procedures
Esophageal	Considered by most authors to reflect core temperature Ease of insertion	Slight potential for oral or esophageal trauma, bleeding Not useful in awake patients Inaccurate if placed too close to the stomach
Nasopharynx	Considered by most authors to reflect core temperature Ease of insertion	Potential for nasopharyngeal trauma, bleeding Less useful in awake patients Inaccurate if breathing through nares
Tympanic	Considered by most authors to reflect core temperature Accurate if contact probe is used Ease of insertion Possible for awake patients	Slight potential for tympanic membrane trauma Possible to push ear wax from canal to membrane Infrared device less accurate
Axillary	Safe, noninvasive, ease of placement Reasonable correlation with core in adducted arm when placed close to axillary artery	Not a direct measurement of core temperature Influenced by IV fluids Easily dislodged

Modified from Dorsch JA, Dorsch SF. *Understanding Anesthesia Equipment*. 5th ed. Philadelphia: LWW; 2008; Langham GE, et al. Noninvasive temperature monitoring in postanesthesia care units. *Anesthesiology*. 2009;111(1):90-96; Sessler DI. Temperature monitoring and perioperative thermoregulation. *Anesthesiology*. 2008;109(2):318-338; Lenhardt R. Monitoring and thermal management. *Best Pract Res Clin Anaesthesiol*. 2003;17(4):569-581.

PA, Pulmonary artery; *UTI*, urinary tract infection.

core and peripheral temperatures. This is key to appreciating the value of core versus peripheral temperature measurement.[42]

Hyperthermia or core temperatures exceeding 38° C, can be seen intraoperatively. The genetic predisposition to drug-induced malignant hyperthermia is well documented. Other causes of fever, such as infection or hypermetabolic states, typically are not seen in patients electively brought to surgery. Certain recreational drugs such as amphetamines, Ecstasy, or cocaine can raise the body temperature through an increased rate of metabolism.[47] Drugs such as atropine can inhibit the sweating response, resulting in impaired regulatory response and a rise in the core temperature. In the anesthesia setting these effects are typically overshadowed by the multiple factors in place that serve to lower core temperature.

Hypothermia, or core temperature below 36° C, occurs for multiple reasons. Upon entering many operating rooms, one cause of hypothermia becomes obvious to anyone, especially the patient: the ambient room temperature. Reports suggest that the greatest amount of heat loss occurs during the first hour in the perioperative setting and that patients in rooms at a temperature of 21° C will all develop hypothermia. Radiant heat loss, or that transfer of body heat into a cooler environment, accounts for the majority of heat loss in the patient undergoing surgery. This is followed by evaporative loss from liquids on the skin, such as from cleansing or perspiration or through the expiration of warm, moist air. In addition, convective heat loss (through moving cool air) and conductive heat loss (through contact with a cooler object such as an operating room table) contribute. Redistribution of lower-temperature blood from the vasodilated, anesthetized periphery to the central compartment also accounts for significant heat loss.[42,48] General and regional anesthesia inhibit thermoregulation and cause significant vasodilation such that temperature monitoring is warranted. During local anesthesia or sedation, temperature monitoring should be considered under circumstances in which the patient is at risk of hypothermia and should, at the very least, always be immediately available. It is important to note that normal core body temperature can vary between individuals as well as within individuals at different points within their circadian rhythms.[47] As a result, monitoring the patients' temperature is most beneficial when done continuously rather than intermittently and is most valuable when evaluated for trends.

Temperature Monitoring Modalities. Temperature is an important parameter in the complete monitoring of homeostasis in the perioperative period. The AANA and ASA practice standards allow for some discretion on the part of the anesthesia provider in deciding under what circumstances temperature monitoring should occur. The ASA states that body temperature monitoring should occur whenever significant changes in temperature are "intended, anticipated, or suspected." The AANA states that temperature should be monitored "on all pediatric patients receiving general anesthesia and when indicated, on all other patients."[3,4]

To ensure monitoring is done and active warming strategies employed, it is essential that the anesthetist be well aware of the factors that place patients at risk for perioperative hypothermia. Some of these risk factors include high ASA status, lengthy or involved surgical procedures, combined epidural and general anesthesia, surgery of long duration, elderly patients, and those with lean body mass. Interestingly, another identified risk factor for hypothermia is failure to monitor temperature. Protective factors of increased body weight, higher preoperative temperature, and warmer rooms were noted to help maintain normothermia.[49,50]

Technology used for temperature monitoring varies often by site measured. Thermistor, thermocouple, and platinum wire devices are frequently used with electronic monitors and have shown to be accurate and reliable. In addition, liquid crystal temperature monitors have been employed for skin temperature monitoring. Although these are noninvasive and convenient, they lack specific accuracy both in measurement and in interpretation between readings by separate observers.[14]

There has been some debate as far as how best to measure temperature, and indeed, each site has certain advantages and disadvantages (Table 17-4). The sense of touch is not reliable to

assess the patients' temperature, but the sensation of being uncomfortable in a cold operating room can serve as an alert that the patient is most likely cold as well and would benefit from temperature monitoring and warming modalities. Skin temperature measurement is convenient and noninvasive; however, its accuracy as a reflection of core body temperature is unreliable. The use of temporal artery temperature monitoring has become a popular modality. Temporal artery temperature measurements use infrared technology to measure blood temperature close to the surface with a device swiped across the forehead and down along the temporal artery. Some studies suggest this approximates oral and axillary temperatures reasonably close; however, others question their accuracy.[46,51]

Core temperature monitoring is believed to be the most reflective of thermal status in humans. This includes temperature monitoring at the tympanic membrane, distal esophagus, nasopharynx, or pulmonary artery.[46] When considering sites for core temperature monitoring, the Society for Critical Care Medicine's Fever Task Force concluded that the intravenous or bladder thermistor measures core temperature most accurately. They further state that the electronic probe measurement orally or by rectum is also reliable.[52] The type of surgery may play an important role in determining the optimal location for temperature monitoring. For example, in liver transplantation, bladder temperature has been shown to closely approximate pulmonary artery temperature measurements. Esophageal monitoring may be less reflective of core temperature during open heart surgery because of the exposed thoracic cavity. For many surgeries the tympanic membrane may be considered an ideal site, particularly because of its close proximity to the brain, therefore providing an accurate reflection of brain temperature. It should be noted, however, that tympanic membrane temperature measurement using aural probes with thermocouples provides this reliable assessment as opposed to the popular but less accurate use of infrared technology.[53]

ADDITIONAL MONITORING ISSUES

Monitoring for Procedures Outside of the Operating Room

As healthcare delivery and technology have changed, so has the role of the anesthetist. One area of change is the location in which anesthesia is delivered. It has become common administer all forms of anesthesia in areas outside of the traditional operating room setting. Multiple factors could be anticipated to increase anesthesia risk outside of an operating room. These include decreased availability of anesthesia personnel, less adjunct equipment, and unfamiliarity with supportive staff and settings. Procedures and settings often involve risk of allergic reactions to radiologic dyes, sharing of access to airway, and (in general) support staff with less experience with the anesthetized patient.

There is a growing need for studies of anesthesia morbidity and mortality as they relate to setting. A review of the ASA closed-claims database was done by Robbertze and colleagues[11] to assess for trends and look for insight into how to best provide anesthesia in these remote settings. Reviewers noted that anesthesia claims in these settings had a higher severity of injury and more often demonstrated that anesthesia was administered below the accepted standard level of care. The most common mechanism of injury was inadequate oxygenation or ventilation. Close review of these cases emphasizes that monitoring standards during anesthesia administered outside of the operating room must never be lower than what one would otherwise use. In fact, the circumstances may necessitate even closer vigilance. Frequent review and refinement of airway management skills is crucial in caring for patients in these settings. Focused attention and pressure is being applied in many areas to recognize and prevent the dangerous effects of potent opioids and other sedative drugs given for pain and procedural sedation. Emphasis should be placed on ensuring adequate ventilation and oxygenation through close visualization, monitoring of $ETCO_2$, and pulse oximetry.[24] Education, training, and certification are crucial for nonanesthesia nurses, physicians, or other providers involved in the administration of sedation in the absence of a nurse anesthetist or anesthesiologist. It behooves a healthcare facility to have strict policies in place, and such policies should be reviewed by the anesthesia providers.

ANESTHESIA EDUCATION AND PATIENT MONITORING

Teaching clinical monitoring begins in the classroom and is reinforced and emphasized in the clinical learning environment. As with all aspects of anesthesia education, teaching the art and science of clinical monitoring of the patient must be well thought out. Many educational programs and anesthesia departments use some form of simulation-based education as a supplement to clinical experience. Simulation learning is designed to give additional interactive practice and can also serve to review critical incidents and adverse events. Research offers evidence that debriefing following the simulated event is of value.[54,55] The use of simulated clinical experience can assist in developing critical decision-making skills through repetition. It is worth noting that although the simulated experience can measure response, a certain lack of realism occurs because of the sense of anticipation of the soon-to-be-designed event. As a result, a level of "hypervigilance" can occur, masking the true habits of the learner.[56]

A part of vigilance in monitoring lies in developing habits that promote frequent, almost ritualistic, patterns of assessment and visualization. Many students have a tendency to first focus on the electronic devices while forgetting the ongoing physical assessment of the patient. It is the role of the instructor to promote affective routines by explaining the underlying rationale, as well as by example. Another important part of learning to closely monitor the patient is training the senses to notice changes in the clinical picture. Every anesthetist should be able to discern when the changing audible tones of the pulsatile measurement of the pulse oximeter monitor indicate decreasing oxygen saturation. One should rapidly recognize the subtle development of abnormal airway sounds heard through a precordial stethoscope. These are only several of the basic clinical skills essential to anesthesia practice, and the anesthesia student requires time, experience, and appropriate habits to hone them.

Beyond learning the use and interpretation of monitoring methods, the student must also learn to appreciate the potential artifacts that can occur during electronic measurement. Because artifacts can result in false alarms, there exists the potential to ignore important alarms if their validity is uncertain. The student and experienced provider must learn to assimilate all data to make the right interpretation.[57]

FUTURE OF CLINICAL MONITORING

As developments in science allow for improved accuracy, reliability, portability, and ease of use of monitoring devices, undoubtedly the applications will expand. This is a prediction that has been written many times for many years. Modalities such as cardiac output monitoring were once only estimated by invasive techniques but are now frequently monitored noninvasively.

Closer monitoring of metabolic processes such as oxygen uptake or analysis of autonomic nervous system responses through noninvasive means will likely find a place in anesthesia settings as they develop.[58,59] The trend of moving toward electronic medical record keeping will impact the type of monitoring interfaces as well as the documentation of measurements. Although the accuracy and usefulness of these systems are a source of debate, it is likely that there reliability will improve. Automated anesthesia record systems have proved valuable in ways that include avoiding and defending medical malpractice claims.[60]

Advancements in monitoring alarm systems and display capabilities may prove valuable. Continuous auditory and integrated visual displays, including head mounted screens, have been tested and shown to shorten time to response; however, they may bring with them detrimental effects to visual fields and increase noise levels in the operating room.[61,62]

Although the availability of devices and advancements in monitoring capabilities may be an ever-present reality, another harsh reality is the cost associated with obtaining and using them. As healthcare delivery costs continue to increase, there will also be continued pressure to use these resources wisely. Outcome data are crucial to justifying the expense of keeping up with technology. Simply displaying patient-related data for the sake of defining physiologic or disease states without directly benefiting the patient will not justify the potential risk to the patient as well. [63]

The importance of the human factor in anesthesia delivery and monitoring does not appear to be replaceable any time soon. While new devices may prove to be useful tools, it is imperative that the anesthetist remain vigilant and well informed as to their proper use and interpretation. Although studies may be published to demonstrate the capabilities of electronic devices, practitioners continue to fall back on the value of the human senses—as is the case with the simple precordial stethoscope in perceiving apnea or other events—and emphasize the importance of learning to use and interpret them appropriately.[64]

SUMMARY

Clinical monitoring is a human skill that uses all of the senses. The importance of maintaining adequate ventilation and oxygenation has been underscored in reviews of closed-claim studies, thereby emphasizing the need for vigilant, continuous monitoring of these parameters in the patient receiving anesthesia. Of all monitoring modalities, ET_{CO_2} and pulse oximetry have been shown to be of particular value. Hypothermia is an all-too common occurrence under anesthesia, and management must center on prudent temperature monitoring. Clinical standards of care, as developed by the recognized professional anesthesia organization, must be adhered to continuously and reevaluated frequently. Outcome studies are warranted to justify the use of monitoring modalities, and the potential benefits must outweigh the potential risks.

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Clinical Monitoring III

Neurologic System

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CHAPTER 18

The practice of anesthesia requires constant vigilance and evaluation of the patient. Historically, early anesthetists such as John Snow and Arthur Guedel proposed the use of clinical and neurologic signs to evaluate and determine the depth of anesthesia. Snow described the "five stages of narcotism" for chloroform anesthesia.[1] Guedel further refined these signs of anesthesia by developing a table of "clinical signs and stages of anesthesia" the patient passes through during anesthesia.[2] Guedel used neurologic signs such as respiratory rate and rhythm, ocular movement, pupillary size, and reflexes to evaluate the depth of ether anesthesia.[1,2]

Today, the practice of anesthesia incorporates sophisticated technology for neurologic monitoring. The administration of a variety of drugs for anesthesia makes it impractical to depend solely on Snow's or Guedel's clinical signs for assessing anesthetic levels or neurologic function. Monitoring the neurologic status of a patient demands a thorough knowledge of the modern devices used and the skills needed to navigate a rapidly changing clinical environment. Goals for monitoring the neurologic system include the following:

1. Possessing a thorough knowledge of the monitors and modalities available for neurologic monitoring
2. Selecting appropriate neurologic monitor(s) for data acquisition and patient management
3. Understanding the various pathologic and anesthetic effects on patients' response with neurologic monitors
4. Managing neurologic changes during periods of surgical stimulation
5. Recognizing data changes that reflect neurologic changes and ischemia

The neurophysiologic parameters of interest that are monitored during surgery include brain function, blood flow, and metabolism. Monitoring of function is performed by measurement of electrical activity in the brain by means of electroencephalography (EEG), sensory and motor evoked potentials (EPs), and electromyography (EMG). Monitoring of blood flow/pressure is achieved by nitrous oxide wash-in, radioactive xenon clearance, laser Doppler blood flow, and transcranial Doppler sonography. Intracranial pressure can be determined by means of intraventricular catheters, fiberoptic intraparenchymal catheters, subarachnoid bolts, and epidural catheters. Lastly, brain metabolism can be measured either through invasive techniques such as placement of intracerebral Po2 electrodes or noninvasive techniques, such as transcranial cerebral oximetry and jugular venous oximetry.[3] Select methods for monitoring neurologic functions are given in Box 18-1.

This chapter examines the monitors currently used in clinical practice and managing the neurologic function of patients during the perianesthetic period. Brain monitoring methods and their indications, advantages, and disadvantages are noted in Table 18-1.

INTRACRANIAL PRESSURES AND JUGULAR VENOUS OXYGENATION

Intracranial pressure (ICP) monitoring has been successfully used for a number of years; ICP measurement reflects the pressure in the intracranial vault. The ICP changes with an increased volume of fluid as a result of edema or intravascular volume or the presence of a tissue mass, as with a tumor, in the cranium. The normal ICP ranges from 1 to 15 mm H_2O depending on position and normal cerebral vascular compliance. The ICP is directly related to the intrathoracic pressure and changes dramatically with coughing or increased intrathoracic pressures.

Recently the ICP, in conjunction with the jugular venous oxygenation ($SjvO_2$) monitoring, has been used to evaluate intracranial injury with some success. A $SjvO_2$ that ranges between 55% and 75% has been found to be a reasonable predictor of positive outcomes for traumatic brain injury (TBI) if the ICP is also maintained within a normal range. Those patients with a $SjvO_2$ less than 55% or above 75% and an elevated ICP had poor outcomes.[4,5]

ELECTROENCEPHALOGRAM

Normal EEG

The brain is an electrochemical organ generating electrical signals in a specific pattern. The electrical activity displayed through an EEG is sometimes called *electrical brainwaves*. The EEG is actually a measurement of differences in electrical potentials in groups of neurons between brain regions rather than the brain emitting electrical waves.[6] Electrodes used to produce the EEG are placed

BOX 18-1

Specialized Methods for Neurologic Monitoring

- EEG—electroencephalogram
- SSEP—somatosensory evoked potential
- MEP—motor evoked potential
- VEP—visual evoked potential
- BAEP—brainstem auditory evoked potential
- BIS—bispectral index
- PSI—patient state index
- NIRS—near-infrared spectroscopy
- EMG—electromyography
- TCD—transcranial Doppler (sonography or laser blood flow)
- ICP—intracranial pressure (intraventricular catheters, fiberoptic intraparenchymal catheters, subarachnoid bolts, and epidural catheters)
- Brain metabolism (intracerebral oxygen electrodes, transcranial cerebral oximetry and jugular venous oximetry [$Sjvo_2$])
- Bedside xenon cerebral blood flow

on the patient in a standardized sequential configuration (or montage) that examines known electrical potentials. This configuration was internationally standardized by Jasper in 1958 as the 10-20 system and is usually used to record the spontaneous EEG. With this system, 21 electrodes are placed on the surface of the scalp. The positions of the electrodes are determined by following three primary reference points: (1) the *nasal-frontal angle*, which is the depression at the top of the nose; (2) the level aligning with the eyes; and (3) the *inion*, which is the bony lump at the base of the skull on the midline at the back of the head. These reference points allow the practitioner to measure the skull perimeters in the transverse and median planes. Electrode locations are determined by dividing these perimeters into 10% and 20% intervals.[6] Freeman[7] suggested that the electrodes should be placed in areas that emit similar signals to concentrate and better record the electrical activity.

Generally, the basic parameters of the EEG include frequency, amplitude, shape (amplitude and shape constitute morphology of the wave), and time of each of these electrical discharges. The waveforms are then arranged in the following manner. Four common types of brainwaves are noted on the EEG; they are alpha, beta, delta, and theta waves. There are also several variants or subgroups of waves noted during specific activities. Some of these waveform variants are gamma, mu, and lambda waves. Gamma waves are typically seen with high-order activity such as problem solving and analytic thinking. The amplitude of the mu wave is about one half that of the beta wave and is seen more frequently over the motor areas of the brain.[8-10] Lambda waves occur in the awake

TABLE 18-1 Brain Monitoring Methods

Method	Spatial Resolution	Temporal Resolution	Purpose	Advantages	Disadvantages
ICP	Global	Continuous	Measure intracranial compliance	Reliable Quantitative Allows monitoring of CPP	Invasive Risk of infection Risk of hemorrhage
Jugular oximetry ($SjvO_2$)	Global	Continuous	Measure adequacy of hemispheric oxygenation	Quantitative Allows monitoring of $AVDo_2$ and O_2ER	Susceptible to artifacts Local complications (e.g., infection, thrombosis)
EEG	Global	Continuous	Monitoring electrical brain activity Detection of seizures	Technique well standardized Only method to diagnose nonconvulsive seizures	Qualitative Relatively insensitive to secondary insults
SSEP	Global	Continuous	Monitoring integrity of sensory pathways	Technique well standardized Simple	Qualitative Fairly insensitive to secondary insults
MEP TES-MEP	Global	Continuous	Monitoring integrity of motor pathways	Technique well standardized Multimodality monitoring when combined with SSEP (the standard for spinal surgery)	Fairly insensitive to secondary insults
Bedside Xe-133 CBF	Regional	Discontinuous	Measure hemispheric CBF	Quantitative	Only accurate if radiotracer injected into carotid artery Radioactivity
Laser Doppler flowmetry	Local	Continuous	Measure cortical CBF	Accurate Dynamic information	Qualitative Invasive Susceptible to artifacts Only monitors 1-2 mm^3 of tissue
Thermal diffusion flowmetry	Local	Continuous	Measure cortical CBF	Simple Dynamic information	Qualitative Invasive Monitors small volume of tissue
TCD	Regional	Continuous	Measure CBF velocities	Simple Noninvasive Allows measuring PI, VMR	Qualitative and indirect assessment of CBF Difficult to keep probes in place
Brain tissue Po_2	Local	Continuous	Measure cerebral oxygenation	Quantitative Sensitive Probes also measure brain temperature	Invasive Susceptible to artifacts Monitors small volume of tissue
NIRS	Local	Continuous	Measure cerebral oxygenation	Noninvasive	Measures only relative changes Susceptible to artifacts
Microdialysis	Local	Discontinuous	Measure cerebral metabolism	Sensitive Quantitative	Invasive Complicated technique Labor intensive Unclear which is the best parameter to monitor

$AVDo_2$, Arteriovenous oxygen difference; *CBF*, cerebral blood flow; *CPP*, cerebral perfusion pressure; *EEG*, electroencephalogram; *ICP*, intracranial pressure; *NIRS*, near-infrared spectroscopy; *O_2ER*, oxygen extraction rate; *PI*, pulsatility index; *Po_2*, partial pressure of oxygen; *TCD*, transcranial Doppler; *SSEP*, somatosensory evoked potentials; *MEP*, motor evoked potentials; TES-MEP, transcranial electrical stimulation motor evoked potentials; *VMR*, vasomotor reactivity.

Adapted from Rabinstein AA. Principles of neurointensive care. In Daroff et al, eds. *Bradley's Neurology in Clinical Practice*. 6th ed. Philadelphia: Saunders; 2012;805.

patient and are usually present when staring, reading, or looking at objects for long periods, as happens with videogames and TV.[11] It can be difficult to distinguish artifact and normal variations of the EEG from the four common types of known brainwaves.[12-14]

The head and much of the scalp may be inaccessible during intracranial surgical procedures so the standard 16-channel EEG is rarely used. Intraoperative monitoring during craniotomy is usually accomplished with a 2- to 4-channel recording, with computer processing to simplify the interpretation. To interpret an EEG properly, it is necessary to remember that an EEG reflects how "awake" or metabolically active the brain is. Electrical activity in the brain is a process that requires energy that is dependent on certain substrates, such as oxygen or glucose. Depression of EEG activity and characteristic changes in the EEG can be seen with reduction in cerebral blood flow, oxygen, or glucose delivery. During an awake-state, the high-frequency and low-amplitude beta waves are most prominent. There is a transient increase in the beta waves with the onset of ischemia or hypoxia, with eventual development of large-amplitude theta and delta waves. With the increase in ischemia or hypoxia, the beta waves begin to disappear and there is an appearance of low-amplitude delta waves. This progresses to electrical activity suppression with occasional bursts of activity. The onset of irreversible damage can be seen when there is complete electrical silence with a flat EEG.

Monitoring the EEG intraoperatively for the development of delta waves allows for the recognition of an increased risk of ischemic damage to the brain. To simplify EEG interpretation, the anesthetic delivery should ideally be "stable" and not changing during the critical surgical portions of the case. Also, any changes in anesthetic delivery should be communicated to the EEG technician. The EEG can only provide information of the cerebral cortex function, and not much information on the subcortical brain, spinal cord, or the cranial and peripheral nerves.[3,15,16]

Anesthetic Effects on EEG

Induction Agents

Induction doses of etomidate and propofol all cause similar effects on the EEG by increasing the frequency of beta waves and decreasing their amplitude. This beta-rhythm EEG activity correlates with the patient losing consciousness after drug administration; a dose-related depression is seen with anesthetic drugs.[17,18]

One difference noted with the administration of etomidate is that myoclonus, frequently seen with its use, is not reflected on EEG signals.[19] Coincidently, the EEG frequency decreases as the serum levels of etomidate rise, thereby leading to burst suppression. Burst suppression can be achieved with both of these induction agents in their higher dosage ranges. *Burst suppression* is an alternating high-frequency activity with 0.5- to several-second periods of electrical suppression. This type of electrical activity is unpredictable, and the duration constantly varies. Burst suppression is also typically seen with a decrease in cerebral circulation and oxygenation, as well as with hypothermia, particularly during cardiopulmonary bypass surgery. Many of these effects can be additive. Burst suppression EEG patterns remain somewhat controversial relative to cardiopulmonary bypass surgery. However, to reduce cerebral oxygen requirements and provide neuroprotective properties, burst suppression may be desirable during manipulation of brain tissues.[20-22] Burst suppression can be achieved during anesthesia using a variety of anesthetic agents. These agents include etomidate, propofol, and the inhalation agents, which all provide varying levels of suppression of electrical activity with increasing depth; effects usually remain bilateral and uniform.[17,19,23] Unilateral burst suppression is usually indicative of ischemia or injury to the brain. Forethought should be given to the use of sevoflurane in patients with known epileptiform EEG activity; the activity may be accentuated by these inhalation agents in their lower concentrations.[18,24,25]

PROCESSED EEG WAVEFORMS

The interpretation of a raw EEG can many times be difficult and depend on the quality of the waveform, lead placement, any artifact or electrical interference that might be present, and the skill level of the clinicians in interpreting the waveforms. To further analyze the EEG, multiple methods are used, including compressed spectral array (CSA) and density spectral array (DSA). The CSA and DSA are obtained, calculated, and displayed by collecting, assessing, and providing a summary of each of the waves (alpha, beta, theta, delta) over a period of time. A mathematical description for the timeframe, using the amplitude and frequency of the waves, is accomplished by using a fast Fourier transform (FFT) algorithm. Applying an FFT algorithm is typically thought of as breaking down a signal into a variety of components and then reconstructing the useful information into an analysis of the complex signals. The cell phone, TV, and radio are examples of devices in which this technology is best known. The Fourier analysis also results in a compressed view of EEG waveforms. The compressed data are presented in a two- or three-dimensional graph. Depending on the display used, these data appear as either a compressed spectral array (CSA) or a dot matrix called a *density spectral array* (DSA), as seen in Figure 18-1.[26]

The processed information collected and displayed for the CSA and DSA is analyzed for the waveform relationships using the amplitude and frequency and illustrated in two- or three-dimensional graphs. These relationships are expressed as the spectral edge frequency (SEF), median frequency (MF), and relative delta power (RDP). Most commonly, the SEF is used and represented by the EEG frequency and power activity, which falls below 90% (SEF90).[27,28] Figure 18-2 shows an EEG power spectrum demonstrating the SEF of waveforms within 90% of power and frequency. As frequency declines below a predetermined power, the spectral edge changes. In the presence of general anesthesia or injury, frequency and power decline, thereby causing a change in the spectral edge. The modern EEG calculates the computerized spectral array, which is then used during anesthesia to determine the "depth of anesthesia" or unilateral injury, based on the processed results. The compressed spectral array (CSA) in Figure 18-3 shows the spectral edge shifted to the right, indicating lower power and frequency in brainwave activity. This pattern is typically found during deep sedation and sleep, and in Figure 18-3 is produced by the presence of 0.2% isoflurane anesthesia, indicating the patient's brainwave activity is suppressed. General anesthesia produces a reduction in high-frequency waves and an increase in low-frequency amplitudes. In Figure 18-2, the spectral edge is positioned well to the left, indicating a higher power and frequency, suggesting that the patient is awake.[29-31]

Considerations for Inhalation Anesthetics and EEG Interpretation

Interpreting the EEG in the presence of anesthetic drugs can be confounding because the different drug classes used for anesthesia may affect the EEG in different ways. Instead, generalized assumptions can be made from the interpretation of the EEG. There are two major reasons the EEG remains difficult to correlate with the course of the anesthetic and patient outcomes. The first major

variable preventing exact correlation between the EEG and anesthetic depth is the combination of the many different drugs used to induce and maintain general anesthesia. Dose-related effects are seen with each general inhalation and intravenous anesthetic. The inhalation agents affect the frequency and amplitude of the EEG waveforms (Table 18-2).[29-34] Alpha waves seen primarily in the occipital and posterior lobes are increasingly abolished with inhalation anesthesia. Beta activity is usually seen in the frontal lobe and typically increases slightly with general anesthesia. The second major variable involves environmental factors and manipulation of the brain intraoperatively, adding to the complexity of interpretation. Extensive research with bispectral analysis (BIS) has sought to clarify EEG interpretation by analyzing the EEG electrical signals, processing them, and displaying the result as a final numeric value of 0 to 100. BIS measurement is effective in determining the level of anesthesia produced with inhalation agents but remains less predictable with pediatric patients and during regional and intravenous anesthesia.[35]

Processing Devices

Several devices on the market today use a combination of processed EEG signals to determine the depth of anesthesia. The BIS machine (Aspect Medical Systems) is the most widely used and relies on a combination of bispectral analysis, power spectral analysis, and time domain analysis in combination with a mathematical algorithm that produces an index of the hypnotic state of the patient. Other available monitors include the following:

- S/5 Entropy module (GE Healthcare)
- Cerebral state monitor (Danmeter)
- SNAP II monitor (Stryker)
- AEP Monitor/2 (Danmeter)
- SEDLine/patient state analyzer (Hospira)

The most frequently used monitor for assessing anesthetic depth based on the processed electroencephalogram is the bispectral index (BIS) monitor. The BIS monitor processes a single frontal electroencephalographic signal to calculate a dimensionless number that provides a measure of the patient's level of consciousness.

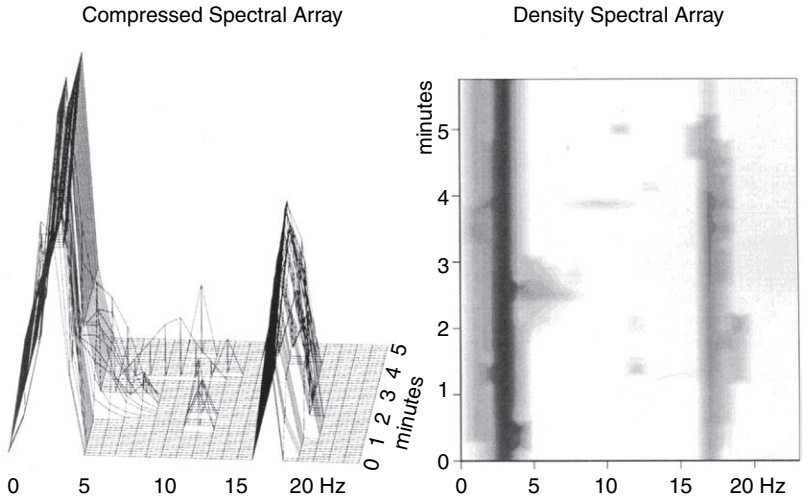

FIGURE **18-1** The compressed spectral array (CSA) histogram on the left is the compression and transformation of raw EEG waveform data and plotted over time. The density spectral array (DSA) on the right is created by converting each brainwave value into a shade of gray and then plotting them on the DSA graph. (From Rampil IJ. A primer for EEG signal processing in anesthesia. *Anesthesiology.* 1998;89[4]:980-1002.)

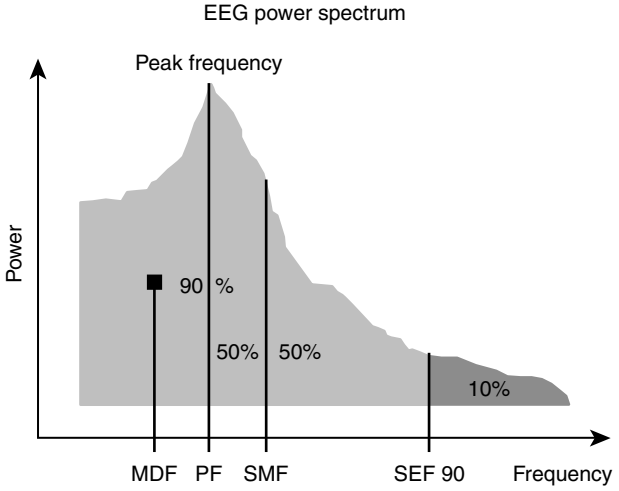

FIGURE **18-2** EEG power spectrum demonstrating the spectral edge frequencies of waveforms within 90% of power and frequency. (Adapted from Rampil IJ. A primer for EEG signal processing in anesthesia. *Anesthesiology.* 1998;89[4]:980-1002.)

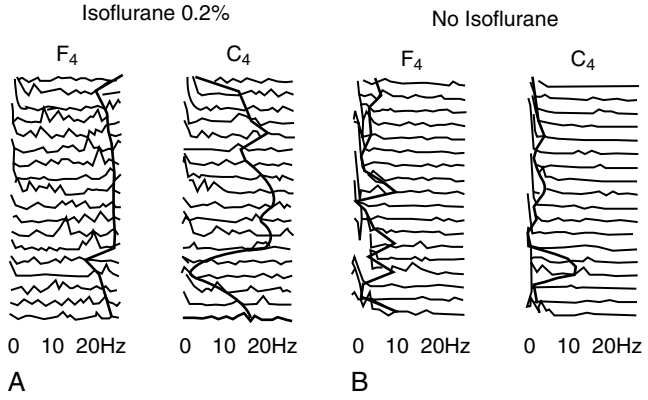

FIGURE **18-3** **A,** The solid line indicates a compressed spectral edge with the administration of isoflurane 0.2%. **B,** The solid line indicates the compressed spectral edge with no anesthesia. (Adapted from Heyer EJ, et al. Erroneous conclusion from processed electroencephalogram with changing anesthetic depth. *Anesthesiology.* 2000;92[2]:603.)

BIS values range from 100 (awake) to 0 (no brain activity). BIS values between 40 and 60 suggest adequate general anesthesia for surgery. Values below 40 indicate a deep hypnotic state. Targeting a range of BIS values between 40 and 60 is advocated to prevent anesthesia awareness while still allowing a reduction in the administration of anesthetic agents.[36] The success of the BIS monitor to prevent awareness remains a matter of controversy. BIS-guided anesthesia reduces the incidence of awareness with recall in high-risk patients.[37] A recent study comparing BIS-guided anesthesia to measurement of the end-tidal anesthetic concentration (ETAC) found that ETAC, which is already routinely monitored, was superior in preventing recall.[38] It has been suggested that deep anesthesia as defined by a sustained BIS value less than 40 for greater than 5 minutes is associated with increased postoperative mortality (B-Aware trial).[39] The concern was that with additional risk factors such as hypotension, high concentrations of anesthetic gases and patient co-morbidities, adverse outcomes are increased. Other studies do not support the B-Aware trial results.[40] Several large-scale trials are ongoing that address these important issues.[41]

These devices have their limitations. Most important is a time delay that is steadily being remedied by faster processors. The intraoperative gold standard is still the 16- to 32-channel analog EEG monitored by an experienced technician. Studies evaluating whether systems with processing software using fewer channels are comparable to 16- to 32-analog EEG encephalography are not available.

Near-Infrared Spectroscopy

Near-infrared spectroscopy (NIRS) is a relatively new method of analyzing brain hemodynamics, especially hemoglobin oxygenation and blood volumes, by using the near-infrared spectrum of electromagnetic waves from approximately 600 to 2500 nanometers (nm). Near-infrared spectroscopy can better penetrate deep into thick tissues, allowing noninvasive physiologic interpretation of oxygenation by evaluating, in real time, the transmission and absorption of infrared light in the hemoglobin in brain tissue. As each area of the brain is evaluated with NIRS, the local blood volume is also analyzed, thus determining flow to that area.

Constant monitoring with NIRS allows the anesthetist to quickly determine regional volume and hemoglobin changes in the brain tissue. Not only is NIRS used to evaluate oxygenation and blood volume during anesthesia, it can also facilitate motor-function monitoring of patients, with strong clinical correlations.

Contamination of the NIRS signal is an issue that has recently been studied and arises with the use of the unit. The contamination of the oxygenation signal occurs with increased levels of hypoxia in the tissues on the scalp, leading to distorted signals and readings of brain oxygenation. When using the NIRS monitor, the nurse anesthetist must be careful to consider the peripheral oxygenation of the scalp or the NIRS signal may not fully or solely reflect the oxygenation of the brain.[42,43] Because NIRS devices differ, some caution in their use and interpretation is encouraged.[44-46]

EVOKED POTENTIALS

Evoked potentials (EPs) are electrical potentials that are measured in response to some type of stimulus. These stimuli can be changed or completely depressed with the administration of anesthesia. In the operating room, EPs are used to help alert surgeons and aid adjustments to surgical strategy, to confirm their decisions, and help them improve subsequent procedures and outcomes, therefore avoiding neurologic damage. This is all done to preserve or improve neurologic structures at risk and prevent irreversible damage. It is also sometimes effective in localizing anatomic structures. Auditory, visual, motor, and somatosensory stimuli are commonly used for clinical EP studies during surgical procedures. Attempting to preserve neural function with EPs can be daunting. Once the basic science of measurement is understood, interpretation and diagnosis can be challenging, owing to harsh operating room environments. Injuries to neural structures can arise from heat (electrocautery), mechanical stress (retraction), ischemia (ligation and vessel damage), and loss of functional integrity (transection). Some if not most nerves encountered during surgical procedures lack perineurium, which protects against longitudinal retraction, and epineurium, which protects against retraction. The "elastic limit" of such nerves is around 20%, suggesting that stretching the nerve farther may produce irreversible damage to the nerve itself.[47] Evoked potentials also can be affected by hypothermia, hypotension, positioning, and anesthetic agents themselves. These systemic effects usually develop slowly and show more potential to be reversible defects rather than permanent.

It is important to remember that some injuries may be reversible, but early detection is the key to reducing more serious complications. Early detection must then be paired with good communication among the anesthesia provider, surgeon, and neurophysiologist. Adequate understanding of EPs is essential if anesthesia providers are to have productive dialogue to guide care for

TABLE 18-2 Effects of Inhalation Anesthetics on EEG

Inhalation Agent	Low-Dose Inhalation Anesthesia	Moderate-Dose Inhalation Anesthesia	High-Dose Inhalation Anesthesia	EEG Amplitude	Dose for Burst Suppression
Desflurane	<Alpha waves >Beta waves	>Beta waves	Diffuse delta and theta	↑Low dose ↑Anesthetic dose ↑ or 0 High dose	>1.2 MAC
Isoflurane	<Alpha waves >Beta waves	>Beta waves	Diffuse delta and theta	↑Low dose ↑Anesthetic dose ↑ or 0 High dose	>1.5 MAC
Sevoflurane	<Alpha waves >Beta waves	>Beta waves	Diffuse delta and theta	↑Low dose ↑Anesthetic dose ↑ or 0 High dose	>1.2
Nitrous oxide (alone)	>Beta waves	>Beta waves	>Beta waves	↑Low dose ↑Anesthetic dose ↑ High dose	Not seen in clinical concentrations

↑, Increase; *0*, no effect; *MAC*, minimum alveolar concentration; *EEG*, electroencephalogram.

Adapted from Seubert CN, Mahla ME. Neurologic monitoring. In Miller RD, ed. *Miller's Anesthesia*. 7th ed. Philadelphia: Churchill Livingstone; 2010:1477-1514.

the patient. There currently is no set standard for the amount of change in latency or amplitude that necessitates warning the surgeon. A rule of thumb offered by several sources states that a 50% decrease in amplitude or a 10% decrease in latency should exist before a warning is needed.[42] A better plan of care would be to ask the surgeon and neurophysiologist prior to surgery what they deem an acceptable amount of change in the EP before warning.

One important question all anesthesia providers should ask is this: What are the best anesthetic agents to use for surgical procedures when using evoked potentials? A fine balance must be established between adequately anesthetizing patients while at the same time optimizing conditions that monitor neurologic structures and preserve them. Each different type of EP has a unique interaction with the anesthetics delivered. However, there are some generic rules to help guide the clinician. The first rule is that lipophilic agents that interfere with neuronal membrane conduction also interfere with subcortical conduction. Therefore these agents cause an increase in both interpeak latencies and control conduction time. The second rule is that anesthetic agents that interfere with EEG also interfere with EP. Changes occur because the component frequencies of the EP are the same as the EEG. Lastly, intravenous agents, at equipotent doses to inhalation agents, will have less effect than inhaled agents. However, when combinations of drugs are used for anesthesia, like those used in balanced anesthesia techniques, they too can have additive effects.

Somatosensory Evoked Potentials

Somatosensory evoked potentials (SSEPs) are used to monitor a number of neural structures along both the peripheral and central somatosensory pathways. Stimulation for SSEPs is created by stimulating peripheral nerves electrically. These stimulations can be induced through mechanical devices, but electrical stimulation gives a more robust response and may be better controlled. A supermaximal electrical stimulation is not required to elicit a response from the nerve. SSEPs are usually induced by stimulation of a peripheral nerve, which contains both a sensory and motor component combining to provide a mixed signal. Typically, the lower extremities can be monitored by stimulating the posterior tibial nerve located between the Achilles tendon and medial malleolus of the ankle. The upper extremities are monitored by placing the stimulus at the median nerve located between the tendons of the flexor carpi radialis and the palmaris longus. If these common sites cannot be accessed, two alternate sites are the common peroneal in the popliteal fossa (may be used for the lower extremity) and the ulnar nerve (either at the wrist or ulnar notch) for the upper extremities.

Recording electrodes used for SSEPs are placed at C2, C3, and C4, referencing to F2 of the montage for cortical SSEPs. An electrode placed over cervical spine C7 is used for subcortical SSEPs. For upper limb SSEP studies, electrodes are placed over Erb's point both ipsilateral and contralateral to the stimulus. Erb's point is located on the side of the neck, 2 to 3 cm above the clavicle and in front of the transverse process of the sixth cervical vertebra. Pressure over this point elicits the Duchenne-Erb paralysis, and electrical stimulation over this area elicits various potentials measured in the arm. For lower limb studies, the electrode is placed at the iliac crest. Several different characteristics of SSEPs can be measured. Peak latencies are the easiest to measure and standardize, but like other characteristics, they can vary with age, tissue mass, electrical stimulus, and limb length. Spinal SSEP electrodes are placed over the spinal cord. SSEPs usually are *processed* signals, meaning they are processed as an average, with electrical filters to remove background noise, instead of providing real-time electrical waveforms. Interpretation of the compound action potential depends on the site of stimulus and distance to the recording electrodes.

Almost all anesthetic agents produce change in latency or amplitude, with the exception of ketamine, etomidate, and opiates.[48] Anesthesia and SSEPs provide a challenge for the anesthetist; the less anesthesia one administers, the better the SSEP monitoring results. Many researchers report that better monitoring conditions for SSEPs are obtained with narcotic-based anesthetics, less than 1 MAC (minimum alveolar concentration) total end-tidal inhaled concentration of inhalation agent, and nitrous oxide. If monitoring SSEPs alone, use of paralytic agents is acceptable, and potentials can be measured. However, in the absence of paralytics, motor responses can be elicited, and the nurse anesthetist needs to make sure that adequate anesthesia is provided for the operative procedure to prevent recall and extreme catecholamine responses.

Although sometimes limited in their evaluation of neurologic diseases, the value of SSEPs in the operative setting is high.[49] Because changes in SSEPs are sensitive to cerebral ischemia, they have multiple uses in vascular surgery. During carotid endarterectomy procedures, SSEPs can help determine the need for shunting intraoperatively. If changes are immediate, SSEPs can indicate high-risk or neurologic injury during aortic cross-clamping. During cerebral aneurysm surgery, changes in SSEPs can possibly indicate occlusion of parental vessels, directing the positioning of important aneurismal vascular clips.

Brainstem Auditory Evoked Potentials

Brainstem auditory evoked potentials (BAEPs) are used to monitor the entire auditory pathway from the distal auditory nerve to the midbrain, inadvertently allowing monitoring of basic brainstem function. The stimulus used is typically a standard broadband repeating click. Repetition is generally around 10 Hz, and the intensity is around 65 to 70 decibels (dB) above the click-perception threshold. The stimulus is delivered via earphone. Because an external earphone is impractical, an earphone placed in the auditory canal, or "insert earphone," is used. For best results, care must be taken (1) to place the transducer after the head is positioned so as not to cause abrasive injury to the ear canal and (2) that the internal auditory canal is free of any built-up cerumen or fluid. Such things as fluid, saline, cerebrospinal fluid, and soap can dampen or change the sound and delay responses. Recording electrodes are determined by the type of evoked BAEPs performed on the patient. There are several common evoked responses used as BAEPs that will be discussed further.

Brainstem auditory evoked potentials have five main peaks represented by roman numerals (Figure 18-4). Peak I relates to the peripheral portion of the cochlear nerve inside the internal auditory canal. Peak II relates to the cochlear nucleus and the area where the eighth cranial nerve enters the brainstem. Peak III correlates to the area of the brainstem at the level of the cochlear nucleus and potentially the ipsilateral superior olivary nucleus. Peaks IV and V relate to the brainstem along the ascending auditory pathway between the cochlear nucleus and the inferior colliculi. Measured peaks must be compared with relative norms for age, sex, intensity, polarity, and repetition rate.

Brainstem auditory evoked potentials are clinically useful in that they are very resistant to alteration by anything other than structural pathology in the brainstem. This means that BAEPs are not significantly affected by barbiturates, benzodiazepines, ketamine, nitrous oxide, propofol, or muscle relaxants. There is one reported case of abolishment of the wave with the use of lidocaine infusion.[50,51] However, inhalation agents can mildly affect BAEPs'

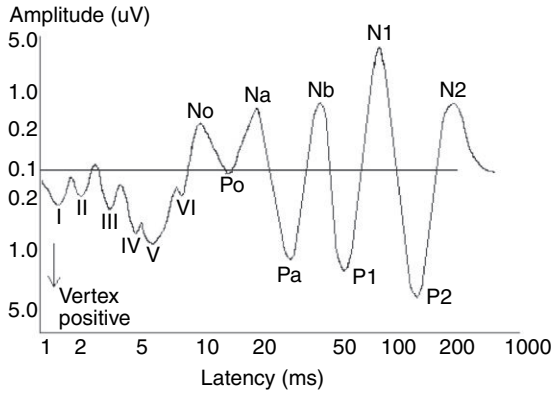

FIGURE **18-4** Auditory evoked potentials—common labeled potentials *(Roman numerals)* that can be measured to assess different areas of the auditory and brainstem pathways. Peak I relates to the peripheral portion of the cochlear nerve inside the internal auditory canal. Peak II relates to the cochlear nucleus and the area where the 8th cranial nerve enters the brainstem. Peak III correlates to the area of the brainstem at the level of the cochlear nucleus and potentially the ipsilateral superior olivary nucleus. Peaks IV and V relate to the brainstem along the ascending auditory pathway between the cochlear nucleus and the inferior colliculi. Peak VI relates to the medial geniculate body and VII (not shown) relates to auditory radiations. (Modified from Barlow HB, Mollon JD. *The Senses*. Cambridge, England: Cambridge University Press; 1982.)

latency and amplitude, and their effect is proportional to the dose of inhalation agent administered.[50]

A common effect on BAEP during anesthesia and in the operating room environment is hypothermia. Even mild hypothermia (patient temperature less than 35° C) has been associated with decreased latency and prolonged interpeak intervals during BAEP.[52] BAEPS can also be exaggerated, as demonstrated by an increase in latency with low P_{CO_2} seen during hyperventilation.[42]

The auditory nerve can be directly monitored during the surgical procedure by the surgeon. The monitoring electrode is placed on the nerve itself after surgical exposure, and its response is measured as an *auditory nerve compound action potential* (AN-CAP). When the eighth nerve is involved, the AN-CAP is referred to as the *eighth nerve potential* (8NP). The AN-CAP, like the BAEP, can be used to determine auditory nerve insult or injury.

For auditory brainstem responses (ABRs), the noninverting (positive) electrode is placed at C2 or high on the forehead. The inverting (negative) electrode is typically placed on the mastoid or earlobe. However, if neither of these sites is practical, owing to surgical exposure, then the tragus of the ear may be used as an alternate site.

Electrocochleography (ECochG) is a specific test used to provide information about the cochlea and the distal section of the auditory nerve. It is typically used to evaluate and/or verify blood supply to the cochlea. The measure itself is called the *ECochG-CAP*. The inverting electrode is placed near the cochlea, tympanic membrane, or the cochlear promontory. The noninverting electrode is placed on the opposite ear.

Otoacoustic emissions (OAEs) are sometimes used, but this test is not an evoked potential. Because a stimulus is not used, there is only a recording device. No stimulus is required because the normal cochlea does not just receive sound but can produce low-intensity sounds called *OAEs*, produced specifically by the cochlea and most probably by the cochlear outer hair cells as they expand and contract. These sound transmissions can be recorded; they are typically used to assess auditory hair-cell function and not internal structure of the ear.

Motor Evoked Potentials and Electromyography

Motor evoked potentials (MEPs) are used to monitor the functional integrity of motor tracts, particularly in the corticospinal tract. Stimuli used for MEPs can be either electrical or magnetic. Either the motor cortex or spinal cord can be used for sites of stimulation. Magnetic stimulation of the motor cortex can be accomplished using a rapidly changing magnetic field (compared with a constant field from magnetic resonance imaging [MRI]). Based on the Faraday law, electrical current is created in a nearby conductor, generating the stimulus. Although useful, magnetic stimulation is cumbersome in the operating room because of the interference of magnetic fields with other operating-room equipment, as well as the size and position of equipment during the procedure. Magnetic stimulation also generates intense heat that needs to dissipate to safe levels and therefore can prolong procedures. Magnetic fields also produce a high-intensity noise, however brief, so ear protection is recommended. Contact with magnetic stimulation is contraindicated in patients with pacemakers, spinal or bladder stimulators, epilepsy, metallic foreign body, or previous craniotomy. Direct stimulation of the motor cortex may also be produced by cutaneous electrodes on the scalp or electrodes placed directly on the brain after surgical exposure. Electrical stimulation is more commonly used for spine cases.

Potentials are recorded as neurogenic potentials in the distal spinal cord or peripheral nerve. They also can be recorded as myogenic potentials of innervated muscle. While SSEP can assess the dorsal column (fasciculus cuneatus and gracilis) and the lateral sensory tract of the spinal cord, it also can make assumptions on changes in anterior motor tracts because the stimulation is a mixed nerve (motor and sensory) signal. However, because they are not directly measured, motor deficits have been seen in spinal cord cases in which SSEPs have been normal. Advances in technology and the refinement of methodologies are significantly changing intraoperative neurophysiologic monitoring of the spinal cord. The clinical application of spinal D wave and muscle MEP recordings is becoming standard in many procedures. D wave changes have proven to be the strongest predictors of maintained corticospinal tract integrity and therefore of motor function/recovery. Combining the use of muscle MEPs with D wave recordings provides the most comprehensive approach for assessing the functional integrity of the spinal cord motor tracts during select surgeries. MEPs are now considered the gold standard for monitoring the motor pathways; SSEPs continue to be valuable for assessing the integrity of the dorsal column. Multimodal monitoring combining SSEP and MEP monitoring is rapidly approaching the standard for spinal surgery.[53]

Stimulation and monitoring of motor components of nerves are important in the operating room, but they require an active stimulus to produce an action potential. Electromyography (EMG) can be both passive and active. EMG has the capability to stimulate a motor nerve and monitor the known innervated muscle groups, as well as passively "listen" to all muscle groups. The ability to passively monitor nerves allows the surgeon to become more aware of what nerve is being stimulated with surgical manipulation.

EMG analysis of the facial nerve for related surgeries has been used and researched extensively. Other cranial nerves can and have been used for monitoring purposes as well. Monitoring needle electrodes are typically placed in the orbicularis oculi and the orbicularis oris muscles. To assess the cervicofacial and temporofacial divisions of the facial nerve as it divides from the posterior aspect of the parotid gland, both of these muscles require monitoring. Frequency and density of discharges elucidate the type of damage to the actual nerve. Simple benign contact with the nerve causes few random discharges. A response train is associated with more significant

TABLE 18-3 Monitoring of Cranial Nerves

Cranial Nerve		Monitoring Site or Method*
I	Olfactory	No monitoring technique
II	Optic	Visual evoked potentials
III	Oculomotor	Inferior rectus muscle
IV	Trochlear	Superior oblique muscle
V	Trigeminal	Masseter muscle and/or temporalis muscle (sensory responses can also be monitored)
VI	Abducens	Lateral rectus muscle
VII	Facial	Orbicularis oculi and/or orbicularis oris muscles
VIII	Auditory	Auditory brainstem responses
IX	Glossopharyngeal	Stylopharyngeus muscle (posterior soft palate)
X	Vagus	Vocal folds, cricothyroid muscle
XI	Spinal accessory	Sternocleidomastoid and/or trapezius muscles
XII	Hypoglossal	Genioglossus muscle (tongue)

From Sloan, et al. Evoked potentials. In Cottrell JE, Young WL, eds. *Cottrell and Young's Neuroanesthesia*. 5th ed. Philadelphia: Mosby; 2010:115-130.
*Unless otherwise specified, monitoring is performed via electromyographic activity of the muscle(s) listed.

TABLE 18-4 Nerve Roots and Muscles Most Commonly Monitored

Spinal Cord Nerve(s)		Muscle(s)
Cervical	C2-C4	Trapezoids, sternocleidomastoid
	C5, C6	Biceps, deltoid
	C6, C7	Flexor carpi radialis
Thoracic	C8-T 1	Adductor pollicis brevis, abductor digiti minimi
	T5-T6	Upper rectus abdominis
	T7-T8	Middle rectus abdominis
	T9-T11	Lower rectus abdominis
	T12	Inferior rectus abdominis
Lumbar	L2	Adductor longus
	L2-L4	Vastus medialis
Lumbosacral	L4-S1	Tibialis anterior
	L5-S1	Peroneus longus
Sacral	S1-S2	Gastrocnemius
	S2-S4	Anal sphincter

From Sloan, et al. Evoked potentials. In Cottrell JE, Young WL, eds. *Cottrell and Young's Neuroanesthesia*. 5th ed. Philadelphia: Mosby; 2010:115-130.

nerve irritation. Neurotonic discharges are associated with nerve irritation, as well as impending nerve damage. Elimination of environmental factors should be considered prior to diagnosing nerve damage. Trains of stimulation also can be caused by thermal changes (electrocautery or cold irrigation), drilling, traction, and/or nerve ischemia. The choice of anesthesia is essentially unrestricted, with the exception of avoiding paralytic agents. Additionally, the efficacy of partial paralysis has not been studied extensively. Monitoring methods for cranial and spinal nerves are shown in Tables 18-3 and 18-4.

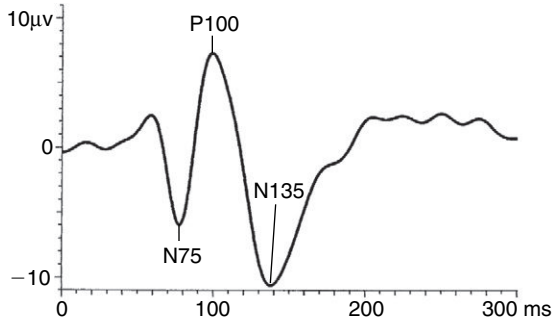

FIGURE **18-5** Pattern reversal visual evoked potentials. The three peaks that characterize the potential and are subsequently measured are denoted as *N75*, *P100*, and *N135*. (Adapted from Odom J, et al. Visual evoked potentials standard. *Doc Ophthalmol*. 2004; 108:115-123.)

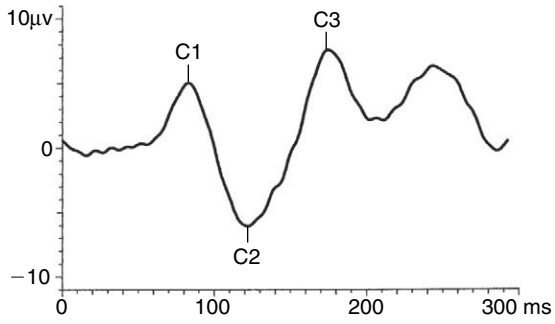

FIGURE **18-6** Pattern onset/offset visual evoked potential. The three peaks that characterize the potential and are subsequently measured are denoted as *C1*, *C2*, and *C3*. (Adapted from Odom J, et al. Visual evoked potentials standard. *Doc Ophthalmol*. 2004;108:115-123.)

Visual Evoked Potentials

Visual evoked potentials (VEPs) are used to monitor the function of the visual pathway, which comprises the retina to the occipital cortex and everything in between, including the optic nerve and optic chiasm. A visual stimulus is presented to the subject for a selected number of times, and the cerebral responses are amplified, averaged by a computer, and displayed. The two major classes of VEP stimulation are patterned and unpatterned (luminance). Typically, awake tests consist of a pattern stimulus. The two most common pattern stimuli are pattern reversal and pattern onset/offset stimuli. Pattern reversal stimulus consists of black-and-white checks (checkerboard) that change phase (same luminescence) at a predetermined number of reversals per second (Figure 18-5). Pattern onset/offset stimulus consists of a black-and-white checkerboard that exchanges with a diffuse background with the same luminescence (Figure 18-6).

Because such stimulation cannot be used in conjunction with anesthesia or even sedation, a stroboscopic flash (luminescence) stimulus must be used in such cases. The flash VEP is created from a flash that has a predetermined strength against a dim background of certain luminance. Recording electrodes are fixed to the scalp and, as always, placed relative to bony landmarks. The active electrode is placed on the scalp over the visual cortex at Oz, with the reference electrode at Fz. The ground electrode can be placed at the forehead, vertex (Cz), mastoid, earlobe (A1or A2), or linked earlobes.

Monocular stimulation is typically used to avoid masking of unilateral conduction abnormality. Care should be taken to ensure

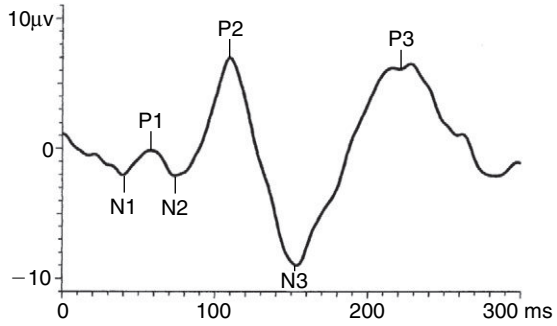

FIGURE **18-7** Flash visual evoked potential. The three positive deflections that characterize the potential and are subsequently measured are denoted as *P1*, *P2*, and *P3*. The three negative deflections that characterize the potential and are subsequently measured are denoted as *N1*, *N2*, and *N3*. (Adapted from Odom J, et al. Visual evoked potentials standard. *Doc Ophthalmol*. 2004;108:115-123.)

that no light enters the eye not being stimulated. Closure with a patch and tape are usually sufficient to block light. Close assessment must be made of the eyes preoperatively and should be noted in the record because they may affect recorded outcomes. Examples of such consideration include extreme pupil size or anisocoria (inequality of pupil diameter). Pupils do not need to be dilated for flash VEPs, and the cornea may need to be carefully moistened from time to time to prevent the cornea from drying. Mydriatics and miotics should not be used with awake tests. It is also important to compare VEPs with appropriate age- and sex-related normal values.

The action potential of VEPs varies, depending on the type of stimulus used. Flash VEPs consist of a series of negative and positive waves, with the earliest detectable response occurring around 30 ms post-stimulus. For flash VEP, the N2 and P2 peaks are the most robust components, peaking around 90 and 120 ms, respectively (Figure 18-7). Unfortunately, flash VEPs are more variable between subjects than between pattern responses. Some question the usefulness of intraoperative VEPs because in anesthetized patients, stable recording was either not obtainable or not consistent across subjects.[54,55] Indications for monitoring evoked potentials are noted in Box 18-2.

SUMMARY

The use of neurologic monitors does not guarantee prevention of neurologic injury. However, the use of neurologic monitors adds one more tool to aid the nurse anesthetist in patient assessment. Several factors contribute to intraoperative EEG changes, making the monitoring device more challenging to interpret. Some of these factors include hypothermia, hyperthermia, volatile and intravenous anesthetic agents, surgical intervention, previous neurologic injury, and excessive auditory and visual stimulation. Providing anesthesia for neurologic surgical procedures requires knowledge in both basic and advanced anesthesia techniques. The anesthetist should not only use all the usual techniques for safe anesthesia practice but also many times must apply these principles while being at a distance from the airway, particularly in cranial cases. Postoperative neurologic changes can occur, so continued monitoring is essential to reduce the incidence of preventable permanent changes. Cooperation and communication between the surgeon and the nurse anesthetist remains a vital key for safe neurologic monitoring and surgical outcomes.

BOX 18-2

Indications for Monitoring Evoked Potentials

- Spinal fusion/deformity surgery (e.g., tethered cord surgery, scoliosis repair, meningomyelocele surgery)
- Spinal instrumentation or hardware placement (e.g., pedicle screws, rods)
- Spinal tumor resection
- Spinal trauma/fracture repair
- Spinal vascular surgery
- Plexus surgery
- Peripheral nerve surgery
- Thoracoabdominal aortic aneurysm surgery
- Epilepsy surgery
- Brainstem or posterior fossa surgery
- Aneurysm repair
- Aortic cross-clamping
- Carotid endarterectomy
- Cerebral tumor resection
- Cortical mapping and/or regional cortical function
- Probe localization during stereotactic neurosurgery
- Facial nerve monitoring during acoustic neuroma resection

From Newmark JL, Sandberg WS. Noninvasive physiologic monitors. In Sandberg WS, et al, eds. *The MGH Textbook of Anesthetic Equipment*. Philadelphia: Saunders; 2011:143.

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Preoperative Evaluation and Preparation of the Patient

CHAPTER 19

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A crucial element of the perioperative care of the patient includes a timely and thorough preoperative assessment. A fine-tuned approach to patient evaluation then enables appropriate interventions when required to properly prepare the patient for the upcoming anesthesia and surgery. For any patient scheduled to undergo anesthesia, preoperative evaluation is compulsory to help identify factors that increase the risk associated with anesthesia and the status of the patient relative to the proposed surgery. Essential goals of preoperative assessment and preparation of the patient include the following:

- Optimize patient care, satisfaction, comfort, and convenience.
- Minimize perioperative morbidity and mortality by accurately assessing factors that influence the risk of anesthesia or might alter the planned anesthetic technique.
- Minimize surgical delays or preventable cancellations on the day of surgery.
- Determine appropriate postoperative disposition of the patient (i.e., given the patient's status, whether the procedure is best performed on an ambulatory, inpatient, or intensive care basis).
- Evaluate the patient's overall health status, determining which if any preoperative investigations and specialty consultations are required.
- Formulate a plan for the most appropriate perianesthetic care and postoperative supportive patient care.
- Communicate patient management issues effectively among care providers.
- Educate patient regarding surgery, anesthesia, and expected intra- and postoperative care, including postoperative pain treatments, to reduce patient anxiety and increase patient satisfaction.
- Ensure time-efficient and cost-effective patient evaluation.

During the preoperative visit, patient assessment begins with a thorough review of the patient's medical records and patient interview, followed by the physical examination. A comprehensive medical history and physical examination are the cornerstones of a systematic approach to continued patient preparation. Information gathered from this evaluative process guides further individualized assessment (e.g., obtaining diagnostic tests, specialist consultation). The extent of this preoperative workup depends on the existing medical condition of the patient, the proposed surgical procedure, and the type of anesthesia. Significant findings from this initial evaluation enable the anesthesia provider to make adjustments in the patient's care (i.e., initiate specific treatment modalities to optimize the patient's condition for the proposed surgery and anesthesia).

Important strategies for achieving high-quality, cost-effective patient evaluation include the following[1]:

- Educating the practitioner (e.g., regarding the cost of diagnostic tests) and thereby modifying practice patterns
- Developing and implementing evidence-based practice guidelines
- Using clinical pathways (interdepartmental teamwork required)
- Disseminating information regarding protocols, thereby avoiding duplication of services
- Performing economic analyses of services, including cost-effectiveness, and cost-benefit studies
- Rendering efficient resource management
- Providing for outcomes measurement

PREANESTHESIA ASSESSMENT CLINIC

The preanesthesia assessment clinic has emerged as the most effective means of providing convenient "one-stop shopping" designed to (1) permit patient registration, (2) obtain a medical history and perform a physical examination, (3) promote patient teaching, (4) meet or schedule appointments with medical consultants, and (5) complete any required preoperative diagnostic testing. Successful preanesthesia assessment clinics have realized a reduction in patient anxiety, direct cost, last-minute surgical cancellations, overall length of hospitalization after surgery, and diagnostic testing, as well as improvement in patient education and a shift from inpatient to outpatient surgery status.[2] The preanesthesia assessment clinic allows patients scheduled for elective surgery to be evaluated and their condition optimized sufficiently in advance of the surgery.

Timing of Patient Assessment

To allow ample time for necessary risk assessment, preoperative testing, and specialty consultations, ideal preoperative assessment for surgery and anesthesia should take place well in advance of the proposed surgery. Patients with complex medical conditions should be evaluated at least 1 week before the scheduled procedure. Because of the present economic realities, patients undergoing more complex procedures and those who have complicated medical conditions (Box 19-1)[3] are frequently not admitted to the hospital before the day of surgery. Preoperative evaluation on the day of surgery can result in last-minute discoveries (e.g., of inappropriate fasting, suspected difficult airway, preexisting medical condition) that may result in surgical delay or cancellation. The timing of the preanesthesia assessment does not appear to influence outcome of anesthesia.[4] In one study, no difference in the cancellation rate for ambulatory patients was observed between groups seen within 24 hours and groups seen within 1 to 30 days of the scheduled surgery.[5] Governmental requirements may mandate that the preanesthesia evaluation be completed and documented by a qualified anesthesia practitioner within 48 hours prior to surgery.[6] This focused evaluation must be performed by a practitioner qualified to administer anesthesia.

BOX **19-1**

Conditions That Would Benefit from Early Preoperative Evaluation

General
- Medical conditions inhibiting ability to engage in normal daily activity
- Medical conditions necessitating continual assistance or monitoring at home within the past 6 months
- Admission within the past 2 months for acute episodes or exacerbation of chronic condition
- Use of medications (e.g., anticoagulants or monoamine oxidase inhibitors) for which modification of schedule or dosage might be required

Cardiocirculatory
- History of angina, coronary artery disease, myocardial infarction, symptomatic arrhythmias
- History of cardiac rhythm device in case device interrogation or reprogramming by appropriate personnel will be necessary
- Poorly controlled hypertension (diastolic greater than 110 mmHg, systolic greater than 160 mmHg)
- History of congestive heart failure

Respiratory
- Asthma or chronic obstructive pulmonary disease that requires chronic medication; acute exacerbation and progression of these diseases within the past 6 months
- History of major airway surgery, unusual airway anatomy, or upper or lower airway tumor or obstruction
- History of chronic respiratory distress requiring home ventilatory assistance or monitoring

Endocrinologic
- Diabetes treated with insulin or oral hypoglycemic agents (unable to control with diet alone)
- Adrenal disorders
- Active thyroid disease

Hepatic
- Active hepatobiliary disease or compromise

Musculoskeletal
- Kyphosis or scoliosis causing functional compromise
- Temporomandibular joint disorder with restricted mobility
- Cervical or thoracic spine injury

Oncologic
- Patients receiving chemotherapy
- Other oncologic process with significant physiologic residua or compromise

Gastrointestinal
- Morbid obesity (greater than 140% ideal body weight)
- Hiatal hernia
- Symptomatic gastroesophageal reflux

Modified from Barash PG (ed). *ASA Refresher Courses in Anesthesiology.* Vol 24. Philadelphia: Lippincott, Williams, & Wilkins; 1996.

CHART REVIEW

To provide the basis for and direction of the patient interview and physical assessment, the patient's past and current medical records should be reviewed preoperatively. Ideally the anesthesia provider will have the opportunity to review the patient's medical records before the interview with the patient or caregiver.

Past Medical Records

For a patient who has undergone surgery at the same institution in the past, previous anesthesia records should be retrieved and reviewed, especially if complications are suspected. If past medical records are not available, the patient must provide details of significant anesthetic experiences. If this information suggests that the patient has an unusual condition (e.g., atypical plasma cholinesterase, susceptibility to malignant hyperthermia), surgery may be delayed so that medical records can be obtained for review to provide further information that might affect patient care, or measures should be taken (e.g., avoidance of succinylcholine; provision of trigger-free anesthetic technique) to avoid consequences associated with the condition.

Patient Chart or Electronic Medical Record

A review of the current medical record includes verifying that the surgical and anesthesia consents are accurate and complete. The names of the patient and surgeon, the date, and the proposed procedure should be matched with those on the operating room schedule. Demographic or baseline data, such as the age, height, and weight of the patient, can often be obtained from the admitting record. Vital-sign trends and input-output totals are transcribed from graphic flow sheets, which may also contain pertinent data (e.g., daily blood glucose values for the diabetic patient).

Progress notes and consultation reports provide a valuable overview of the health history and physical status of the patient. Medical treatments, such as drug dosages and schedules, may be derived from these materials, but diagnostic test results should be obtained directly from their original sources. This retrieval of primary data prevents the possible misinterpretation of data that were transcribed incorrectly. Knowledge gleaned from a review of progress notes and consultative reports enables the anesthesia provider to formulate supplementary questioning, seek further specialist consultations, or obtain additional diagnostic testing as needed.

Baseline data concerning the patient, such as cultural diversity, coping mechanisms, or patient limitations (e.g., hearing impairment), can often be derived from nursing notes and can effectively guide the anesthesia provider in conducting a thorough preoperative interview. Increasingly the anesthetist must be able to appropriately interact with culturally diverse populations to properly evaluate and educate patients.

A preanesthesia questionnaire is included on the patient's chart (Figure 19-1). This questionnaire should be part of the admission paperwork to be completed by the patient or the patient's caregiver and consists of a concise checklist regarding the patient's health history and medical care. When properly completed and readily available on the chart, the preanesthesia questionnaire enables the anesthesia provider's visit with the patient to be accomplished more efficiently. Interview questions and physical assessment are appropriately directed toward abnormal findings and areas of concern.

PATIENT INTERVIEW

The preoperative interview may be conducted in person or by telephone. The in-person patient interview is preferred, but for

QUESTION	YES	NO	COMMENTS
Height:____ (cm) Weight:____ (kg)			
Current medications, including over-the-counter & herbal (dose, frequency):			
Allergies (include drugs, foods, & environmental items, e.g., latex):			
Previous surgeries/hospitalizations (list):			
Scheduled surgery/procedure:			
Anesthesia History			
Problems with anesthesia -- self or blood relative?			
Respiratory			
Lung or breathing problems?			
Cough? If yes, do you bring up anything when you cough?			
Asthma? If yes, what is current treatment?			
Cold, flu, respiratory infection within the past 6 weeks?			
Diagnosed with sleep apnea? Do you snore?			
Ever required supplemental oxygen therapy?			
Abnormal chest x-ray?			
Smoke now or in past? If so, what type, how much, and for how many years?			
Exposed to passive smoke?			
Can you walk up two flights of stairs without getting short of breath?			
Do you have trouble walking one block?			
Cardiovascular			
Short of breath at night?			
Heart murmur?			
Heart attack, angina (with activity; at rest), or chest pain related to your heart?			
Irregular heartbeat or pacemaker?			
Congestive heart failure?			
Abnormal electrocardiogram?			
Problems with high blood pressure?			

FIGURE **19-1** Preanesthesia questionnaire.

QUESTION	YES	NO	COMMENTS
Renal			
Kidney, bladder, or urine problems?			
Hepatic			
Jaundiced, now or in past?			
Liver problems (e.g., hepatitis)?			
Use alcohol? If so, how much, how often, and when did you last use alcohol?			
Gastrointestinal			
Acid reflux, hiatal hernia, ulcer, or heartburn?			
Recent diarrhea?			
Neurologic			
Stroke, seizures, episodes of unconsciousness or fainting, or other neurologic problems?			
Numbness or weakness in an arm or leg?			
Frequent headaches?			
Eye problem or problems with your vision?			
Hearing problems?			
Endocrine			
Diabetes or high blood sugar?			
Thyroid problems?			
Steroids (e.g., prednisone) during the past year?			
Musculoskeletal			
Back or neck problems?			
Arthritis?			
Physical disabilities?			
Hematologic			
Bleed easily?			
Anticoagulants (e.g., blood thinners) within the past month?			
Ever been anemic?			
Evaluated for sickle cell anemia?			
Object to blood products under any circumstances?			

FIGURE **19-1, cont'd** Preanesthesia questionnaire.

QUESTION	YES	NO	COMMENTS
Cancer			
Diagnosed with cancer?			
Received treatment for cancer?			
Obstetric			
Could you be pregnant? If yes, how many weeks?			
Airway			
Chipped or loose teeth, dentures, caps, bridgework?			
Problems with opening your mouth? Temporomandibular joint (TMJ) problems?			
Difficult airway management with previous anesthesia?			
Psychosocial			
Ever had mental health treatment?			
Taken prescribed psychiatric medications?			
Used "street" or "recreational" drugs? If so, when did you last use?			
Birth & Developmental (pediatrics)			
Child's delivery premature or at term?			
Neonatal complications?			
History of low heart rate or periods of low or absent respirations?			
Sudden infant death syndrome (SIDS) in your family?			
Do you have any medical problems that have not been discussed?			

FIGURE **19-1, cont'd** Preanesthesia questionnaire.

patients who are unable to visit the hospital setting (e.g., who live far from the hospital or have transportation constraints), an opportunity to participate in a telephone interview should be made available. Regardless of the location or approach used, the interview promotes a trusting relationship between the patient and anesthesia provider. When the interview is performed in a caring and unhurried manner, the patient's degree of trust and confidence in anesthesia care is enhanced. Furthermore, compliance with perioperative instructions is increased when the patient is treated with respect; an example of such respect is using the surname (Mr. Smith, Mrs. Jones) unless instructed differently by the patient.

The title of the anesthesia provider and his or her specific role in the patient's perioperative care should also be defined. The patient is entitled to know whether the interviewer is a Certified Registered Nurse Anesthetist, student registered nurse anesthetist, anesthesiologist, or medical resident in anesthesiology. The professional appearance and attitude of the anesthesia provider also can create a positive impression during the preoperative visit.

The environment of the preoperative interview should be staged to maximize the quality and effectiveness of the interaction. Adequate lighting enhances effective communication with the patient. Distractions such as an operating television set can be eliminated. The anesthesia provider should ensure that the time and location of the interview, whether it occurs in person or by telephone, are convenient and private for the patient. A return visit or call may be necessary if the patient is eating or receiving medical therapy.

Because the preoperative interview is a private interaction between the patient and the anesthesia provider, a tactful request that visitors remain outside the interview area, unless the patient wishes family members to be present, will be necessary. Otherwise, the patient may not volunteer confidential health information, such as a history of substance abuse or sexual history. In certain

situations, however, assistance from a family member or caregiver is required. The health history may be provided, for example, by the parent of a pediatric patient or by an interpreter for a patient with cognitive or language barriers.

The patient interview is designed to achieve specific objectives (Box 19-2).[7] The interview process, along with patient education, yields beneficial consequences of reduced patient anxiety and increased patient satisfaction. A valuable step in preparing the patient or responsible caregivers (e.g., family members, legal guardian) for the scheduled surgery includes an educational process during which the staff counsels the patient concerning fundamental perioperative issues (Box 19-3).[7] Reinforcing information to the patient verbally and in writing is essential to gaining patient compliance. Coordinating the patient's visit to the preanesthesia assessment clinic to include educational time is ideal for the patient.

Medical History

The extent of a patient's health history depends partly on the amount of information available in the chart before surgery. If the surgeon has already documented a thorough medical history and physical examination, the interview can focus on confirming major findings and obtaining information that directly relates to the anesthetic management of the patient. The anesthesia provider must obtain and document a detailed health history, however, if the history is unavailable in the chart during the preoperative visit.

The health history should be obtained in an organized and systematic way, as with the preanesthesia questionnaire, to minimize possible omission of important data. Open-ended and direct questions targeting each category of the checklist can be posed. With this approach, more detailed and graded responses are elicited from the patient. To avoid overwhelming or confusing a patient, questions are asked separately and formulated in comprehensible or layperson's terms.

Surgical History

The surgical history of a patient may be learned from the chart or preoperative interview. Most patients only vaguely recall surgical experiences, even from childhood operations. Information regarding complications related to previous operations, such as a peripheral nerve injury or uncontrolled blood loss, should be elicited to determine the need for further investigation.

Anesthetic History

Past anesthetic experiences are often not as easily defined as the surgical history. It is vitally important to determine the reaction of a patient to previously administered anesthetics. Adverse reactions to anesthetic agents and techniques (e.g., prolonged vomiting, difficult airway, malignant hyperthermia, postoperative delirium, anaphylaxis, and cardiopulmonary collapse) may have simply been an annoyance to the patient or could have been life threatening. Preoperative knowledge of these complications allows the anesthetic approach to be modified and the recurrence of the complication thereby prevented. Causative factors are also thoroughly investigated in patients who note that a previous operation was aborted. Difficulties with airway management can alter the approach to endotracheal intubation, if indicated. Vague reports of fever and convulsions merit further investigation to rule out an episode of malignant hyperthermia.

Familial Anesthetic History

Numerous inherited diseases involving metabolic derangements may affect a patient's reaction to stress and certain drugs, including anesthetic agents. The patient is specifically asked whether any family member ever experienced an adverse reaction to anesthesia during surgery. Familial tendencies for diseases such as atypical plasma cholinesterase, malignant hyperthermia, porphyria, or glycogen storage diseases (e.g., glucose-6-phosphate dehydrogenase deficiency) are then investigated. A diagnosis should be established before the surgery proceeds, because adjustments in the anesthetic management of the patient may be required.

Drug History

A preoperative drug history provides an excellent guide for the direction and depth of the patient interview and assessment. Drug

BOX 19-2

Objectives of the Preoperative Interview

- Ensure that the goals of preoperative assessment are met.
- Provide preoperative education to the patient and family.
- Obtain written documentation of informed and witnessed consent.
- Acquaint the patient and family with the surgical process (to reduce stress and increase familiarity).
- Evaluate the patient's social situation with respect to surgery (e.g., support network).
- Motivate the patient to comply with preventive care strategies (e.g., smoking cessation, improvement of cardiovascular fitness).

Modified from Cassidy J, Marley RA. Preoperative assessment of the ambulatory patient. *J Perianesth Nurs*. 1996;11(5):334-343.

BOX 19-3

Patient Education Objectives

- Promote interactive communication between patient and care provider.
- Encourage patient participation in making decisions about perioperative care.
- Maximize and enhance patient self-care skills and participation in continuing care during the postoperative phase.
- Increase the patient's ability to cope with his or her health status.
- Increase patient compliance with perioperative care.
- Provide individualized preoperative instructions regarding the following:
  - Where and when laboratory tests, consultations, and diagnostic procedures will be completed
  - Appropriate time at which the patient should cease ingestion of food and drink
  - Personal considerations (e.g., comfortable clothes to wear; no jewelry or makeup; what personal items to bring; leave valuables at home; bring favorite toy, comforter, or book)
  - Postoperative considerations and instructions (e.g., anticipated recovery course, discharge instructions, how to deal with complications)
  - Person to contact if the patient's physical condition changes (e.g., upper respiratory tract infection, cancellation)
- Detail the process of arrival and registration on arrival to the surgical facility (i.e., time and location of arrival).
- Review advance directive information as required by law in some states.
- Explain the surgical facility policies to the patient and family.

Modified from Cassidy J, Marley RA. Preoperative assessment of the ambulatory patient. *J Perianesth Nurs*. 1996;11(5):334-343.

dosages, schedules, and durations of treatment are reviewed and the patient questioned about the purpose and effectiveness of these medications. An interview with a patient receiving β-adrenergic blockers, for example, can focus in greater detail on the cardiovascular system. Patients on medications for hypertension or angina pectoris require further investigation and possibly specialty consultation if they have not been recently evaluated.

Adverse Drug Effects and Interactions. During the preoperative evaluation, current drug therapy must be carefully reviewed for side effects and potential interactions with anesthetic agents. Table 19-1 lists selected drugs and their potential anesthetic interactions.[4,8-17] One drug-management strategy is to discontinue particular drugs preoperatively in the hope of reducing the potential for adverse interactions. The therapeutic benefits of these drugs

TABLE 19-1 Potential Drug Interactions Affecting Perianesthesia Care

	PERIANESTHESIA CONCERN		
Drug Category	**Intraoperative Concerns**	**Management**	**Discontinuation Issues**
Drugs Affecting the Cardiovascular System			
Angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers	Hypotension, especially on anesthesia induction, with or without bradycardia; intolerance to hypovolemia; vasoplegic syndrome	Optimize hydration; moderate doses of vasopressor as needed; withhold on morning of surgery if indication for use is for hypertension only, otherwise continuation may improve regional blood flow and oxygen delivery and preserve renal function; consider withholding in patients taking amiodarone, on multiple (three or more) antihypertensives, or in whom even a brief period of hypotension is unacceptable; cautious ambulation after position change; omit AM dose on day of surgery	Increased risk of atrial fibrillation and rebound hypertension if discontinued
β-adrenergic blockers	Hypotension; bradycardia	Optimize hydration; β-adrenergic blockers should be continued in patients undergoing surgery who are receiving β-blockers to treat angina, symptomatic arrhythmias, or hypertension	Discontinuation may increase perioperative cardiovascular morbidity and development of withdrawal symptoms (e.g., increased nervousness, tachycardia, headache, nausea, exacerbation of myocardial ischemia, or sudden death)
Calcium channel blockers	Decrease systemic vascular resistance and blood pressure via peripheral vasodilation; exhibit a negative inotropic effect by slowing sinus automaticity and arterioventricular conductivity; demonstrate a negative chronotropic effect by slowing the sinoatrial and arteriovenous (AV) nodes and prolonging AV nodal conduction	Optimize hydration; phenylephrine as needed to maintain atrial pressure; continue chronic calcium channel blocker therapy preoperatively in patients with normal or slightly impaired heart function; exercise caution in patients with left ventricular dysfunction (ejection fraction <40%)	
Diuretics	Hypokalemia; hypovolemia	Monitor potassium levels preoperatively; maintain hydration; consider need for urinary drainage catheter for moderately long cases	Patients rarely become symptomatic if morning dose withheld; patients appreciate lack of urinary urgency while awaiting surgery; it might be desirable to continue in patients for whom diuretics are part of treatment for chronic renal failure or congestive heart failure
Antiarrhythmics	Cardiac depression; prolonged neuromuscular blockade; amiodarone—hypotension and atropine-resistant bradycardia requiring ventricular pacing	Monitor serum drug levels as needed; amiodarone—large doses of vasopressors or inotropes and pacemaker capability	Discontinuation rarely recommended, because usually not prescribed for benign arrhythmias; amiodarone—impractical to discontinue because half-life is 58 days; withhold concurrent medications (e.g., ACE inhibitors)

Continued

TABLE 19-1 Potential Drug Interactions Affecting Perianesthesia Care—cont'd

	PERIANESTHESIA CONCERN		
Drug Category	**Intraoperative Concerns**	**Management**	**Discontinuation Issues**
Drugs Affecting Hemostasis			
Antiplatelet drugs and nonsteroidal antiinflammatory drugs (NSAIDs)	Increased bleeding; impaired platelet function; altered renal function; gastrointestinal bleeding	Cardiology consultation for patients with coronary stents previously placed less than 1 year ago; continue aspirin perioperatively in patients previously treated; antiplatelet drugs, e.g., clopidogrel (5-7 days), ticlopidine (7-10 days) , should be discontinued prior to high-risk surgery; unless surgery puts patient at particular risk for increased or catastrophic bleeding or impaired renal function, it is reasonable to continue NSAIDs up to morning of surgery; if desirable to discontinue NSAIDs preoperatively, short-acting NSAIDs should be withheld for at least 1 day, longer-acting agents for 2-3 days	Increased risk of blood clot formation and embolism with discontinuation
Anticoagulants (heparin, Coumadin, low-molecular-weight heparins [LMWH])	Increased hemorrhage	Baseline hemoglobin and hematocrit; may reverse heparin with IV protamine; may reverse Coumadin with vitamin K or fresh frozen plasma	Heparin—discontinue IV 6 hr before surgery and check PTT; Coumadin—discontinue 3-5 days (5 days if INR <1.5 is required) before surgery and check INR or PT; LMWH—discontinue 12 hr before surgery
Fibrinolytic drugs (streptokinase, urokinase, tissue plasminogen activator)	Hemorrhage	Antifibrinolytic agent (aprotinin) may be indicated	Discontinuation usually not an option when administered for treatment of life-threatening conditions (e.g., acute myocardial infarction, massive pulmonary embolus)
Hypoglycemic Agents			
Insulin	Hyperglycemia; hypoglycemia	Monitor serum glucose; use insulin-supplementation protocol	Morning dose either withheld or reduced and adjustments in therapy based on periodic serum glucose determinations
Oral hypoglycemic agents	Hyperglycemia; hypoglycemia	Monitor serum glucose; avoid dehydration	Withhold oral hypoglycemic agents beginning on day of surgery
Drugs Affecting the Central Nervous System			
Monoamine oxidase inhibitors (MAOIs)	Hypertension secondary to indirect-acting sympathomimetic drugs causing release of norepinephrine; excitatory state (from meperidine) or depressive phenomena secondary to opioid administration	Avoid known triggering agents such as meperidine (may precipitate seizure and hypertensive crisis), pentazocine, dextromethorphan, anticholinergics, and indirect-acting sympathomimetic agents (e.g., ephedrine)	Older, nonselective, irreversible monoamine oxidase inhibitors—discontinue for 2 wk with risk of serious psychiatric consequences (serious depression, suicidality, paranoid delusions) or provide MAOI-safe anesthesia if drugs continued; newer, reversible inhibitors of monoamine oxidase A—have short half-life (1-3 hr); therefore discontinue drug on morning of surgery; consider changing irreversible MAOIs to a reversible MAOI in the weeks prior to surgery, then only discontinuing reversible MAOI on morning of surgery
Tricyclic antidepressants	α-Adrenergic blocking activity and potentiation of sympathomimetic effects of epinephrine and norepinephrine, resulting in hypertensive crisis; cardiac arrhythmias; lowers seizure threshold	Consider baseline ECG; norepinephrine should be considered the vasopressor of choice for related hypotension	Discontinuation can lead to cholinergic symptoms (i.e., GI), movement disorders, and cardiac arrhythmias; relapse rate is higher when discontinued

TABLE 19-1 Potential Drug Interactions Affecting Perianesthesia Care—cont'd

	PERIANESTHESIA CONCERN		
Drug Category	**Intraoperative Concerns**	**Management**	**Discontinuation Issues**
Selective serotonin reuptake inhibitors	Serotonergic potentiation with GI symptoms, headache, agitation	Continue to avoid withdrawal syndrome	Withdrawal may induce psychosis, agitation, dizziness, palpitations, etc.
Lithium	T-wave smoothing, ventricular arrhythmias, myocarditis; sinus dysfunction can lead to extreme atropine-resistant sinus bradycardia; dehydration will lead to increases in lithium blood levels	Continue pre- and perioperatively; check serum levels prior to surgery; obtain thyroid function tests if indicated; monitor serum sodium, avoid sodium wasting diuretics; optimize hydration	No withdrawal effect after abrupt discontinuation; high risk of recurrence of depression and total affective relapse
Antiparkinsonian agents		Carbidopa/levodopa: continue until the morning of surgery and restart as soon as possible after surgery to avoid withdrawal syndrome; Selegiline: stop 2 wk prior to surgery when possible; Bromocriptine, amantadine, pergolide: continue; Entacapone, tolcapone: Continue to avoid withdrawal syndrome (check liver enzymes before surgery)	

Data from Doak GJ. Discontinuing drugs before surgery. *Can J Anaesth*. 1997;44(5 Pt2):R112-R123; Pass SE, Simpson RW. Discontinuation and reinstitution of medications during the perioperative period. *Am J Health Syst Pharm*. 2004;61(9):899-912; Schirmer U, Schurmann W. Preoperative administration of angiotensin-converting enzyme inhibitors. *Anaesthesist*. 2007;56(6):557-561; Baillard C. Preoperative management of chronic medications. *Ann Fr Anesth Reanim*. 2005(11-12);24:1360-1374; Huyse FJ, et al. Psychotropic drugs and the perioperative period: a proposal for a guideline in elective surgery. *Psychosomatics*. 2006(1);47:8-22; Fleischmann KE, et al. 2009 ACCF/AHA focused update on perioperative beta blockade: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. *Circulation*. 2009;120(21):2123-2151; Hoeks SE, Poldermans D. European Society of Cardiology 2009 guidelines for preoperative cardiac risk assessment and perioperative cardiac management in noncardiac surgery: key messages for clinical practice. *Pol Arch Med Wewn*. 2010;120(7-8):294-299; Lieb K, Selim M. Preoperative evaluation of patients with neurological disease. *Semin Neurol*. 2008; 28(5):603-610; De Hert S, et al. Preoperative evaluation of the adult patient undergoing non-cardiac surgery: guidelines from the European Society of Anaesthesiology. *Eur J Anaesthesiol*. 2011;28(10):684-722; White CM, et al. Effect of preoperative angiotensin converting enzyme inhibitor or angiotensin receptor blocker use on the frequency of atrial fibrillation after cardiac surgery: a cohort study from the atrial fibrillation suppression trials II and III. *Eur J Cardiothorac Surg*. 2007;31(5):817-820; Whinney C: Perioperative medication management: general principles and practical applications. *Cleve Clin J Med*. 2009;76(suppl 4): S126-S132.
ECG, Electrocardiogram; *INR*, international normalized ratio (prothrombin time); *IV*, intravenous; *PT*, prothrombin time; *PTT*, partial thromboplastin time; *GI*, gastrointestinal.

are weighed against the risks of abrupt discontinuation. Abrupt discontinuation of long-standing medication may lead to the development of undesirable withdrawal symptoms. With occasional exceptions, the majority of medications are continued preoperatively. Should a decision be made to withhold a particular drug before surgery, sufficient time should be allowed for metabolic clearance (ideally three to five half-lives).[8]

Drug Allergies

A patient's drug history should include information regarding allergic reactions to certain foods and medications. Prior allergic responses are investigated so they can be differentiated from adverse drug reactions. Use of certain antibiotics and opioids may be avoided because of gastrointestinal side effects. These do not represent a true allergic response, however. A distinction between allergic reactions and adverse effects is crucial, because an allergy to a drug is an absolute contraindication to its use. Medications within the same classification of a drug allergy should be avoided, and heightened awareness of a potential allergic reaction is required during the perioperative period.

Latex Sensitivity

Patient sensitivity to latex products has recently been identified as a frequent basis of allergic reaction. Up to 20% of intraoperative anaphylactic reactions have been attributed to latex sensitivity.[18]

The preoperative questioning of patients should include inquiry regarding specific latex sensitivity or allergy. Patients at increased risk for latex sensitivity should be cared for in a no-latex setting and scheduled as the first case of the day to reduce the likelihood of aeroallergen latex exposure. The diagnosis of latex allergy is based on the findings of the history and physical examination and if necessary, in vivo (skin-prick test is the most sensitive) and in vitro testing. Preoperative testing is indicated only when there is a family history of reactions or when patients report experiencing symptoms such as a rash, swelling, or wheezing when exposed to latex.[19] Patients at high risk for latex sensitivity include those with a history of the following[18]:

- Chronic exposure to latex-based products (e.g., industrial workers using protective gear; occupational exposure to latex)
- Spina bifida, urologic reconstructive surgery
- Repeated surgical procedures (more than nine)
- Intolerance to latex-based products (e.g., balloons, rubber gloves, condoms, dental dams, rubber urethral catheters)
- Allergy to food and tropical fruits (e.g., avocado, banana, buckwheat, celery, chestnut, kiwi, mango, papaya, passion fruit, peach)
- Intraoperative anaphylaxis of uncertain cause
- Healthcare professionals, especially with a history of atopy or severe dermatitis, hand eczema

Social History

The addictive nature of tobacco and alcohol, as well as illegal drugs, exerts a detrimental influence on several aspects of life in the United States.

- Approximately 22.6 million Americans aged 12 years of age or older (9%) were classified as illicit drug users in 2010.[20]
- Nearly one quarter of all deaths (75,000 annually)[21] in the United States are caused by addictive substances.[22]
- The economic burden of addiction (e.g., healthcare expenditures, missed work, crime) is estimated at more than $400 billion annually.[22]

Certain drugs, despite their social or recreational application, may be associated with adverse and life-threatening consequences with long- or short-term use or overdose. The social history provides an excellent opportunity to explore the extent of self-medication. Open-ended questions, posed in a professional and nonjudgmental manner, are most likely to elicit detailed information from the patient. At this time, the patient can also be educated about the adverse consequences of substance abuse; especially as such substances affect anesthetic care.

Tobacco Use

Many patients arrive for anesthesia and surgery with a history of tobacco smoking. In the United States, some disturbing statistics are associated with this form of substance abuse:

- One in five deaths in the United States is related to smoking. Cigarette smoking is the leading cause of preventable premature death in the United States (approximately 443,000 premature deaths annually).[23]
- In 2010, 27% (70 million) of Americans aged 12 or older smoked.[20]
- Teen smoking rates have declined from 15.2% in 2002 to 10.7% in 2010.[20]
- Smokers die 14 years earlier than nonsmokers.[24]
- Exposure to secondhand smoke causes 3400 deaths a year from lung cancer and 46,000 deaths from coronary heart disease; 776 newborns a year die from sudden infant death syndrome attributed to secondhand smoke.[25]

The inhaled components of tobacco smoke lead to multiple pathophysiologic changes within the body. Nicotine and carbon monoxide are just two of the more than 6000 noxious components that have been identified in tobacco smoke.[26] Nicotine, a toxic alkaloid, produces ganglionic stimulant effects and is the tobacco component that affects the cardiovascular system.[27] Acute side effects of nicotine include increased heart rate, blood pressure, myocardial contraction, myocardial oxygen consumption, myocardial excitement, and peripheral vascular resistance. Net effects of nicotine's cardiovascular influence include impaired coronary blood flow and an adverse myocardial oxygen supply/demand ratio.[28] Carbon monoxide readily occupies the oxygen-binding sites of hemoglobin (approximately 250 to 300 times greater affinity for hemoglobin than oxygen).[29] Oxygen transport to the tissues and resultant oxygen use is thereby drastically reduced. In the heavy smoker, carboxyhemoglobin may be as high as 15%, which effectively reduces the patient's oxyhemoglobin percentage accordingly. The adverse effects of nicotine on the cardiovascular system and carbon monoxide on oxygen-carrying capacity are short lived (half-life of nicotine is 40 to 60 minutes[30]; half-life of carbon monoxide if room air is breathed is 130 to 190 minutes).[31]

Patients should be instructed to stop smoking at least 12 to 48 hours before surgery. *Short-term (e.g., 12 hours) preoperative abstinence from tobacco smoke reduces the deleterious effects of nicotine and carbon monoxide on cardiopulmonary function.*[32] Smoking cessation for even 1 night before surgery reduces heart rate, blood pressure, and circulating catecholamine levels[33] and allows carboxyhemoglobin values to return to normal levels.[34]

Patients who smoke have a higher incidence (a nearly sixfold increase[35]) of postoperative pulmonary complications (pneumonia and atelectasis).[36] A smoking history of more than 20 pack years equates to an increased risk of perioperative complications.[37] Smoking cessation of less than 4 weeks does not reduce the risk of postoperative respiratory complication.[4,38] Longer periods of smoking cessation (8 weeks or longer) result in a marked improvement in pulmonary mechanics (e.g., enhanced ciliary function, decreased mucous secretion and small airway obstruction, and enhanced immune function).[39] Patients who stopped smoking less than 2 months before surgery had nearly four times the pulmonary complications (e.g., purulent sputum, secretion retention, bronchospasm, pleural effusion, pneumothorax, segmental pulmonary collapse, pneumonia) of those who abstained from smoking for longer than 2 months.[40] However, even short-term smoking cessation is effective in reducing postoperative complications when compared with patients who continued to smoke up until the time of surgery.[39] A reduction in postoperative wound-related complications occurs in patients who stop smoking preoperatively.[41] Patients who smoke should be advised to quit even immediately prior to surgery, without fear of worsening pulmonary outcomes or increasing psychological stress as a result of acute abstinence.[42] Effective interventions, including behavioral support and nicotine replacement therapy, should be made available to smokers considering abstinence at this time.[43]

The influence of environmental tobacco smoke (also known as *secondhand* or *passive smoke*) on children has been found to produce disturbing respiratory consequences, including increased reactive airway disease, abnormal results of pulmonary function tests, and increased respiratory tract infections.[44,45] The perioperative complications in children exposed to smoke include laryngospasm, coughing on induction or emergence, breath holding, postoperative oxyhemoglobin desaturation, and hypersecretion.[46]

Alcohol Intake

An estimated 14 million Americans are dependent on alcohol, with 105,000 deaths annually attributed to alcohol abuse.[47] Perioperative complications, such as arrhythmias, infection, and alcohol withdrawal syndrome, are increased two- to fivefold in chronic excessive alcohol users.[48] Postoperative complications can by reduced with 4 or more weeks of abstinence prior to surgery.[49] Information regarding the type and amount of alcohol regularly consumed and the frequency of consumption is important in the evaluation for anesthesia and surgery. Often an accurate assessment of a patient's alcohol intake may be difficult to obtain. The Alcohol Use Disorders Identification Test (AUDIT), a self-reporting questionnaire designed to identify problem drinkers, can be incorporated into the preoperative interview of suspected problem drinkers.[50] A less confrontational and a reliable approach to evaluating a patient's potential for an alcohol problem uses the mnemonic *CAGE*, which refers to the following four questions[51]:

1. Do you feel you should *c*ut down on your alcohol consumption?
2. Have people *a*nnoyed you by criticizing your drinking habits?
3. Have you felt guilty about your drinking?
4. Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover (*e*ye-opener)?

A patient reporting more than two positive responses is at high risk for alcoholism and an increased likelihood of experiencing withdrawal symptoms.[52] Both AUDIT and CAGE have been shown to be effective in identifying the abusive alcohol consumer.[53]

In the heavy drinker, it is important to determine whether the patient has experienced seizures, abrupt withdrawal syndrome, or delirium tremens as a consequence of alcohol abuse. Clinical signs suggestive of alcohol withdrawal include increased hand tremors, autonomic hyperactivity (e.g., sweating, tachycardia, systolic hypertension), insomnia, anxiety, restlessness, nausea or vomiting, transient hallucinations (visual, tactile, or auditory), psychomotor agitation, and grand mal seizures.[52]

Chronic alcohol abuse results in the development of tolerance, physical dependence, and multisystem organ dysfunction. Tolerance to alcohol is evidenced by a resistance or cross-tolerance to other central nervous system (CNS) depressants. For example, the anesthetic requirement of hypnotics, opioids, and inhalation agents is increased in the chronic alcoholic; however, exaggerated responses to anesthetic agents are likely during periods of acute intoxication or advanced alcoholism. This effect is attributed to the additive depressant effects of alcohol and anesthetic agents. Enzymatic function and plasma albumin concentrations may also be reduced in patients with alcoholic hepatic insufficiency. As a result, greater circulating concentrations of unbound intravenous agents may result in an exaggerated and prolonged drug effect.[54] This enhanced drug response has not been shown to occur with propofol in patients with moderate liver cirrhosis.[55]

An insidious progression of multisystem organ dysfunction is also characteristic of long-term alcohol abuse. Numerous illnesses are attributable to the toxic adverse effects of advanced alcoholism on overall health and nutrition. Predictably, postoperative morbidity and mortality rates are increased in alcoholic patients as a result of poor wound healing, infection, bleeding, pneumonia, and further hepatic deterioration.[56,57]

Illicit Drug Use

Use of illicit drugs (e.g., cocaine, cannabis, "crack," lysergic acid diethylamide-25 [LSD], amphetamines, heroin, hallucinogens, inhalants, prescription-type psychotherapeutics used nonmedically) is a significant healthcare issue in the United States. The most popular recreational drugs continue to be cocaine and marijuana. Monthly drug abuse among Americans include 17 million marijuana users, 7 million prescription-type psychotherapeutic nonmedical drug users, 1.5 million cocaine users, 1.2 million hallucinogen users, and 731,000 methamphetamine users in 2010.[20] Americans use 80% of all opioids available in the world.[58] The use of these substances increases the risk for adverse consequences and drug interactions during anesthesia. An accurate illicit drug history is often difficult to obtain because of the patient's fear of legal reprisal or refusal to believe a drug problem exists. During the physical examination, the anesthesia provider should look for signs that indicate illicit drug use by the patient. A diagnosis of recent or continuing drug abuse should be suspected in patients exhibiting the following on physical examination[59]:

- Evidence of drug injection (e.g., track marks or scarring), thrombotic veins, phlebitis, tattoos (may be used to mask the sites), ablation of venous return leading to unilateral edema of the nondominant hand, subcutaneous skin abscesses
- Ophthalmologic changes, such as pupillary constriction from opioid use, pupillary dilation with amphetamine use, nystagmus from phencyclidine (PCP) use
- Lymphadenopathy secondary to nonspecific activation of the immune system as a result of repeated injections of impurities
- Malnourishment as a result of amphetamine abuse (opioid users tend to be well nourished)
- Poor dental care and bruxism (involuntary grinding and clenching of teeth) from amphetamine use
- Nasal perforation from cocaine abuse

BOX 19-4

Signs and Symptoms of Acute Substance Abuse

Cannabis (Marijuana or Hashish)
- Tachycardia, labile blood pressure, headache
- Euphoria, dysphoria, depression, occasional anxiety and panic reactions, psychosis (rare)
- Poor memory and decreased motivation with chronic use

Cocaine and Amphetamines
- Tachycardia, labile blood pressure, hypertension, myocardial ischemia, arrhythmias, pulmonary edema
- Excitement, delirium, hallucinations to psychosis
- Euphoria: feeling of excitation, well-being, and enhanced physical strength and mental capacity
- Hyperreflexia, tremors, convulsions, mydriasis, sweating, hyperpyrexia, exhaustion, coma with overdose

Hallucinogens: LSD, PCP
- Sympathomimetic and weak analgesic effects
- Altered perception and judgment; high doses may progress to toxic psychosis
- PCP produces dissociative anesthesia with increasing doses

Opioids
- Respiratory depression, hypotension, bradycardia, constipation
- Euphoria (most marked with heroin)
- Pinpoint pupils with overdose; decreased level of consciousness to coma

From Cheng DCH. The drug addicted patient. *Can J Anaesth*. 1997;44(5 Pt2):R101-R111; Cavaliere F, et al. Anesthesiologic preoperative evaluation of drug addicted patient. *Minerva Anestesiol*. 2005;71(6):367-371. *LSD*, Lysergic acid diethylamide-25; *PCP*, phencyclidine.

Primary concerns for the anesthesia provider are the likelihood of the patient exhibiting acute abuse or possible withdrawal syndrome.[60] Signs and symptoms of acute abuse of the more common substances are listed in Box 19-4.[59,60] Elective surgery should be delayed or canceled in patients suspected of being under the influence of an illicit drug until further patient evaluation can be performed. Suspicion of acute substance abuse should be followed up with a urine screen for drug identification. Abstinence syndrome typically exhibits increased sympathetic and parasympathetic responses resulting in hypertension, tachycardia, abdominal cramping and diarrhea, tremors, anxiety, irritability, lacrimation, mydriasis, algid sweat, and yawning.[61]

Synthetic Androgens

Anabolic steroids are self-administered in an attempt to increase muscle mass, strength, and growth, and improve athletic performance, but such actions can result in hepatic and endocrine system dysfunction. Risks associated with long-term androgen steroid supplementation include impaired liver function, cholestatic jaundice, hepatic adenocarcinoma, peliosis hepatis, myocardial infarction (MI), atherosclerosis, hypercoagulopathy, stroke, hypertension, dyslipidemia, and psychiatric and behavioral disturbances in susceptible patients.[62-65] The hepatotoxic effects have important implications for the anesthetic management of a chronic steroid abuser, particularly with agents metabolized by the liver, and such patients should undergo preoperative liver function testing.

TABLE 19-2 Clinically Important Effects and Perioperative Concerns of Selected Herbal Medicines and Recommendations for Discontinuation of Use Before Surgery

Herb: Common Name(s)	Relevant Pharmacologic Effects	Perioperative Concerns	Preoperative Discontinuation
Echinacea: purple coneflower root	Activation of cell-mediated immunity	Allergic reactions; decreased effectiveness of immunosuppressive actions of corticosteroids and cyclosporine; potential for immunosuppression with long-term use; inhibition of hepatic microsomal enzymes may precipitate toxicity of drugs metabolized by the liver (e.g., phenytoin, rifampin, phenobarbital)	No data
Ephedra: ma huang	Increased heart rate and blood pressure through direct and indirect sympathomimetic effects	Risk of myocardial ischemia and stroke from tachycardia and hypertension; ventricular arrhythmias with halothane; long-term use depletes endogenous catecholamines and may cause intraoperative hemodynamic instability (control hypotension with direct vasoconstrictor, e.g., phenylephrine); life-threatening interaction with monoamine oxidase inhibitors	At least 24 hours before surgery
Garlic: ajo, *Alium sativum*	Inhibition of platelet aggregation (may be irreversible); increased fibrinolysis; equivocal antihypertensive activity	Potential to increase risk of bleeding, especially when combined with other medications that inhibit platelet aggregation	At least 7 days before surgery
Ginkgo: duck foot tree, maidenhair tree, silver apricot	Inhibition of platelet-activating factor	Potential to increase risk of bleeding, especially when combined with other medications that inhibit platelet aggregation	At least 36 hours before surgery
Ginseng: American ginseng, Asian ginseng, Chinese ginseng, Korean ginseng	Lowers blood glucose; inhibition of platelet aggregation (may be irreversible); increased PT-PTT in animals; many other diverse effects	Hypoglycemia; potential to increase risk of bleeding; potential to decrease anticoagulation effect of warfarin	At least 7 days before surgery
Kava: awa, intoxicating pepper, kawa	Sedation, anxiolysis	Potential to increase sedative effect of anesthetics; potential for addiction, tolerance, and withdrawal after abstinence unstudied	At least 24 hours before surgery
St John's wort: amber, goat week, hardhay, *Hypericum*, klamatheweed	Inhibition of neurotransmitter reuptake, monoamine oxidase inhibition is unlikely	Induction of cytochrome P-450 enzymes, affecting cyclosporine, warfarin, steroids, protease inhibitors, and possibly benzodiazepines, calcium channel blockers, and many other drugs; decreased serum digoxin levels	At least 5 days before surgery
Valerian: all heal, garden heliotrope, vandal root	Sedation	Potential to increase sedative effect of anesthetics; benzodiazepine-like acute withdrawal; potential to increase anesthetic requirements with long-term use	No data

Modified from Ang-Lee MK, et al. Herbal medicines and perioperative care. *JAMA*. 2001;286:208-216; Kaye AD, et al. Perioperative anesthesia clinical considerations of alternative medicines. *Anesthesiol Clin North America*. 2004;22:125-139; Hogg LA, Foo L. Management of patients taking herbal medicines in the perioperative period: a survey of practice and policies within anaesthetic departments in the United Kingdom. *Eur J Anaesthesiol*. 2010;27(1):11-5.
PT-PTT, Prothrombin time–partial thromboplastin time.

Herbal Dietary Supplements

Patients should be questioned regarding their use of nonprescription herbal medications to determine the herb's name, the duration of herbal therapy, and the dose taken. If patients are in doubt as to the herbal medications they are taking, they should be encouraged to bring the herbal products with them to their preoperative workup. Certain herbal products are known to influence blood clotting, affect blood glucose levels, produce CNS stimulation or depression, or interact with psychotropic drugs (Table 19-2).[66,67]

PATIENT EVALUATION: OVERVIEW OF SYSTEMS

Upper Airway

Assessment of the airway should be performed preoperatively in every patient, regardless of the plan of anesthetic management. It is important to evaluate the patient before anesthesia to identify those patients at risk for difficult airway management. The initial physical examination of the patient includes careful inspection of the teeth, inside of the mouth, mandibular space, and neck in a

TABLE 19-3 Components of the Preoperative Airway Physical Examination

Airway Examination Component	Cautionary Findings
Length of upper incisors	Relatively long
Relation of maxillary and mandibular incisors during normal jaw closure	Prominent "overbite" (maxillary incisors anterior to mandibular incisors)
Relation of maxillary and mandibular incisors during voluntary protrusion of the jaw	Patient mandibular incisors anterior to (in front of) maxillary incisors
Interincisor distance	Less than 3 cm
Visibility of uvula	Not visible when tongue is protruded with patient in sitting position (e.g., Mallampati class greater than II)
Shape of palate	Highly arched or very narrow
Compliance of mandibular space	Stiff, indurated, occupied by mass, not resilient
Thyromental distance	Less than three ordinary fingerbreadths
Length of neck	Short
Thickness of neck	Thick
Range of motion of head and neck	Patient cannot touch tip of chin to chest or cannot extend neck

From American Society of Anesthesiologists Task Force on Management of the Difficult Airway. Practice guidelines for management of the difficult airway: an updated report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway. *Anesthesiology*. 2003;98(5):1269-1277.

sequential fashion to determine predictors of airway management difficulties (Table 19-3).[68] Certain body structural features, metabolic disease states, and congenital or acquired structural anomalies are associated with difficult airway management (Box 19-5).[69] The combination of subtle or minor physical anomalies may result in a difficult tracheal intubation, even when each factor individually is not expected to pose a problem.

Tests for Prediction of Difficult Intubation

Several screening tests for predicting difficult endotracheal intubation are recommended as part of the preoperative patient evaluation. No single test should be relied on exclusively when the airway is evaluated; a combination of evaluative criteria should be used to increase the predictive value for difficult intubation.

Mallampati Classification. A popular technique for airway assessment is the modified Mallampati airway classification, which entails examination of tongue size relative to the oral cavity.[70] During the assessment for the Mallampati classification, the patient is seated upright with the head in neutral alignment, while the examiner sits opposite the patient at eye level. The patient is asked to open the mouth as wide as possible and maximally extrude the tongue. The patient is encouraged not to phonate during this maneuver because phonation may inappropriately elevate the soft palate. The airway is then classified based on the structures visible on direct examination of the oropharynx (Figure 19-2).[70] Endotracheal intubation is generally easy in a patient with a Mallampati class I airway and can be expected to be difficult in a patient with a Mallampati class III or IV airway. Mallampati airway classification has been criticized as not being a reliable or sensitive predictor of difficult intubating conditions.[71] Because of the unusually high incidence of false-positive and false-negative findings associ-

BOX 19-5

Conditions Associated with Difficult Airway Management

Head
- Mass defects (e.g., encephalocele, soft-tissue sarcoma)
- Macrocephaly (e.g., severe hydrocephaly, Dandy Walker syndrome, mucopolysaccharidoses [Hurler syndrome])
- Interference with airway access (e.g., thoracopagus conjoined twins, stereotactic frame)

Facial Anomalies
- Maxillary and mandibular deformities
- Maxillary hypoplasia (e.g., Apert's syndrome, Crouzon's disease)
- Mandibular hypoplasia, microgenia, micrognathia (e.g., Pierre Robin syndrome, Treacher Collins syndrome, Goldenhar's syndrome, cri du chat syndrome, Nager syndrome)
- Mandibular hyperplasia (e.g., cherubism)
- Temporomandibular joint anomalies
- Reduced mobility (e.g., arthrogryposis multiplex congenita, diabetes, Dutch-Kentucky syndrome, Hecht-Beals syndrome), ankylosis (inflammatory, congenital, traumatic, infectious)

Thoracoabdominal
- Morbid obesity, sleep apnea syndrome, Prader-Willi syndrome
- Kyphoscoliosis
- Prominent chest or large breasts
- Full-term or near-term pregnancy

Mouth and Tongue Anomalies
- Microstomia
- Congenital anomalies (e.g., Freeman-Sheldon [whistling face] syndrome)
- Acquired anomalies (e.g., burn)
- Stomatitis (e.g., noma)
- Tongue disease
- Macroglossia
- Congenital (e.g., Beckwith-Wiedemann syndrome, Down syndrome, congenital hypothyroidism, Pompe's disease)
- Swelling (e.g., burns, trauma, Ludwig angina)
- Tumors (e.g., hemangiomas, lymphangioma)
- Protruding upper incisors (e.g., Cockayne's syndrome)
- Foreign body

Nasal Pathology
- Choanal atresia
- Tumors (e.g., encephaloceles, gliomas, foreign body)

Palate Pathology
- Arch and cleft defects
- Soft-palate swelling and hematomas

Pharynx
- Adenoid and tonsillar disease
- Hypertrophy
- Tumors and abscesses
- Lingual tonsils
- Pharyngeal wall pathology
- Retropharyngeal and parapharyngeal abscesses
- Inflammatory disease (e.g., epidermolysis bullosa, erythema multiforme bullosum)
- Scarring (e.g., Behçet's syndrome)

Continued

BOX **19-5—cont'd**

Conditions Associated with Difficult Airway Management

Laryngeal Pathology
- Supraglottic
- Laryngomalacia
- Supraglottis (epiglottitis)
- Glottic
- Congenital lesions (vocal cord paralysis, laryngeal web, cyst, laryngocele)
- Papillomatosis
- Granuloma formation
- Foreign body
- Subglottic
- Congenital stenosis
- Infectious (croup)
- Inflammatory (edema, traumatic stenosis)

Tracheal and Bronchial Tree Pathology
- Tracheomalacia (e.g., Larsen syndrome)
- Croup
- Bacterial tracheitis
- Mediastinal masses
- Vascular malformation
- Foreign body aspiration
- Other (e.g., tracheal stenosis, webbing, fistula, diverticulum)

Neck
- Mass lesions
- Lymphatic malformation, hemangioma, teratoma, goiter, abscess
- Skin contracture (postburn, inflammatory [scleroderma, epidermolysis bullosa, erythema multiforme bullosum])
- Webbed (e.g., Turner syndrome)

Spine
- Limited cervical spine mobility
- Congenital (e.g., Klippel-Feil syndrome)
- Acquired (e.g., surgical [fusion], trauma [vertebral fracture], inflammatory [ankylosing spondylitis])
- Cervical spine instability
- Congenital (e.g., Down syndrome, Larsen syndrome, Möbius syndrome, Morquio syndrome)
- Acquired (e.g., trauma [subluxation, fracture], inflammatory [rheumatoid arthritis])

Modified from Holzman RS. Airway management. In: Davis PJ, Cladis FP, Motoyama EK (eds). *Smith's Anesthesia for Infants and Children*. 8th ed. Philadelphia: Mosby; 2011:344-364; Wheeler M, et al. The pediatric airway. In: Cote CJ, Lerman J, Todres ID, eds. *A Practice of Anesthesia for Infants and Children*, 4th ed. Philadelphia: Saunders; 2009:279-292.

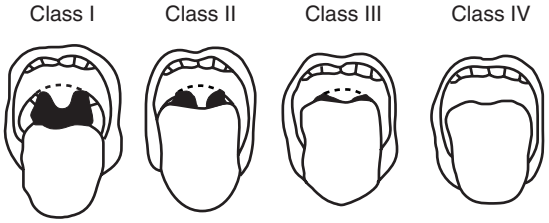

FIGURE **19-2** Modified Mallampati classification of pharyngeal structures. *Class I*, Soft palate, tonsillar fauces, tonsillar pillars, and uvula visualized. *Class II*, Soft palate, tonsillar fauces, and uvula visualized. *Class III*, Soft palate and base of uvula visualized. *Class IV*, Soft palate not visualized. (From Samsoon GL, Young JR. Difficult tracheal intubation: a retrospective study. *Anaesthesia*. 1987;42:487-490.)

BOX **19-6**

Calculation of Ideal Body Weight and Body Mass Index

Ideal Body Weight (IBW)
IBW (male) = 105 lb + 6 lb for each inch >5 ft
IBW (female) = 100 lb + 5 lb for each inch >5 ft

To Calculate Body Mass Index (BMI):
BMI = Weight in kg/(height in meters)^2

Example 1:

70 kg/1.7 m^2 = 70 kg/2.89 m = 24 kg/m^2

Example 2:

125 kg/1.7 m^2 = 125 kg/2.89 m = 43 kg/m^2

ated with the system, it should not be used as the only means of screening for the difficult airway.

Thyromental Distance. Thyromental distance can be quantified to enable prediction of difficulties with laryngoscopy. Thyromental distance represents the straight distance, with the neck fully extended and the mouth closed, between the prominence of the thyroid cartilage and the bony point of the lower mandibular border. In adults, a thyromental distance of less than 7 cm, which is approximately three adult fingerbreadths, is associated with difficult endotracheal intubation because the pharyngeal and laryngeal axes may not properly align, and difficult laryngoscopy can be anticipated.[72]

Interincisor Distance. The degree of mouth opening, largely a function of the temporomandibular joint, is a vital component of airway assessment. Limited temporomandibular joint movement is a well-recognized contributor to difficult endotracheal intubation. An adult should be able to open the mouth at least 4 cm, allowing two large fingers to be placed between the upper and lower incisors. An interincisor gap of less than two fingerbreadths is associated with difficulty in endotracheal intubation.[73] Some patients who are able to open their mouths sufficiently while awake experience limitations in temporomandibular joint mobility after anesthesia is induced. This limited movement renders the visualization of laryngeal structures difficult. In this situation, forward protrusion of the mandible can be attempted for opening the mouth adequately to allow direct laryngoscopy.[74]

Head and Neck Movement (Atlantooccipital Function). Moderate flexion of the neck on the chest and full extension of the atlantooccipital joint aligns the oral, pharyngeal, and laryngeal axes into the McGill, or "sniff," position. In this position, less tongue obscures the laryngeal view during laryngoscopy. Limitations to atlantooccipital joint extension, which are frequently attributed to cervical arthritis or a small C-1 gap, enhance the convexity of the neck and push the larynx anteriorly. This situation can impair laryngoscopy and render endotracheal intubation difficult.

Mandibular Mobility. Have the patient demonstrate the ability to move the jaw forward and bite their upper lip. Being able to protrude the mandible in front of the central incisors indicates relative ease for maneuvering the laryngoscope.

BOX **19-7**

Obesity-Related Comorbidities

Cardiovascular
- Hypertension
- Coronary heart disease
- Hypertrophic cardiomyopathy
- Peripheral vascular disease
- Thromboembolic disease
- Stroke

Dermatologic
- Dermatitis
- Cellulitis
- Panniculitis
- Hirsutism (presence of excess body and facial hair)

Endocrine
- Dyslipidemia (e.g., high total cholesterol, low levels of high density lipoprotein [HDL] cholesterol, or hypertriglyceridemia)
- Liver dysfunction
- Type 2 diabetes
- Gout

Gastrointestinal
- Gallbladder disease (cholelithiasis)
- Hiatal hernia, heartburn
- Gastroesophageal reflux disease (GERD)

Genitourinary
- Complications of pregnancy
- Menstrual irregularities
- Stress incontinence

Malignancies
- Some cancers (e.g., endometrial, uterine, cervical, ovarian, breast, prostate, esophagus, liver, pancreas, kidney, gallbladder, and colorectal)

Maternal
- Pregnancy-induced hypertension (PIH)
- Induced labor, prolonged labor, difficult delivery
- Increased primary cesarean section rate (greater than 50%)
- Increased perinatal mortality
- Pulmonary embolism
- Wound infection
- Maternal death

Musculoskeletal
- Osteoarthritis
- Degenerative joint disease

Psychological
- Depression
- Anxiety disorders

Pulmonary
- Chronic obstructive pulmonary disease (COPD)
- Restrictive pulmonary disease
- Reactive airway disease
- Obstructive sleep apnea
- Pulmonary hypertension

From Marley RA, Hoyle B, Ries C. Perianesthesia respiratory care of the bariatric patient. *J Perianesth Nurs*. 2005;20(6):404-431.

Dentition

The incidence of perianesthetic dental injury in patients undergoing general anesthesia involving endotracheal intubation ranges from 0.02% to 0.07% and is associated with patients who have preexisting poor dentition and characteristics linked with difficult laryngoscopy and intubation (e.g., limited neck motion, previous head and neck surgery, craniofacial abnormalities, history of previous difficult tracheal intubation). Because dental injuries are the most common reason for anesthesia-related medicolegal claims (accounting for one third of all claims in the United States),[75] a preanesthesia inspection of the teeth should be performed and documented for each patient. Otherwise, fractured or missing teeth may be falsely attributed to damage occurring during airway instrumentation. The patient with protuberant or loose maxillary incisors should also be informed of the increased risk of tooth injury or loss with laryngoscopy. An informed consent to proceed with the anesthetic plan, despite this dental risk, must then be documented. If the patient is properly informed of the likelihood of dental damage, the anesthesia provider may not be held liable should dental injury occur.[76]

The location and condition of crowns, braces, and other significant dental work are also noted. Prosthetic devices such as partial plates and dentures are removed before surgery, unless they significantly improve the mask fit. An extremely loose tooth may be extracted before laryngoscopy to prevent its aspiration during anesthesia.

Musculoskeletal System

Obesity

Evaluation of the musculoskeletal system usually begins with a general assessment of the size and stature of the patient. Baseline height and weight information can be obtained from the admission data or by direct questioning of the patient during the health history interview. Body weight is then compared with normal values for a given height in relation to the patient's age and gender. Ideal body weight, for example, can be determined for men and women (Box 19-6). The actual weight of the patient is compared with the calculated ideal body weight. Body weight that is 20% in excess of the ideal body weight at a particular height constitutes obesity. A body weight that is twice the ideal body weight is deemed morbidly obese.

A more scientific approach to describing weight in relation to height uses the measure of body mass index (BMI). Box 19-6 presents the formula for calculating BMI and incorporates it into examples for an average and an overweight individual of the same height. The adult patient weight classification based on BMI is as follows: overweight, 25 to 29.9 kg/m^2; moderate obesity, 30 to 34.9 kg/m^2; severe obesity, 35 to 39.9 kg/m^2; and morbidly obese, greater than or equal to 40 kg/m^2.[77] Two thirds of the adult population in the United States are overweight or obese.[78] Obese patients are at risk of illness from a multitude of conditions (Box 19-7) that require detailed workup.[77]

The morbidly obese patient is at greater risk for cardiopulmonary aberrations, sleep-disordered breathing, and abnormal airway issues. Preoperative assessment scheduled in advance of the surgery should reflect careful attention to these concerns.[77] Appropriate diagnostic testing prior to bariatric surgery has been proposed (Box 19-8).[79,80] Much of this testing centers around the likelihood of patients presenting for bariatric surgery with preexisting metabolic complications or nutritional deficiencies. The extent of preexisting comorbid medical conditions needs to be thoroughly evaluated

BOX **19-8**

Recommended Diagnostic Testing of Candidates for Bariatric Surgery

- 12-lead electrocardiogram—if at least one risk factor for coronary heart disease, poor functional capacity, or both
- Chest radiograph (posteroanterior and lateral)— if BMI 40 kg/m^2 or greater
- Complete blood cell count
- Glycosylated hemoglobin
- Serum chemistries with parameters for liver and kidney function
- Fasting blood glucose
- Lipid profile (total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol)
- Thyroid function (thyrotropin)
- Coagulation studies
- Ferritin
- Vitamins ($B_{12,}$ 25-Hydroxyvitamin D, other fat-soluble vitamins if considering a malabsorptive procedure)
- Minerals and trace elements, for example, zinc, selenium, calcium, magnesium

Adapted from Eldar S, et al. A focus on surgical preoperative evaluation of the bariatric patient—the Cleveland Clinic protocol and review of the literature. *The Surgeon*. 2011;9(5):273-277; Poirier P, et al. Cardiovascular evaluation and management of severely obese patients undergoing surgery: a science advisory from the American Heart Association. *Circulation*. 2009;120(1):86-95; Thompson J, et al. Anesthesia case management for bariatric surgery, *AANA J*. 2011;79(2):147-160.

preoperatively, typically by internal medicine physicians. Serious or life-threatening comorbid conditions associated with obesity are noted in Box 19-9.[79] Patients should receive cardiac assessment in accordance with the American Heart Association guidelines.[81] Asymptomatic patients should be screened for coronary disease if they have an abnormal baseline electrocardiogram; a history of coronary artery disease/valvular disease; or are more than 50 years of age with at least two of the following: metabolic syndrome, diabetes, hypertension, smoking, dyslipidemia, or family history of coronary disease.[82] Patients without comorbid conditions may not require further preoperative workup because diagnostic testing should be individualized based on identified needs.[83]

Obstructive sleep apnea is a breathing disorder distinguished by periodic, partial, or complete obstruction of the upper airway during sleep.[84] More than 70% of patients presenting for bariatric surgery have obstructive sleep apnea.[83] Particular attention is given to a history of snoring, apneic episodes, frequent arousals during sleep (vocalization, shifting position, extremity movements), morning headaches, and daytime somnolence. The physical examination would include airway evaluation, nasopharyngeal characteristics, neck circumference, tonsil size, and tongue volume.[84] A concise, easy to use screening questionnaire for undiagnosed obstructive sleep apnea, known as STOP-Bang (Box 19-10),[85,86] has been shown to be highly sensitive for categorizing obstructive sleep apnea severity.[87,88]

Polysomnography is the current "gold standard" test for establishing a clinical diagnosis of obstructive sleep apnea. If the findings of the history and physical examination are suggestive of obstructive sleep apnea, a decision in consultation with the surgeon should be made regarding obtaining a preoperative sleep study. If the diagnosis of obstructive sleep apnea is confirmed, the patient will be evaluated to determine optimal levels of continuous positive airway pressure (CPAP) therapy. Patients already receiving CPAP therapy will be asked to bring their cleaned home CPAP units to the hospital for postoperative application as needed. If the hospital is to provide the CPAP device, the patient needs to be queried as to the type of interface device the patient uses, pressure settings, and whether supplemental oxygen is required.

Particular attention is given to airway evaluation to determine the likelihood of difficult endotracheal intubation. Patients who

BOX **19-9**

Comorbid Conditions Associated with Obesity

- Known sleep apnea in which patient is noncompliant with continuous positive airway pressure (CPAP)
- $HbA1_C$ (glycosylated hemoglobin) greater than 8% (average blood sugar greater than 200 mg/dL)
- Diabetic nephropathy, retinopathy, or neuropathy
- Cirrhosis
- Pulmonary hypertension
- Pseudotumorcerebri (with severe headaches or impending vision loss)
- Significant coagulopathy (including history of pulmonary embolus, bleeding diathesis, hypercoagulable syndrome, excessive bleeding, more than one deep venous thrombosis, taking Coumadin or clopidogrel medication)
- Chronic steroid therapy
- Oxygen dependent (does not necessarily have to be constant)
- Wheelchair-bound most of the time
- Systemic disease and poor functional capacity (including multiple sclerosis, inflammatory bowel disease, scleroderma, lupus, cancer)
- Severe venous stasis ulcers
- Recent complaint of chest pain (undiagnosed)

Adapted from Eldar S, et al. A focus on surgical preoperative evaluation of the bariatric patient—the Cleveland Clinic protocol and review of the literature. *The Surgeon*. 2011;9(5):273-277.

BOX **19-10**

STOP-Bang Questionnaire for Obstructive Sleep Apnea Screening

STOP

1. Snoring—Do you *snore* loudly (louder than talking or loud enough to be heard through closed door)?	Yes	No
2. Tired—Do you often feel *tired*, fatigued, or sleepy during the daytime?	Yes	No
3. Observed—Has anyone *observed* you stop breathing while you sleep?	Yes	No
4. Blood Pressure—Are you now being or have you been treated for high blood *pressure*?	Yes	No

BANG

BMI—greater than 35 kg/m^2?	Yes	No
Age—greater than 50 years?	Yes	No
Neck circumference greater than 40 cm?	Yes	No
Gender—male.	Yes	No

A high risk of obstructive sleep apnea is defined as a score of 3 or more; low risk of obstructive sleep apnea, a score of less than 3.

Adapted from Seet E, Chung E. Obstructive sleep apnea: perioperative assessment. *Anesthesiol Clin*. 2010;28(2):199-215.

are obese or have short, thick necks or have obstructive sleep apnea have a higher incidence of difficult or failed endotracheal intubation (1:20) than the general population (1:2200).[77] If a problem is anticipated and an awake or fiberoptic tracheal intubation is planned, proper patient preparation, which includes a drying agent and proper upper airway anesthesia, should be instituted.

The patient should be questioned about the use of antiobesity drugs such as amphetamines, nonamphetamine Schedule IV appetite suppressants, and antidepressants (e.g., fluoxetine, sertraline).

Ankylosing Spondylitis and Rheumatoid Arthritis

Disorders of the musculoskeletal system include degenerative disk disease (osteoarthritis), ankylosing spondylitis, and rheumatoid arthritis. The chronic pain and inflammation of spinal or extraspinal joints associated with these diseases limit the degree of patient mobility. Tolerance for positions required during surgery and regional anesthesia techniques should therefore be ascertained preoperatively. Traditional ankylosing spondylitis treatments (nonsteroidal antiinflammatory drugs, sulfasalazine, methotrexate, and local corticosteroid injections) and biologic therapies (tumor necrosis factor [TNF]-alpha antagonists) may be included in pharmacologic regimens for such patients.[89,90] A thorough family history and previous dental, obstetric, surgical, traumatic injury, transfusion, and drug histories should be elicited from patients taking these drugs to evaluate the propensity for bleeding. A history suggestive of a bleeding disorder (e.g., excessive bruising or prolonged bleeding) should lead to a patient work-up that may include measurement of international normalized ratio (INR), platelet count, prothrombin time, and activated partial thromboplastin time.[91]

If the dosage and duration of corticosteroid therapy are considerable in patients with rheumatoid arthritis, perioperative supplementation also may be necessary to avoid hemodynamic instability. Patients considered at risk for adrenal insufficiency include those who received the hydrocortisone equivalent of more than 20 to 30 mg daily for longer than 2 weeks during the previous year and those who are receiving replacement corticosteroid treatment for adrenal insufficiency.[92] Patients with proven or suspected adrenal insufficiency or suppression should be evaluated for perioperative steroid coverage (Table 19-4).[93-96]

Although less common than osteoarthritis, ankylosing spondylitis and rheumatoid arthritis have greater implications for anesthetic management. Systemic manifestations are extensive during the advanced stages of both disorders. Patients frequently have pain, inflammation, and limited mobility in affected joints, such as those in the back and hands. Extreme ankylosis and joint deformity often make peripheral venous access and intraoperative positioning a challenge. On physical examination, limited range of motion of the temporomandibular joint and cervical spine, and reduced mouth opening, can make tracheal intubation more difficult.[97] In rheumatoid arthritis, this limitation is compounded by restrictions in vocal cord movement or tracheal stenosis caused by cricoarytenoid arthritis. These changes may be evidenced by preoperative hoarseness, stridor, painful speech, or dysphagia. Restrictive lung disease, polychondritis, pleural and pericardial effusions, and cardiac conduction abnormalities may be present during advanced stages of ankylosing spondylitis or rheumatoid arthritis.[98,99]

Neurologic System

Preoperative evaluation of the neurologic system includes the determination of CNS or peripheral nervous system dysfunction.

TABLE 19-4 Recommendations for Perioperative Glucocorticoid Coverage

Degree of Surgical Stress	Recommended Dose
Minor (inguinal hernia repair)	Preoperative corticosteroid dose + hydrocortisone 25 mg or equivalent
Moderate (lower extremity revascularization, total joint replacement)	Preoperative corticosteroid dose + hydrocortisone 50-75 mg or equivalent
Major (cardiac surgery, aortic aneurysm repair)	Preoperative corticosteroid dose + hydrocortisone* 100-150 mg or equivalent every 8 hr for 48-72 hr

From Nagelhout J, Elisha S, Waters E. Should I continue or discontinue that medication? *AANA J.* 2009;77(1):59-73.
*Hydrocortisone has mineralocorticoid activity at doses above approximately 100 mg per day. The mineralocorticoid activity of hydrocortisone may produce undesirable side effects including fluid retention, edema, and hypokalemia. It is preferable to use a glucocorticoid without mineralocorticoid activity, such as methylprednisolone, when the total dose of hydrocortisone exceeds 100 mg per day. Methylprednisolone 4 mg is equivalent to hydrocortisone 20 mg.

An initial neurologic examination consisting of the following should be performed[100]:

- *Musculoskeletal (motor) system:* Observe the patient's gait, ability to perform toe-and-heel walk, ability to maintain the arms held forward; evaluate the patient's grip strength
- *Sensory system:* Physical distinction of vibration, pain, and light touch on the patient's hands, feet, and limbs
- *Muscle reflexes:* Deep, superficial, and pathologic
- *Cranial nerve abnormalities*: Obtained by patient medical history and observation
- *Mental status and speech pattern:* Appearance, mood, thought processes, cognitive function

Knowledge of clinical manifestations of neurologic disease is essential for the preoperative evaluation of patients with CNS or peripheral nervous system disorders. Signs and symptoms of increasing intracranial pressure and cerebral ischemia, for example, may include papilledema; unilateral mydriasis; headaches, made worse by coughing; nausea and vomiting; slurred speech, disorientation, and altered levels of consciousness; flaccid hemiplegia or hemiparesis; abducens or oculomotor palsy; neck rigidity; and respiratory disturbances. Hypertension, with corresponding decreases in heart rate, represents a physiologic attempt to enhance cerebral perfusion when intracranial pressure is high. The appearance of Q waves, deep and inverted T waves, prolonged QT intervals, and ST-segment elevations on the electrocardiogram (ECG) may reflect hypothalamic ischemia and sympathetic overactivity. These abnormalities are most often attributed to vasospasm after a subarachnoid hemorrhage, but myocardial ischemia should be ruled out before surgery.[101] Fever and leukocytosis also can follow a subarachnoid hemorrhage as a result of meningeal irritation by subarachnoid blood. The progression of neurologic dysfunction to coma, obtundation, and decerebrate rigidity worsens the overall prognosis of the patient with an intracranial mass or hemorrhage. This prognosis mirrors that of a patient who has sustained an acute head injury. The patient with an initial Glasgow Coma Scale (Table 19-5)[102] score of less than 8 is considered comatose. Patients with a score of 8 or less usually require tracheal intubation and mechanical hyperventilation.[103]

Diagnostic reports should be reviewed so that the extent of neurologic and coexisting disease can be determined. These

TABLE 19-5 Glasgow Coma Scale

Response	Score
Eyes Open	
Spontaneously	4
To speech	3
To pain	2
Never	1
Best Motor Response	
Obeys commands	6
Localizes pain	5
Withdraws (flexion)	4
Abnormal flexion (decortication)	3
Extensor response (decerebration)	2
None	1
Best Verbal Response	
Oriented	5
Confused conversation	4
Inappropriate words	3
Incomprehensible sounds	2
None	1
Range of Scores	3-15

Modified from Teasdale G, Jennett B. Assessment of coma and impaired consciousness: a practical scale. *Lancet*. 1974; 2(7872):81-84.

BOX 19-11

Active Cardiac Conditions for Which the Patient Should Undergo Evaluation and Treatment Before Noncardiac Surgery

Unstable Coronary Syndromes
- Unstable or severe angina
- Recent myocardial infarction (MI) within 30 days

Decompensated Heart Failure
Significant Arrhythmias
- High-grade atrioventricular block
- Symptomatic ventricular arrhythmias
- Supraventricular arrhythmias with uncontrolled ventricular rate (greater than100 beats/min at rest)
- Symptomatic bradycardia
- Newly recognized ventricular tachycardia

Severe Valvular Disease
- Severe aortic stenosis (mean pressure gradient greater than 40 mmHg, area less than 1 cm^2 or symptomatic)
- Symptomatic mitral stenosis

Clinical Risk Factors
- History of ischemic myocardial disease
- Currently stable but history of heart disease
- History of cerebrovascular disease
- Diabetes (insulin dependent)
- Renal failure (serum creatinine [SCr] greater than 2 mg/dL)

From De Hert S, et al. Preoperative evaluation of the adult patient undergoing non-cardiac surgery: guidelines from the European Society of Anaesthesiology. *Eur J Anaesthesiol*. 2011;28(10):684-722.

reports include the results of electromyography, conduction velocity studies, electroencephalography, computed tomography (CT), magnetic resonance imaging (MRI), and cerebral arteriography studies. Consultation with a neurologist and obtaining preoperative electromyography, for example, are recommended for patients with complaints of extremity weakness, pain, or paresthesia. This screening is especially important in patients at greater risk for peripheral neuropathy (e.g., patients with long-standing diabetes, patients with uremia, chronic alcoholics with nutritional deficits).

Documentation of symptoms and reports of abnormal preoperative neurologic findings is important in these patients. Preoperative CT that reveals a 0.5-cm midline shift of the brain is significant and can confirm suspicions of intracranial hypertension. The size and location of an intracerebral aneurysm are represented on cerebral arteriography. This information can facilitate the prediction of the surgical approach and guide the evaluation of neurologic involvement. The degree of collateral circulation in the patient with cerebrovascular occlusive disease can be determined from arteriographic films. In a patient with vertebral artery involvement, for example, extremes in head flexion, extension, and rotation are avoided. Because of the associated risks of perioperative myocardial ischemia and infarction in patients undergoing a carotid endarterectomy procedure, a thorough cardiac evaluation by a cardiologist, including 12-lead ECG and stress testing, is advised.[104]

Information gained from the preoperative evaluation of neurologic function can enlighten the management of a patient with a CNS or peripheral nervous system disorder. For example, sedatives are avoided in patients with intracranial hypertension, especially when an altered level of consciousness accompanies the hypertension. Affected patients may be extremely sensitive to the CNS-depressant effects of such drugs as opioids.

Doses, schedules, and adverse effects of therapeutic regimens should also be considered before surgery. Serum concentrations of anticonvulsants such as phenytoin and phenobarbital are measured to determine whether levels are therapeutic. A complete blood cell count is obtained for patients receiving prolonged phenytoin therapy because of the risk of agranulocytosis associated with this drug. As with anticonvulsant therapy, corticosteroid therapy is continued perioperatively in patients with a CNS tumor. Although the exact mechanism of the beneficial effects of corticosteroids is unknown, it is theorized to involve the reduction of cerebrospinal fluid production or cerebral edema as a result of capillary membrane stabilization. Blood glucose levels are also determined for the patient treated with either dexamethasone or methylprednisolone, because hyperglycemia frequently accompanies the use of these drugs. Heightened risks of pulmonary infection and gastrointestinal irritation are unlikely in the patient undergoing perioperative therapy.[105]

Cardiovascular System

Preanesthesia patient evaluation for cardiovascular risk includes the determination of (1) preexisting cardiac disease (e.g., hypertension, ischemic heart disease, valvular dysfunction, cardiac arrhythmias, and cardiac conduction abnormalities, with or without evidence of ventricular failure); (2) disease severity, stability, and prior treatment; (3) comorbidity (e.g., diabetes mellitus, peripheral vascular disease, chronic pulmonary disease); and (4) surgical procedure. The prevalence and adverse consequences of cardiovascular disease make it a prime consideration in the overview of systems. Major cardiovascular risk factors that correlate with increased perioperative morbidity and mortality have been described by the European Society of Anaesthesiology (Box 19-11).[4] The type of surgery for which the patient is scheduled impacts on the likelihood of developing perioperative adverse

BOX 19-12

Surgical Risk Estimates

High Risk (Cardiac risk greater than 5%)
- Aortic surgery
- Major vascular surgery
- Peripheral vascular surgery

Intermediate Risk (Cardiac risk 1%-5%)
- Intraperitoneal
- Transplant (e.g., renal, liver, pulmonary)
- Carotid
- Peripheral arterial angioplasty
- Endovascular aneurysm repair
- Head and neck surgery
- Major neurologic/orthopedic (e.g., spine, hip)
- Intrathoracic
- Major urologic

Low Risk (Cardiac risk less than 1%)
- Breast
- Dental
- Endoscopic
- Superficial
- Endocrine
- Cataract
- Gynecologic
- Reconstructive
- Minor orthopedic (e.g., knee surgery)
- Minor urologic

From De Hert S, et al. Preoperative evaluation of the adult patient undergoing non-cardiac surgery: guidelines from the European Society of Anaesthesiology. *Eur J Anaesthesiol.* 2011;28(10):684-722.

TABLE 19-6 Exercise Tolerance in Metabolic Equivalents (METs) for Various Activities

Estimated Energy Expenditure	Physical Activity
1 MET*	*Poor functional capacity*
	Self-care Eating, dressing, or using the toilet Walking indoors and around the house Walking one to two blocks on level ground at 2 to 3 mph[2]
4 METs	*Good functional capacity*
	Light housework (e.g., dusting, washing dishes) Climbing a flight of stairs without stopping, or walking up a hill longer than 1 to 2 blocks Walking on level ground at 4 mph Running a short distance Heavy housework (e.g., scrubbing floors, moving heavy furniture) Moderate recreational activities (e.g., golf, dancing, doubles tennis, throwing a baseball or football)
Greater than 10 METs	*Excellent functional capacity*
	Strenuous sports (e.g., basketball, cross-country skiing [> 8 km/hr][3], rope skipping, running, soccer, swimming [> 3.5 km/hr], weight training)

Modified from Jetté M, Sidney K, Blümchen G. Metabolic equivalents (METS) in exercise testing, exercise prescription, and evaluation of functional capacity. *Clin Cardiol.* 1990;13(8):555-565; Fleisher LA, et al. ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery. *Circulation.* 2007;116(17):1971-1996.
*MET is defined as the amount of oxygen consumed while sitting at rest and is equal to 3.5 mL oxygen/kg/min.
mph, Miles per hour; *km/hr*, kilometer per hour.

cardiac events (cardiac death, MI) within 30 days following surgery (Box 19-12)[4,14]

The patient's functional capacity, measured in metabolic equivalents (METs), can be simply and accurately assessed preoperatively by asking a set of questions (Table 19-6)[106,107] and is recommended as part of cardiac risk assessment.[14] Patients with good functional capacity (more than 4 METs) may proceed for surgery provided patients with cardiac risk factors are properly managed with statin and beta-blocker therapy.[14] Good functional capacity (more than 4 METs) may be determined by an affirmative answer to two simple questions: (1) Are you able to walk four blocks without stopping regardless of limiting symptoms? (2) Are you able to climb two flights of stairs without stopping regardless of limiting symptoms?[108] The inability to climb two flights of stairs or walk a short distance is indicative of poor functional capacity and is associated with an increased incidence of postoperative cardiac complications in noncardiac surgery.[109,110] Patients with moderate to poor functional capacity (less than 4 METs) should be further assessed to identify cardiac risk factors.[14]

A standard means of categorizing the degree of cardiovascular disability is the New York Heart Association classification tool (Table 19-7).[111] When the patient interview is conducted, specific inquiry should be made regarding the presence of dyspnea, chest pain, fatigability, syncope, palpitation, and the factors that predispose to angina. Lee et al.[112] developed a Revised Cardiac Risk Index (Box 19-13), which offers an improved predictive risk index for major postoperative cardiac complications. Whenever a patient has signs of significant cardiovascular disease, referral to a cardiologist is indicated for assessment and possible intervention.[4]

Hypertension

Hypertension, defined as a systolic blood pressure greater than 140 mmHg or a diastolic pressure greater than 90 mmHg,[113] is the most common circulatory derangement to affect humans (approximately 65 million in the United States; 45% to 50% of adults older than 70 years) and is a major risk factor for coronary artery disease[110,114] and increased perioperative mortality.[115] Increasingly, patients undergoing surgery have stage 2 hypertension and accompanying target-organ damage, or uncontrolled stage 3 hypertension (systolic blood pressure greater than 180 mmHg, diastolic pressure greater than 110 mmHg, or both). This problem can be attributed to the lack of or inadequacy of medical treatment or to patient noncompliance. In such a situation, elective surgery may be postponed for further patient assessment and normalization of the preoperative blood pressure.[116,117] Consultation with an internist can be pursued for the medical evaluation and treatment of the patient with uncontrolled or newly diagnosed hypertension. These recommendations are aimed at reducing the occurrence of perioperative hemodynamic instability and consequently the incidence of myocardial ischemia. Both complications are more likely to occur when hypertension is not effectively treated before surgery.[118] With the goal of reducing perioperative risk, delaying surgery is justified in hypertensive patients with target-organ damage (or suspected damage) such as ischemic heart disease, heart

TABLE 19-7 New York Heart Association Functional Classification of Cardiovascular Disability

Classification	Cardiovascular Status
Class I	*Patients with cardiac disease*
	No functional limitations to physical activity, such as walking or climbing stairs. Ordinary physical activity is not associated with undue fatigue, palpitations, dyspnea, or anginal pain.
Class II	*Patients with cardiac disease who are comfortable at rest*
	Slight functional limitations to physical activity, such as walking or climbing stairs rapidly, or during emotional stress. Patients are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III	*Patients with cardiac disease resulting in marked limitations to physical activity*
	Patients are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitations, dyspnea, or anginal pain.
Class IV	*Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort*
	Symptoms of cardiac insufficiency or anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Modified from Kaplan JA, Reich DL, Savino JS. *Kaplan's Cardiac Anesthesia: The Echo Era*, 6th ed. Philadelphia: Saunders; 2011.

BOX 19-13

Revised Cardiac Risk Index

Risk Categories

- High-risk surgery (aortic, major vascular, peripheral vascular)
- Ischemic heart disease (previous myocardial infarction; previous positive result on stress test, use of nitroglycerin; typical angina; ECG Q waves; previous PCI or CABG)
- History of compensated previous congestive heart failure (history of heart failure; previous pulmonary edema; third heart sound; bilateral rales; evidence of heart failure on chest radiograph)
- History of cerebrovascular disease (previous TIA; previous stroke)
- Diabetes mellitus (with or without preoperative insulin)
- Renal insufficiency (creatinine greater than 2.0 mg/dL)

Estimated Rates for Postoperative Major Cardiac Complications per Number of Risks

- 0 Risk Factors: 0.4%
- 1 Risk Factor: 0.9%
- 2 Risk Factors: 7%
- 3 or more Risk Factors: 11%

From Lee TH, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation*. 1999;100(10):1043-1049; Freeman WK, Gibbons RJ. Perioperative cardiovascular assessment of patients undergoing noncardiac surgery. *Mayo Clin Proc*. 2009;84(1):79-90.
ECG, Electrocardiogram; *PCI*, percutaneous coronary intervention; *CABG*, coronary artery bypass grafting; *TIA*, transient ischemic attack.

failure, renal damage, and cerebrovascular diseases if either of the following scenarios is probable[119]:

- Conditions can be improved by such postponement to the extent that the perioperative risk would be considerably decreased.
- Care may be influenced by further preoperative examination.

Delaying elective surgery in patients with mild to moderate hypertension only for the purpose of blood pressure control may not reduce perioperative risk.[119] A systolic blood pressure below 180 mmHg and diastolic blood pressure below 110 mmHg is not an independent risk factor for perioperative cardiovascular complications.[107]

The practitioner taking the medical history should focus on identifying comorbid diseases, such as diabetes mellitus, and social risk factors (i.e., tobacco use, alcohol or caffeine consumption, illicit drug use [especially cocaine or amphetamines]). What medications the patient takes to manage hypertension should be established. In general, the substances used affect the central and peripheral components of the sympathetic nervous system by altering the synthesis, release, biotransformation, or end-organ action of norepinephrine. Because the circulatory-depressant effects of general anesthesia may be additive, the combination of antihypertensive drugs and anesthetics is of concern. Complaints of syncope and dizziness also are investigated. These symptoms may be the clinical manifestations of cerebrovascular insufficiency, although a diagnosis of drug-induced orthostatic hypotension should be considered preoperatively. This diagnosis can be confirmed by measuring a significant decrease in the blood pressure as the patient rises from the supine position. The lack of hemodynamic compensatory responses that normally accompany positional changes may then predict their absence during anesthesia and surgery.

The physical examination of the patient includes the following[120]:

- *Overall appearance:* Truncal obesity with purpura and striae suggestive of Cushing disease
- *Vital signs:* Measurement of blood pressure in both arms
- *Funduscopic examination:* Hypertensive retinopathy
- *Neck:* Carotid bruits, distended veins, or enlarged thyroid gland
- *Heart:* Abnormal rhythm or size, murmurs, or heart sounds
- *Lungs:* Rales or bronchospasm
- *Abdomen:* Bruits, masses, enlarged kidneys, or abnormal aortic pulsation
- *Extremities:* Delayed or absent femoral pulses secondary to aortic coarctation; evidence of atherosclerosis, peripheral edema
- *Neurologic evaluation:* See the discussion of the neurologic system earlier in this chapter

Ischemic Heart Disease

Myocardial ischemia occurs secondary to insufficient oxygen and nutrient supply (increased demand, reduced blood supply, or both) to meet the metabolic requirements of the myocardial cells. Nearly one third of the estimated 30 million patients undergoing surgery annually in the United States is at high risk for coronary artery disease or factors for cardiovascular disease.[121] Risk factors for ischemic heart disease include advanced age, smoking, diabetes mellitus, hypertension, pulmonary disease, previous MI, left ventricular wall motion dysfunction, and peripheral vascular disease.[122] The preoperative evaluation of a patient with known or suspected ischemic heart disease is aimed at determining the severity, progression, and functional limitations imposed by

cardiovascular disease. Myocardial ischemia, cardiac arrhythmias, and left ventricular dysfunction are usually precipitating factors for patient symptomatology. Complaints of undue fatigue, angina pectoris, palpitations, syncope, or dyspnea should be thoroughly investigated. A 12-lead ECG is reviewed for evidence of myocardial ischemia or infarction, cardiac arrhythmias or conduction abnormalities, and ventricular hypertrophy. Signs and symptoms of myocardial ischemia may not be apparent at rest, however. Therefore the response of the patient to various activities, such as walking a certain distance or climbing several stairs, must be determined (see Tables 19-6[106,107] and 19-7[111]).

Anginal symptoms can also be classified according to the stability of precipitating factors, the frequency of the events, and the duration of pain. Stable angina (characterized as substernal discomfort brought on by exertion, relieved by rest or nitroglycerin or both in less than 15 minutes, and having a typical radiation to the shoulder, jaw, or the inner aspect of the arm)[111] poses no greater threat of MI perioperatively than the absence of anginal symptoms.[123] Unstable angina is defined as newly developed angina occurring within the past 2 months; angina that has progressively worsened, that occurs with increased frequency, intensity, or duration, that is less responsive to medicine, or that occurs when the patient is at rest; or angina that lasts longer than 30 minutes, exhibiting transient ST- or T-wave changes without development of Q waves or diagnostic elevation of enzymes.[111] *Unstable angina is associated with the highest risk for perioperative MI*.[124] In the patient with unstable angina, elective surgery is canceled until the cardiovascular status of the patient has been thoroughly evaluated and optimized. Advanced diagnostic techniques such as coronary angiography and exercise ECG may be used for determination of the extent and functional impairment of ischemic heart disease.

The overall risk of MI after general anesthesia is approximately 0.3% in the population at large.[125] In patients known to have had an MI in the remote past (more than 6 months previously), the risk of perioperative reinfarction increases to approximately 6%. If MI occurred 3 to 6 months previously, the risk of reinfarction is 15%; within 3 months previously, 30%. If reinfarction occurs, the mortality rate is approximately 50%. The highest at-risk period appears to be within 30 days after an acute MI; therefore the ACC/AHA (American College of Cardiology Foundation/American Heart Association) guidelines recommend waiting at least 4 to 6 weeks after an MI before a patient undergoes elective surgery. Patients who have survived coronary revascularization and are asymptomatic are at lower risk of reinfarction when undergoing noncardiac surgery.[107] The new clinical classification of myocardial infarction is noted in Table 19-8.[126]

Coronary Stents. Approximately 528,000 coronary stents are placed annually in United States patients to open clogged coronary arteries.[127] Coronary stents (either bare metal or drug-eluting) were designed to prevent arterial restenosis after percutaneous coronary intervention with balloon angioplasty. Bare metal stents, while beneficial over balloon angioplasty in reducing the incidence of restenosis, experience a restenosis rate of 20%.[128] Drug-eluting stents were developed to further reduce the incidence of stent thrombosis, and restenosis rates approaching 5% after 2 years are reported.[129] Postprocedure pharmacotherapy involves long-term oral dual antiplatelet therapy, consisting of aspirin (continue indefinitely) and clopidogrel (typically continue for at least 1 year) to prevent in-stent coronary artery restenosis.[130] Approximately 5% of these patients will require noncardiac surgery within 1 year after placement of coronary stents.[131] There is an increased risk of coronary stent thrombosis, perioperative MI, hemorrhagic complications, and death in patients having noncardiac surgery performed early after stent placement.[132,133] Box 19-14[134-138] and Figure 19-3[135,139] describe preoperative assessment and management considerations for patients presenting for surgery in which coronary artery stents have been placed.

TABLE 19-8 New Clinical Classifications of Myocardial Infarction

Classification	Description
1	Spontaneous MI related to ischemia due to a primary coronary event, such as plaque erosion and/or rupture, fissuring, or dissection
2	MI secondary to ischemia due to an imbalance of O_2 supply and demand, as from coronary spasm or embolism, anemia, arrhythmias, hypertension, or hypotension
3	Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggesting ischemia with new ST-segment elevation, new left bundle branch block, or pathologic or angiographic evidence of fresh coronary thrombus—in the absence of reliable biomarker findings
4a	MI associated with PCI
4b	MI associated with documented in-stent thrombosis
5	MI associated with CABG surgery

From Thygesen K, et al. Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction: universal definition of myocardial infarction. *J Am Coll Cardiol*. 2007;50(22):2173-2195.
MI, Mycocardial infarction; *PCI*, percutaneous coronary intervention; *CABG*, coronary artery bypass graft.

Left Ventricular Dysfunction

Active left ventricular failure is the prominent cardiovascular risk factor for patients undergoing noncardiac surgery.[140] Patients with ischemic cardiomyopathy are at even greater risk for perioperative MI and ventricular dysfunction.[141] Heart failure is defined by the presence of any of the following: history of congestive heart failure, pulmonary edema, or paroxysmal nocturnal dyspnea; physical examination showing bilateral rales or S_3 gallop; or chest X-ray showing pulmonary vascular redistribution.[107] Prominent signs include moist rales in the lungs, often associated with tachypnea. These extraneous sounds may be confined to the bases, with mild degrees of left ventricular failure, or they may be generalized throughout the lungs, with acute pulmonary edema. As a result of sympathetic nervous system stimulation, resting tachycardia may also be present. A third heart sound (S_3) or ventricular gallop, jugular vein distention, and peripheral edema are significant. In the presence of congestive heart failure as confirmed by a chest radiograph, elective surgery should be postponed until optimal ventricular performance can be achieved.

Patients exhibiting dyspnea of unknown origin or current or prior heart failure with worsening dyspnea or other relevant change in clinical status should undergo preoperative evaluation of left ventricular function if an assessment has not been performed within the previous 12 months.[107] Tests of resting left ventricular function include cardiac magnetic resonance,[142] radionuclide angiography, two-dimensional echocardiography, and contrast ventriculography. Systolic left ventricular dysfunction is defined as a left ventricular ejection fraction less than 50%, with and without accompanying diastolic dysfunction.[143] A left ventricular ejection fraction of less than 35% as determined by

BOX **19-14**

Preoperative Considerations for the Patient with Coronary Stent

Stents
- Type of stent (s) (e.g., BMS, DES)?
- When were stent(s) placed?
- Complications during the revascularization, such as malposition, longer length, overlapping?

Antiplatelet Therapy
- What is antiplatelet regimen?
- What is the recommended duration of antiplatelet therapy?
- Consult interventional cardiologist or patient cardiologist regarding antiplatelet management.

Elective Surgery
Delay until completion of dual antiplatelet therapy (aspirin and clopidogrel) with resultant complete stent endothelialization
- *BMS:* 6 weeks minimum after PTCA
- *DES:* 12 or more months if patient is not at high risk of bleeding after PTCA

Nonelective Surgery
- *Determine risk for surgical bleeding:* If not at high risk, continue dual antiplatelet therapy. Discontinuation of dual antiplatelet therapy, in patients with incomplete stent endothelialization, markedly increases the risk of stent thrombosis, myocardial infarction, and death.
- *High risk for bleeding:* Risk primarily associated with closed space surgeries (i.e., medullary canal spine surgery, intracranial surgery, posterior chamber eye surgery) where increased tissue pressure would be deleterious. If dual antiplatelet therapy must be interrupted, aspirin should be continued, when possible. An evolving treatment option involves "bridging therapy" anticoagulation in which drugs of short duration (glycoprotein inhibitor, e.g., tirofiban, eptifibatide; direct thrombin inhibitor, e.g., bivalirudin; unfractionated heparin; low molecular weight heparin; nonsteroidal antiinflammatory drugs, e.g., flurbiprofen; COX-1 inhibitors) are administered for up to 6 hours during the surgery, with the goal of preventing stent thrombosis while dual antiplatelet therapy is interrupted. Restart dual antiplatelet therapy as soon as possible after the surgery.
- Surgery should be performed in an institution where higher-acuity care and an interventional cardiologist are available when possible. Consult prior to surgery to determine procedural complexities, and determine optimal antiplatelet therapy and requisite patient management.

Data from Hall R, Mazer CD. Antiplatelet drugs: a review of their pharmacology and management in the perioperative period. *Anesth Analg*. 2011; 112(2):292-318; Newsome LT, et al. Coronary artery stents: II. Perioperative considerations and management. *Anesth Analg*. 2008;107(2):570-590; Grines CL, et al. Prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents: a science advisory from the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, with representation from the American College of Physicians. *Circulation*. 2007;115(6):813-818; Khair T, et al. Contemporary approaches to perioperative management of coronary stents and to preoperative coronary revascularization: a survey of 374 interventional cardiologists. *Cardiovasc Revascul Med*. 2011(2);12:99-104; American Society of Anesthesiologists Committee on Standards and Practice Parameters. Practice alert for the perioperative management of patients with coronary artery stents: a report by the American Society of Anesthesiologists Committee on Standards and Practice Parameters. *Anesthesiology*. 2009;110(1):22-23.
BMS, Bare metal stents; *DES*, drug-eluting stents; *PTCA*, percutaneous balloon angioplasty.

echocardiography is associated with greater incidence of postoperative heart failure and death.[144]

Valvular Heart Disease

Basic lesions of valvular heart disease may involve stenosis, incompetence, or both. In adults, aortic and mitral valve lesions are more common than those involving the tricuspid or pulmonic valve. Despite decreasing incidence, rheumatic heart disease is still the most common cause of adult valvular disease. Degenerative disorders (sclerosis, fibrosis) and congenital diseases are less common causes. With stenosis, the chamber proximal to the obstruction must increase the work of maintaining a stroke volume; this eventually results in hypertrophy. Normal valves can episodically accommodate up to seven times the normal cardiac output—for example, in intense physical exercise in the normally active patient. Valvular stenosis usually is chronic and severe before cardiac output decreases. In valvular incompetence, the chambers both proximal and distal to the lesions are involved, because regurgitant flow during one phase of the cardiac cycle is added to forward flow during subsequent systole. Because lesions are almost never entirely unitary, in stenosis some regurgitation is common, and vice versa. It is important to identify the type of valvular lesion before surgery. Evaluation of the clinical symptoms and cardiac catheterization data regarding valve area and gradients, combined with assessment of data from any surgical history (e.g., correction of congenital heart lesions), is an important component of the preoperative evaluation of patients with valvular heart disease.

Severe aortic stenosis poses the greatest patient risk for noncardiac surgery,[107] especially when the cross-sectional area of the aortic valve is less than 1 cm^2. Severe aortic stenosis is associated with a 14-fold greater incidence of perioperative sudden death.[145] For patients in whom aortic stenosis is symptomatic, elective noncardiac surgery should be postponed until after cardiac surgical consultation.[107] Chapter 23 describes the perioperative care of patients with valvular heart disease.

Arrhythmias

Patients with cardiac arrhythmias must have an adequate preoperative evaluation to ascertain the nature of the arrhythmia, associated underlying heart disease, and type of antiarrhythmic therapy. Whether symptoms of palpitations or dizziness have been relieved may be a sign of successful therapy or continuing problems. Other cardiac symptoms such as dyspnea, angina, or syncope may suggest worsening of associated cardiac disease. Treatment of the underlying disease preoperatively may aid in control of arrhythmia in the perioperative period. All patients with a history of symptomatic arrhythmias should undergo electrocardiography with rhythm strip before surgery. Other preoperative laboratory evaluations should include measurement of potassium and magnesium levels, determination of antiarrhythmic drug levels (if possible), and chest radiography (in the presence of structural cardiac disease).

Ventricular arrhythmias are classified into three categories: benign ventricular arrhythmias (unifocal premature ventricular

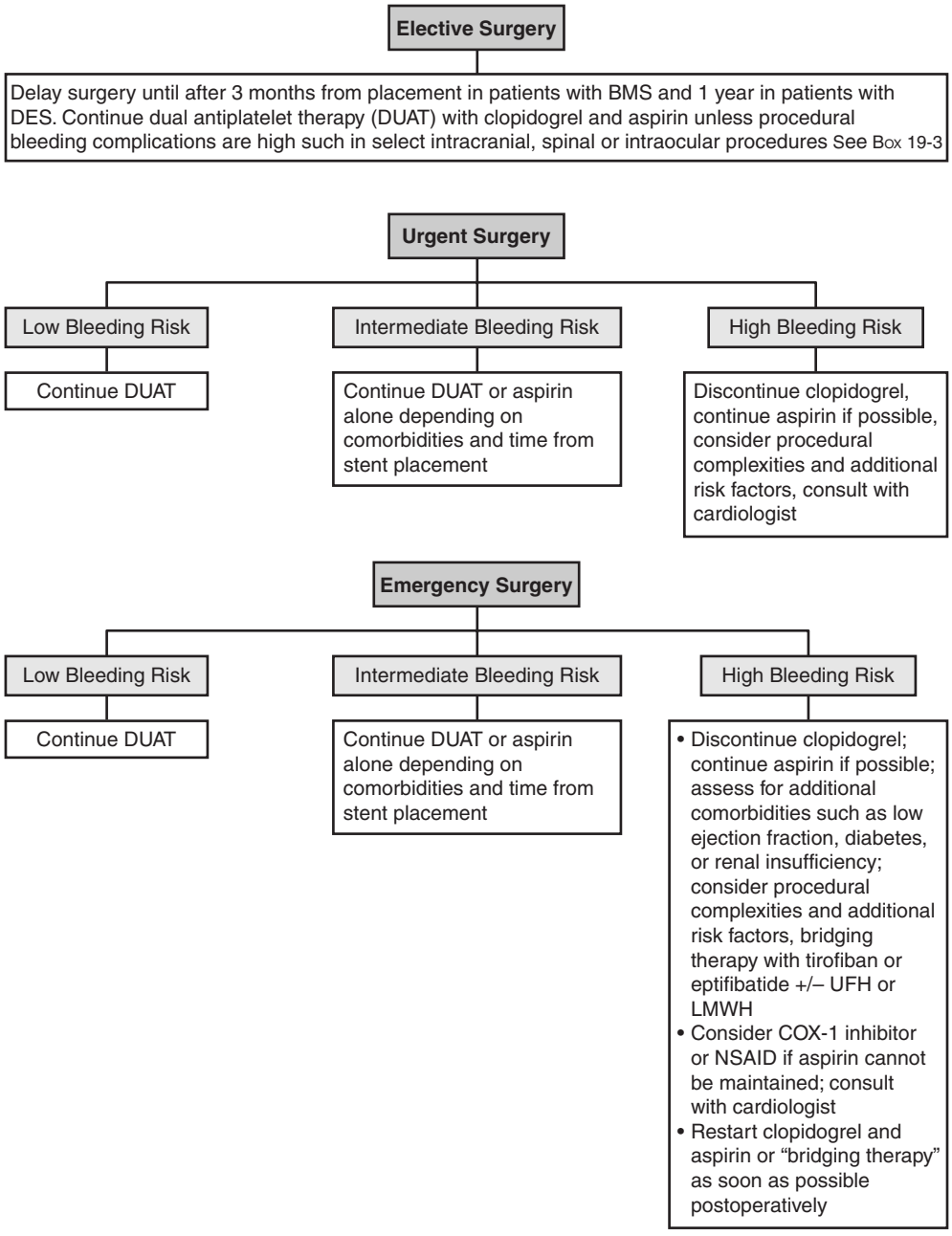

FIGURE **19-3** Perioperative management of patients with coronary stents. (Modified from Newsome LR, et al. Coronary artery stents: II. Perioperative considerations and management. *Anesth Analg*. 2008;107:570-590; Abualsaud AO, Eisenberg MJ. Perioperative management of patients with drug-eluting stents. *J Am Coll Cardiol Intv*. 2010;3:131-142; American Society of Anesthesiologists Committee on Standards and Practice Parameters: Practice alert for the perioperative management of patients with coronary artery stents: a report by the American Society of Anesthesiologists Committee on Standards and Practice Parameters. *Anesthesiology*. 2009;110[1]:22-23.)

contractions); potentially malignant ventricular arrhythmias (patient has known organic heart disease and is on antiarrhythmic therapy); and malignant ventricular arrhythmias (patient has organic heart disease, hemodynamic compromise, and possibly a family history of sudden death).[146] Few data are available to help correlate the risk of arrhythmias and perioperative risk.[111] In the absence of cardiac disease, benign ventricular arrhythmias do not carry a significantly increased surgical risk.[147] In patients with severe coronary artery disease, recent MI, or peripheral vascular disease, arrhythmias may increase perioperative risk.[148,149]

Cardiovascular Implantable Electronic Devices (Pacemaker, Implantable Defibrillators)

When a patient presents for surgery with an implanted cardiac device, preprocedural planning must be employed to minimize risk to patient, and the device. This planning includes knowledge of the device, its indication for use, and functional assessment (Box 19-15).[150-153] Because of the evolving complexity of these devices, direct interrogation by a qualified member of the cardiovascular implantable electronic device (CIED) management team remains the only trustworthy method for evaluating battery status, lead performance, and adequacy of current settings.[154]

BOX **19-15**

Perioperative Guidelines for the Patient with a Cardiovascular Implantable Electronic Device

Preoperative Key Points

- Establish the indication for the permanent pacemaker, for example, symptomatic third-degree heart block, type II second-degree heart block, sinus node dysfunction, recurrent neurally mediated syncope, some forms of cardiomyopathy.
- Establish the indication for the implantable defibrillator, for example, history of cardiac arrest not secondary to a temporary condition.
- Identify device and manufacturer (available from manufacturer's identification card).
- Notify the cardiovascular implantable electronic device (CIED) management team of the planned procedure, including anatomic location of surgery, whether monopolar electrosurgery will be used, and whether other sources of electromechanical interference (EMI) will be present. Have the pacemaker or defibrillator interrogated by a qualified member of the CIED management team (physicians or staff) who monitor the device function shortly before the anesthetic. Pacemakers should be routinely interrogated annually and implantable cardioverter devices (ICDs) every 3 to 4 months. Pacemakers should be assessed within 12 months of elective surgery. ICD function should be assessed within 6 months of surgery.
- Obtain a copy of this interrogation, including current settings. Ensure that the device will pace the heart with appropriate safety margins.
- A prescription for the perioperative management of the patient with the CIED should be communicated to the procedure team from the CIED team.
- Consider replacing any device near the end of its elective replacement period in a patient scheduled to undergo either a major surgery or surgery within 25 cm of the generator.
- Is the patient device dependent for antibradycardia? Determine the patient's underlying rhythm/rate to evaluate the need for backup pacing support.
- Evaluate effect of magnet on pacemaker function. Identify the magnet rate and rhythm if a magnet mode is present and magnet use is planned. Will device automatically reset to preoperative settings when a magnet is removed?
- Program minute ventilation rate responsiveness to "Off," if present.
- Program all rate enhancements to "Off."
- Consider increasing the pacing rate to optimize oxygen delivery to tissues for major cases.
- Inactivation of ICD tachyarrhythmia detection is recommended for all procedures using monopolar electrosurgery or radiofrequency ablation above the umbilicus. ICD arrhythmia detection can be suspended by placement of a magnet over the pulse generator.

Intraoperative Key Points

- Is electromagnetic interference (EMI) likely during the procedure? Interference is unlikely if the device is less than 10 years old and bipolar cautery is greater than 15 cm (below the umbilicus) from device lead or generator.
- Have a magnet immediately available for patients with CIEDs who are undergoing a procedure that may involve EMI.
- Monitor cardiac rhythm/peripheral pulse with pulse oximeter or arterial waveform.
- Disable the "artifact filter" on the electrocardiogram (ECG) monitor.
- Avoid use of monopolar electrosurgery.
- Use bipolar electrocautery system or ultrasonic (harmonic) scalpel if possible; if not possible, then pure cut (monopolar electrosurgery) with short bursts of 5 seconds or less is better than "blend" or "coag."
- Position the electrosurgical unit (ESU) current return pad in such a way that it will prevent electricity from crossing the generator-heart circuit, even if the pad must be placed on the distal forearm and the wire covered with sterile drape.
- If the ESU causes ventricular oversensing, pacer quiescence, or tachycardia, limit the period(s) of asystole or reprogram the device.

Postoperative Key Points

- Have the device interrogated by a qualified member of the team (physician or staff) who monitors the device function postoperatively. Some rate enhancements can be reinitiated, and optimum heart rate and pacing parameters should be determined. The ICD patient must be monitored until the antitachycardia therapy is restored.

Adapted from Gold BS. Preoperative evaluation of the adult outpatient. In: Rosenblatt MA, Butterworth IV JF, Gross JB, eds. *ASA Refresher Courses in Anesthesiology*, Philadelphia: Lippincott; 2011:57-64; Stone ME, Apinis A. Current perioperative management of the patient with a cardiac rhythm management device. *Semin Cardiothorac Vasc Anesth*. 2009;13(1):31-43; Crossley GH, et al. The Heart Rhythm Society (HRS)/American Society of Anesthesiologists (ASA) Expert Consensus Statement on the perioperative management of patients with implantable defibrillators, pacemakers, and arrhythmia monitors: facilities and patient management: executive summary. *Heart Rhythm*. 2011;8(7):e1-e18; American Society of Anesthesiologists. Practice advisory for the perioperative management of patients with cardiac implantable electronic devices: pacemakers and implantable cardioverter-defibrillators: an updated report by the American Society of Anesthesiologists task force on perioperative management of patients with cardiac implantable electronic devices. *Anesthesiology*. 2011 Feb;114(2):247-61.

Pacemakers can mask the toxicity of antiarrhythmic drugs, electrolyte disorders, and myocardial ischemia and irritability. In general, the ECG should be examined for pacemaker malfunction, as evidenced by unexpected pauses. If the patient's heart rate is slower than the pacing rate, pacing spikes should appear on the ECG. To determine whether these pacing impulses are associated with myocardial contractions, the clinician should palpate a peripheral pulse. Evaluation of a pacemaker becomes more difficult when the patient's heart rate is faster than the pacing rate. A Valsalva maneuver slows the patient's rate so that pacing impulses appear on the ECG. Generally, because sensing is lost before pacing, the pacemaker is probably functioning normally if (1) it has been in place for fewer than 2 years, (2) chest radiography demonstrates that leads are intact, and (3) impulses do not appear on the ECG.[155] Chest radiography should provide information on electrode placement, the presence of electrode fracture, and even battery depletion.[156]

If each pacing impulse is not associated with a pulse or if the symptoms that led to pacemaker implantation have returned, cardiology consultation should be considered.[155] Anesthesia providers sometimes must decide whether a transvenous, temporary pacing wire should be inserted preoperatively. Persistent bradycardia not responsive to intravenous administration of atropine or exercise is one indication. Bifascicular block in a patient with a history of

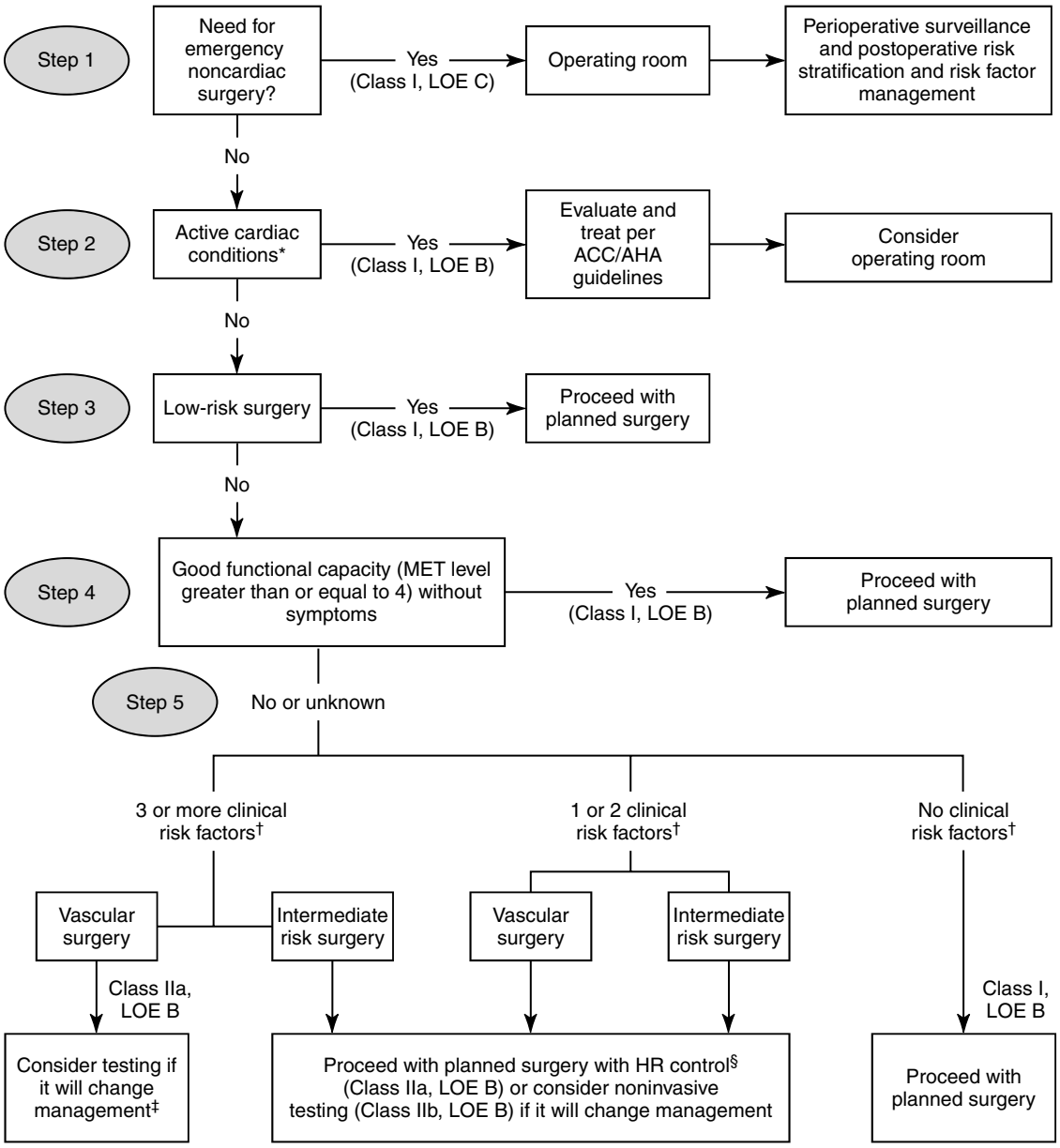

FIGURE **19-4** Cardiac evaluation and care algorithm for noncardiac surgery, based on active clinical conditions, known cardiovascular disease, or cardiac risk factors for patients 50 years of age or older. *See Box 19-11 for active clinical conditions. †Clinical risk factors include ischemic heart disease, compensated or prior heart failure (HF), diabetes mellitus, renal insufficiency, and cerebrovascular disease. ‡Consider perioperative beta blockade for populations in which this has been shown to reduce cardiac morbidity/mortality. *ACC/AHA*, American College of Cardiology/American Heart Association; *HR*, heart rate; *LOE*, level of evidence; *MET*, metabolic equivalent. (From Fleisher LA, et al. ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery. *Circulation*. 2007;116:1971-1996.)

syncope suggests underlying, unrecognized complete heart block. Such patients can benefit from the availability of transvenous pacing.

It also must be determined whether exercising the muscles adjacent to the generator causes dizziness. The presence of this symptom, indicating that myopotentials may be inhibiting the pacemaker, implies that muscle fasciculations caused by succinylcholine and shivering should be avoided.

Diagnostic Testing to Assess Cardiovascular Disease

Multiple tests are available to define the presence of cardiac disease. Preoperative cardiac testing should not be performed unless the results are likely to influence patient management. The ACC/AHA guidelines include an algorithm for determining the appropriateness of preoperative testing (Figure 19-4).[107]

Several noninvasive tests are available for preoperative assessment of the high-risk patient (i.e., three or more risk factors and poor functional capacity). The exercise stress ECG is preferred.[142] Stress testing with exercise or pharmacologic stress agents is designed to increase myocardial work and permit measurement of myocardial response to the increased workload. The exercise stress test not only is a standardized means of obtaining a functional history of angina but also provides excellent documentation

of how ischemia manifests its effects on the cardiovascular system. By examining the stress test report, one can learn the extremes of blood pressure and heart rate the patient can tolerate while awake (although exactly how these correlate with the anesthetized state is a matter of debate), the location of ischemic leads, and whether arrhythmias are associated with ischemia. Significant coronary disease is likely if ST-segment depression is greater than 0.2 mV, if ST depression occurs early in the test, if little increase in blood pressure or heart rate occurs at the time of ST depression, or if hypotension occurs. Hypotension is considered an ominous finding and usually prompts cardiac catheterization.

Perioperative risk is considered low if exercise stress testing does not produce signs of myocardial ischemia at a reasonable workload (greater than 85% of predicted maximum heart rate).[157] Although it is useful in diagnosing coronary artery disease, its value as a preoperative test has been questioned,[112] even in patients undergoing major vascular surgery.[158] Stress testing is not indicated in patients with intermediate risk factors (i.e., fewer than three risk factors), even if major vascular surgery is planned, provided the patient has complete heart rate control with beta-blocker therapy.[108] Patients who are able to tolerate a good exercise stress workload, even those with stable angina, are unlikely to have myocardial dysfunction.[159]

Pharmacologic stress testing can be performed in patients unable to exercise or in those who take digoxin. Two pharmacologic techniques, which incorporate either echocardiography or radionuclide scintigraphy, are used: (1) dipyridamole or adenosine, both of which cause a coronary steal phenomenon by redistributing coronary blood flow without direct negative inotropic effects and (2) dobutamine for inotropic stress testing.[160]

Additional noninvasive studies are available for preoperative testing, such as stress myocardial perfusion scintigraphy (MPS), stress echocardiography, resting transthoracic echocardiography, pharmacologic stress echocardiography, cardiac computed tomography, cardiac magnetic resonance (CMR), and adenosine stress CMR.[142,161] There is insufficient evidence to support the clinical utility and development of appropriate guidelines for these tests at this time.[142]

Cardiac catheterization provides definitive information about the distribution and severity of coronary artery disease and may be indicated for patients with New York Heart Association class III or IV criteria who are undergoing high-risk surgical procedures.[157] Significant stenosis means narrowing of a major coronary artery by more than 70% or narrowing of the left main coronary artery by more than 50%. However, it is important to look beyond the coronary anatomy and concentrate on other findings that can guide perioperative decision making.

Three readily identifiable findings that indicate poor ventricular function are a cardiac index of less than 2.2 L/m^2, a left ventricular end-diastolic pressure of greater than 18 mmHg, and an ejection fraction of less than 40%.[162] Taking note of ischemia-induced dysfunction of the papillary muscles can help in avoiding later confusion about the configuration of the pulmonary wedge pressure waveform and the significance of intraoperative changes in wedge pressure. Wall motion abnormalities should be noted. Areas of akinesis (no movement during systole) usually represent nonviable regions of myocardium and are relatively fixed deficits. In contrast, areas of hypokinesis (reduced contraction during systole) may represent ischemic but nonetheless viable regions of myocardium. This should alert anesthesia providers to a potentially dynamic situation in which alterations in the balance of myocardial oxygen supply and demand can either improve or worsen regional ischemia and associated contractility.

Cardioprotective Pharmacotherapy

Appropriate pharmacologic therapy should be instituted preoperatively in patients exhibiting clinical risk factors (e.g., angina pectoris, prior MI, heart failure, stroke/transient ischemic attack, renal dysfunction, diabetes mellitus requiring insulin therapy) and moderate to poor functional capacity. Patients having up to two clinical risk factors should be managed with statin and beta-blocker therapy preoperatively.[14] If stable left ventricular dysfunction is present, angiotensin-converting enzyme (ACE) inhibitor therapy is recommended.

Statins. In addition to their lipid-lowering benefit, statins are valuable for enhancing endothelial function, improving atherosclerotic plaque stability, decreasing oxidative stress, and reducing vascular inflammation. Common statins used perioperatively include atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin.[163] Recommendations are as follows[14]:

- Institute therapy between 30 days and at least 1 week before high-risk surgery.
- Continue statin therapy perioperatively.

Beta Blockers. Low-dose titration of beta blockers restores the oxygen supply/demand mismatch, reduces perioperative ischemia, redistributes coronary blood flow to the subendocardium, stabilizes plaques, increases ventricular fibrillation threshold, and may reduce the risk of MI and death in high-risk patients.[14] Common beta blockers used perioperatively include atenolol, bisoprolol, nadolol, and metoprolol. Recommendations are as follows[13,164,165]:

- Indicated for patients with high cardiac risk, known ischemic heart disease, or stress-induced myocardial ischemia who present for high-risk surgery such as vascular procedures.
- Continue beta blockers in patients previously treated with beta blockers for ischemic heart disease, symptomatic arrhythmia, or hypertension.
- Institute therapy between 30 days and at least 1 week before high-risk surgery. Avoid acute initiation of high-dose beta-blocker therapy.
- Titrate beta blocker to achieve a resting heart rate of 60 beats per minute.
- Continue beta-blocker therapy postoperatively for approximately a month to maintain a heart rate of 60 to 65 beats per minute with systolic blood pressure greater than 100 mmHg.
- Beta blockers are not recommended in patients scheduled for low-risk surgery without risk factors, or who have absolute contraindications.

ACE Inhibitors. ACE inhibitors are beneficial in reducing heart failure, myocardial infarction, and death when administered in the perioperative period in patients with left ventricular dysfunction.[166] Common ACE inhibitors used perioperatively include captopril, enalapril, lisinopril, benazepril, and ramipril. Recommendations are as follows[14]:

- Recommended in cardiac stable patients with left ventricular dysfunction for intermediate- to high-risk surgery and considered for those scheduled for low-risk surgery.

Respiratory System

A detailed evaluation of the respiratory system is crucial because of the relative frequency of and complications associated with respiratory disease. From an epidemiologic perspective, some form of lung disease is present in nearly 25% of the adult population. The most common problems are chronic obstructive pulmonary diseases (COPDs), such as chronic bronchitis, emphysema, and asthma, which are major predictors for postoperative pulmonary disorders.[167] In their acute or chronic forms, the lung diseases are

second only to coronary artery disease as a cause of death. Patients with COPD are twice as likely to have postoperative pulmonary complications.[168] Risk factors associated with increased postoperative respiratory morbidity and mortality rates include preoperative sepsis, emergency operations, age (older than 60 years), history of smoking, comorbid diseases (e.g., cardiovascular disease, congestive heart failure, diabetes, American Society of Anesthesiologists [ASA] physical status class III or greater), chronic bronchitis, obesity (as little as 20% overweight), type of surgery (abdominal, thoracic), prolonged duration of anesthesia (3 to 4 hours or longer) and elevated creatinine.[168,169] The surgical site (aortic and thoracic surgeries) has been found to be the most important risk factor for the development of postoperative pulmonary complications.[170]

Emphysema and Chronic Bronchitis

The preparation of a patient with two forms of COPD—emphysema and chronic bronchitis—depends largely on the severity of the respiratory disease, as reflected by the preoperative history, physical examination, and diagnostic testing. Elective surgery is postponed when severe dyspnea, wheezing, pulmonary congestion, or hypercarbia ($PaCO_2$ greater than 50 mmHg) is evident. The risk of postoperative respiratory failure in such circumstances is drastically increased. Consultation with a pulmonologist may be necessary for further evaluation and optimization of the respiratory status of the patient before anesthesia and surgery. Interventions to improve the pulmonary status of the patient with chronic bronchitis are the primary focus before surgery. Prophylactic measures that may reduce pulmonary risk are cited in Box 19-16.[171-173] Specific antibiotic therapy is initiated in patients with thick, purulent sputum and pulmonary infiltrates on the chest radiograph.

BOX 19-16

Therapeutic Maneuvers to Decrease Risk of Pulmonary Complications

Preoperative

- Instruction in respiratory maneuvers
- Smoking cessation
- Antibiotic treatment of pulmonary infection
- Antibiotic treatment of chronic bronchitis
- Expectorants
- Psychologic preparation
- Bronchodilator therapy for asthmatics
- Maintenance of good nutrition
- Chest physiotherapy
- Weight reduction

Postoperative

- Adequate pain control with minimization of postoperative opioid analgesia
- Maximal inspiration maneuvers, incentive spirometry, chest physiotherapy
- Mobilization of secretions
- Early mobilization of elderly patients
- Cough encouragement
- Heparin prophylaxis in selected cases

Data from Mohr DN, Lavender RC. Preoperative pulmonary evaluation. Identifying patients at increased risk for complications. *Postgrad Med.* 1996;100(5):241-244,247-248,251-252; Marienau MES, Buck CF. Preoperative evaluation of the pulmonary patient undergoing nonpulmonary surgery. *J Perianesth Nurs.* 1998;13(6):340-348; Wang JS. Pulmonary function tests in preoperative pulmonary evaluation. *Resp Med.* 2004;98(7):598-605.

Administration of prophylactic antibiotics to "sterilize" the sputum is not recommended, because secondary resistant infections may develop and complicate the perioperative management of the patient. To enhance the mobilization and clearance of pulmonary secretions, chest physiotherapy and adequate hydration can be instituted. There is a lack of quality studies demonstrating the benefit of chest physiotherapy for noncardiothoracic surgery. Incentive spirometry may be beneficial in reducing postoperative pulmonary complications after upper abdominal surgery.[4]

The most reliable way to reduce the incidence of perioperative pulmonary complications is to have patients stop smoking cigarettes. Eight weeks after smoking cessation, the pulmonary complication rate correlates with that of nonsmokers.[40] This intervention may not be feasible when initial meetings with the patient occur within days or hours of the scheduled procedure.

Several diagnostic tests are used for clinically differentiating bronchitis and emphysema in patients in the advanced stages of COPD. Arterial blood gases, for example, may document the presence of preoperative hypoxemia or hypercarbia. An abnormally low partial pressure of arterial oxygen (PaO_2) value (less than 60 mmHg), with or without partial pressure of arterial carbon dioxide ($PaCO_2$) retention, often reflects a state of chronic bronchitis. Over time, the patient develops cor pulmonale because of the adverse effects of chronic hypoxemia on pulmonary vasculature. The chest radiograph may suggest a diagnosis of COPD if slight abnormalities on the chest radiograph, including emphysemic bullae and pulmonary hyperlucency (which reflect vascular deficiencies in the lung periphery) are apparent. Diaphragmatic flattening and a vertical orientation of the cardiac silhouette also are characteristic. Chronic bronchitis, on the other hand, is rarely recognized through chest radiography unless secondary infections are present. Preoperative chest radiographs seldom change patient management and have not been shown to impact on the incidence of postoperative pulmonary complications.[4]

In addition to their role in categorizing patients with COPD, pulmonary function tests are occasionally used as diagnostic adjuncts for confirming the severity of airflow obstruction and its reversibility with bronchodilator therapy. In both chronic bronchitis and pulmonary emphysema, a decrease of the forced exhaled volume in 1 second (FEV_1) occurs in comparison with the forced vital capacity (FVC). FEV_1/FVC ratios of less than 80% indicate the presence of an obstructive process. Individual values of pulmonary function test results may be misleading. The FEV_1, for example, may already be low if the vital capacity is also decreased or the patient is uncooperative with the spirometric tests.

Numerous studies have found routine preoperative pulmonary function studies to be poor indicators of postoperative pulmonary complications and are not recommended.[4,174] All patients scheduled to undergo lung resection should have spirometric assessment preoperatively to estimate postoperative FEV_1 and suitability for resection.[168,175] It is not necessary to routinely obtain spirometric data prior to high-risk noncardiothoracic surgery. The value of pulmonary function testing prior to noncardiothoracic surgery is unproven and should be reserved for symptomatic patients suspected of having COPD.[176]

Asthma

Unlike other COPDs, asthma is characterized by reversible airflow obstruction. Inflammation of the airways is the hallmark of asthma. Distal bronchoconstriction results from airway hyperreactivity to stimuli that have little or no effect on normal airways. Precipitating factors include allergens, exercise, upper respiratory tract infections (URTIs), emotional stressors, and unidentified

triggers.[171] Pertinent data obtained from the medical history are detailed in Box 19-17.[177,178]

Information gleaned from these questions will help establish the nature and stability of the disease process. Patients with a history of coexistent cardiovascular disease, copious sputum production, previous perioperative complications from asthma, recurrent nocturnal awakenings from asthma, frequent or continuous systemic corticosteroid requirement, or a recent hospitalization or emergency visit for asthma are considered to be at greater risk for perioperative aggravation of their asthma. Asthma should be under optimal medical management before a patient undergoes elective surgery and anesthesia. If the patient has a persistent cough, dyspnea, wheezing, or tachypnea on the day surgery is scheduled, it is best to reschedule surgery to allow for additional treatment of the asthma.[174]

The need for diagnostic testing is based on the clinician's assessment of the severity of the disease and magnitude of the operative procedure. An ECG is indicated if right ventricular hypertrophy is presumed, typically implying long-standing insufficient therapy. A chest radiograph is considered only if the patient is suspected of having an acute infiltrative process (e.g., pneumonia, pneumothorax in an acute exacerbation) or if a recent change in the patient's physical status is suggestive of a worsening pulmonary condition.[179] Arterial blood gases are usually indicated only when signs of chronic respiratory insufficiency (e.g., hypoxia, hypercarbia) are suspected or in patients with acute asthma who require emergency surgery. If age appropriate, spirometric evaluation consisting of a peak expiratory flow rate should be performed the morning of surgery if active disease is suspected. The results should be compared with the patient's best value in recent weeks. Findings will be as follows:

- *Normal:* 80% to 100% of baseline
- *Moderate exacerbation:* 50% to 80% of baseline
- *Severe episode indicating the need for delay of surgery and more intensive therapy:* Less than 50% of baseline

Peak expiratory flow is of limited use in assessing asthma preoperatively, because other symptoms or clinical signs of poor asthma control are usually present.[179]

Early preoperative patient assessment promotes optimizing pharmacotherapy in the days prior to the scheduled surgery (Table 19-9).[178] Patient medications should be continued up to and on the day of surgery. Prophylactic β-adrenergic metered-dose inhalers should be used on the morning of surgery and accompany the patient to the operating room. Oral medications (e.g., theophylline) may be taken with a sip (1 to 2 oz) of water up to 1 to 2 hours before surgery. Therapeutic serum theophylline levels, 10 to 20 mcg/mL, should be confirmed if theophylline is used. Supplemental stress doses of corticosteroids may be appropriate if the patient has recently taken corticosteroids. Antianxiety premedication should be considered; psychologic triggers such as anxiety are common.

Ensure adequate hydration (e.g., minimize the fasting interval) to reduce airway desiccation and improve mobilization of secretions. If signs and symptoms of infection are present, surgery may be postponed while antibiotic therapy, based on sputum Gram stain and cultures, is initiated.

BOX 19-17

Pertinent Data Obtained from the Medical History

Asthma Control and Current Therapy

- The frequency of asthmatic attacks
- The time interval since the last attack
- Recent asthma exacerbation? How long since the patient was last hospitalized or treated in the emergency department for an asthmatic attack?
- Increased use of inhaled short-acting β-agonists? Use per week?
- Current or past use of inhaled corticosteroids?
- Most recent course of oral corticosteroids?
- What works best for treating an acute asthmatic event?

Asthma History and Complicating Conditions or Factors

- Recent upper respiratory tract infection or sinus infection?
- Recent pneumonia? Was this documented on chest radiograph?
- What triggers an asthmatic attack?
- The severity of attacks: Was endotracheal intubation or intensive care unit admission required?
- History of pulmonary complications with prior surgical procedures?
- History of long-term corticosteroid use or corticosteroid-dependent asthma?

Modified from Karlet M, Nagelhout J. Asthma: an anesthetic update. *AANA J.* 2001 Aug;69(4):317-24; Tirumalasetty J, Grammer LC. Asthma, surgery, and general anesthesia: a review. *J Asthma.* 2006;43(4):251-254.

TABLE 19-9 Guidelines for Preoperative Asthma Pharmacotherapy

Clinical Characteristics of Asthma	Corresponding Preoperative Pharmacologic Therapy
No asthma symptoms	No additional asthma therapy preoperatively
Not on any asthma medications	
No flares in asthma symptoms over past year	
Spirometry does not show significant obstruction	
On bronchodilators only	Initiate therapy with inhaled corticosteroid, beclomethasone 320 mcg per day or equivalent dose, 1 week before surgery
No history of oral corticosteroid use	
Spirometry is not below baseline	If spirometry is below baseline or patient is having flare of symptoms, consider adding prednisone 0.5 mg/kg for 5 days before surgery
Already on inhaled corticosteroid	Continue treatment with inhaled corticosteroid
Spirometry at or below baseline	Treat with prednisone 0.5 mg/kg for 5 days before surgery
	Treat with hydrocortisone 100 mg IV every 8 hours the morning before surgery and postoperatively until stable
Patient is already on oral steroids	Increase dose of oral steroids for 5 days before surgery
	Treat with hydrocortisone 100 mg IV every 8 hours the morning before surgery and postoperatively until stable

From Tirumalasetty J, Grammer LC. Asthma, surgery, and general anesthesia: a review. *J Asthma.* 2006;43(4):251-254.

Upper Respiratory Tract Infection

Children with URTIs, particularly those younger than 1 year, have an increased risk (twofold to sevenfold increase) of respiratory-related adverse events intraoperatively and postoperatively (e.g., bronchospasm, laryngospasm, hypoxemia, atelectasis, croup, stridor). Signs and symptoms of URTI include sore throat; inflamed and reddened nasopharyngeal and oropharyngeal mucosa; sneezing; rhinorrhea (clear secretions) or mucopurulent nasal secretions; nasal congestion, including watery eyes; malaise; bulging, tender eardrums with associated inflammation; nonproductive cough; fever of 37.5° to 38.5° C (greater than 38° C associated with lower respiratory tract involvement); laryngitis or tonsillitis; viral ulcers in the oropharynx; and white blood cell count greater than 12,000 cells/mm^3 with a left shift. Positive chest findings such as pulmonary congestion and rales are usually associated with lower respiratory tract involvement.

Each case should be reviewed individually. The decision to operate frequently depends on the urgency of the surgery, the duration and complexity of the surgery, and the need for instrumentation of the airway (Figure 19-5).[180] Children with uncomplicated URTIs may undergo elective procedures without significantly increasing anesthesia complications.[181] It is important to obtain a specific history to distinguish a chronic state from an acute, superimposed infectious process, which has predictive value for morbidity. Parents will be the best resource for establishing baseline conditions. If the parents state that the child typically has a cold or chronic runny nose (clear rhinorrhea) and is in his or her optimal state (afebrile, without respiratory distress), short elective procedures may be considered. If the child has a productive cough from lower respiratory tract involvement or an infectious-appearing runny nose, elective surgery should be postponed. However, it may be necessary to schedule children who have chronic URTIs for procedures such as myringotomy with ventilation tube placement or tonsillectomies, because URTIs are commonly associated with these conditions. Exercise caution with children younger than 5 years (consider postponing the procedure for children less than age 1 year) because risks are increased. If the child is older than 1 year with a resolving URTI, it is reasonable to proceed with minor procedures not requiring endotracheal intubation (intubation with URTI increases risk 11-fold).

Infectious nasopharyngitis (without lower respiratory tract involvement) requires postponing the surgery for 2 weeks after peak symptoms.[182] If the child exhibits signs and symptoms of lower respiratory tract involvement, it is prudent to postpone an elective surgical procedure for 4 to 6 weeks, the time necessary to minimize airway hyperactivity.

Laboratory testing may consist of a complete blood count, including differential. The value of obtaining a preoperative white blood cell count has been questioned because it is of little value and rarely is a factor in determining whether to proceed with the surgery.[183] Nasal or throat cultures may be obtained if signs of an infectious process are observed. A chest radiograph is not warranted, especially if chest sounds are clear. Pulmonary function tests and arterial blood gas analysis rarely offer any useful information.

Gastrointestinal System

Evaluation of the gastrointestinal system includes preoperative determination of the presence of nausea and vomiting, diarrhea, occult or overt gastrointestinal bleeding, abdominal or referred pain, abdominal distention, palpable masses, dysphagia, or gastric hyperacidity, with or without reflux. The fluid and electrolyte status of the patient is reviewed, especially when gastrointestinal symptoms are associated with weight loss or malabsorption. Active bleeding requires preoperative hemoglobin concentration measurement. The hematocrit value may be falsely elevated as a result of hemoconcentration in patients with acute or chronic bleeding. Radiographic and CT scans of the abdomen are reviewed for evidence of obstruction or masses. The presence of peptic ulcer disease or esophageal hiatal hernia is also ascertained. For affected patients, prophylactic measures to reduce the risk of aspiration and its adverse pulmonary sequelae (e.g., aspiration pneumonitis) are instituted before surgery.

Hepatobiliary System

Preoperative evaluation of the hepatobiliary system includes screening for the presence of acute or chronic liver parenchymal disease, such as hepatitis or cirrhosis, or cholestatic liver disease. Because of the tremendous reserve of the liver, progression of hepatic disease is often insidious. Signs and symptoms may be inapparent or vague until physiologic functions of the hepatobiliary system (Box 19-18) are markedly affected. Liver function tests are also limited in their ability to reflect the acuity and extent of hepatobiliary disease.[184] Considerable damage to the liver may be evident before laboratory test results are altered.

During the early stages of hepatitis or cirrhosis, the clinical presentation ranges from one in which the patient is asymptomatic with normal liver function tests to one in which the patient has malaise, weight loss, abdominal discomfort, and mild jaundice with mild elevations in bilirubin levels. In cases of unexplained jaundice or elevated transaminase levels, suspicions of hepatobiliary dysfunction should be thoroughly investigated by a preoperative consultation with a gastroenterologist. Elective surgery is postponed until a definitive diagnosis and treatment are established and indicators of active inflammation (e.g., transaminase levels, cellular infiltration on liver biopsy, etc.) have subsided.[185] Further decompensation of hepatic function may follow anesthesia and surgery, notably after intraabdominal procedures. Figure 19-6 offers an algorithm for the preoperative assessment of the patient with known or suspected liver disease.[186]

Progression of hepatobiliary disease to overt hepatic failure may be evidenced by gross abnormalities of liver function test results, including coagulopathies; extreme jaundice with or without cyanosis; generalized tremors and increased deep tendon reflexes; ascites, spider nevi, and hepatosplenomegaly; hepatorenal failure; and signs of hepatic encephalopathy.[187] Elective surgery is avoided at this time because surgery on a patient with hepatic failure is associated with an extremely high incidence of morbidity and mortality. Anesthesia may be required, however, for a patient who requires a palliative or emergent procedure. Placement of a portocaval shunt and the surgical control of hemorrhage from esophageal varices are common procedures, given the growing number of patients with advanced liver disease. Anesthetic management is supportive in such situations and is focused on minimizing the risk of further hepatobiliary deterioration. Administration of phytonadione (AquaMEPHYTON) and transfusion of fresh frozen plasma and cryoprecipitate may be required for the correction of preoperative coagulopathies. Sedative premedicants are avoided in the disoriented or somnolent patient in whom hepatic encephalopathy has been diagnosed. Because of the rapid development of hypoglycemia, the patient's blood glucose level is checked preoperatively. The acid-base balance, electrolyte status, and extent of hepatorenal reserve may be determined by arterial blood gas analysis, serum multiphasic profiles, and liver function tests.[187]

The interpretation of liver function tests should be approached cautiously. Differential diagnosis of parenchymal versus cholestatic liver disease is limited by the insensitivity and nonspecificity

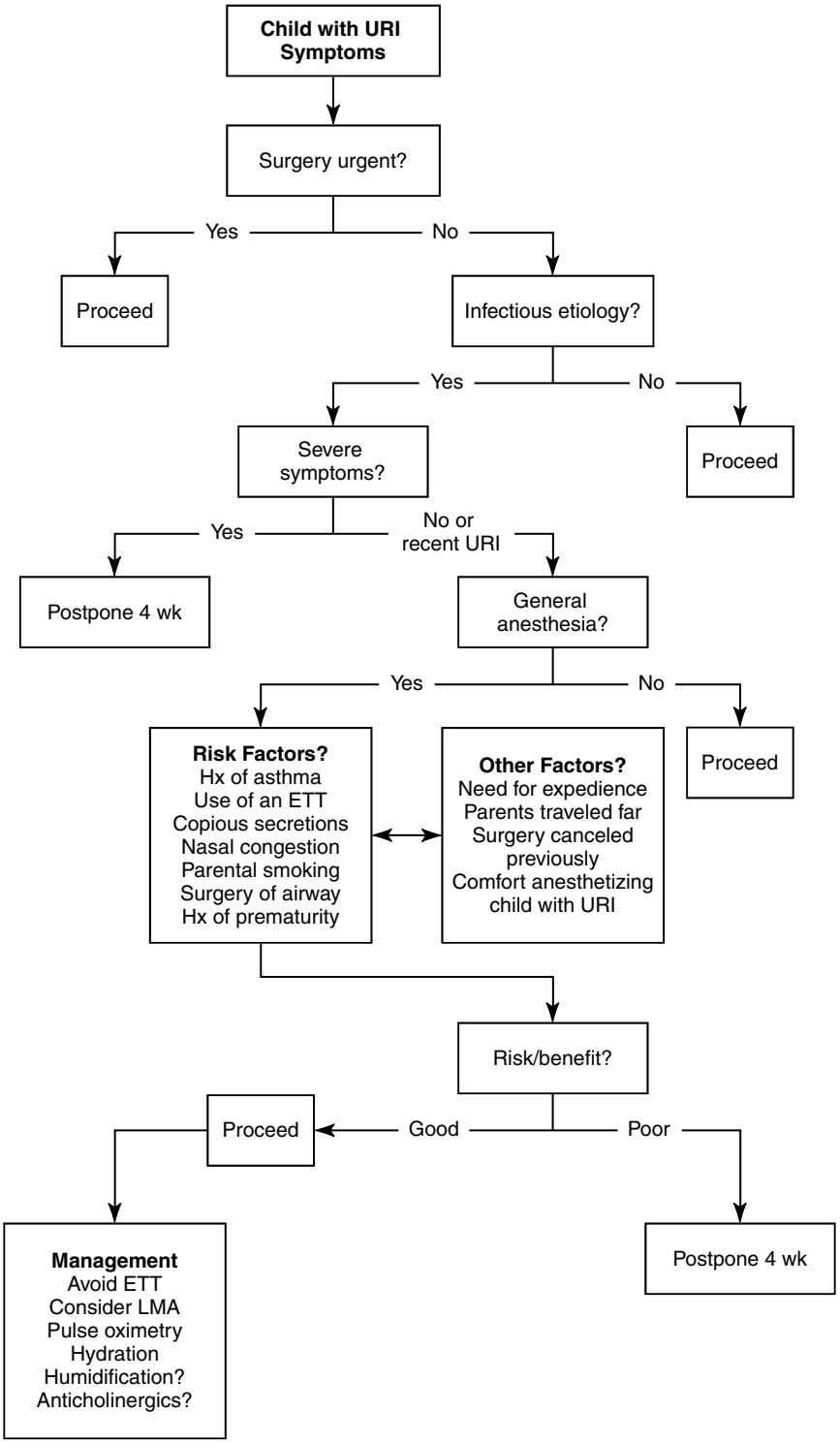

FIGURE **19-5** Suggested algorithm for the assessment and anesthetic management of the child with an upper respiratory infection. *Hx*, History; *ETT*, endotracheal tube; *LMA*, laryngeal mask airway; *URI*, upper respiratory infection. (From Tait AR, Malviya S. Anesthesia for the child with an upper respiratory tract infection: still a dilemma? *Anesth Analg.* 2005;100:59-65.)

of current laboratory analysis, especially serum transaminase and alkaline phosphatase levels.[188] Aspartate transaminase (AST), or serum glutamic oxaloacetate transaminase (SGOT); alanine transaminase (ALT), or serum glutamic pyruvic transaminase (SGPT); and lactate dehydrogenase (LDH) are commonly measured hepatocellular enzymes also distributed throughout cells of the lungs, heart, kidneys, and skeletal muscles. Increases in their serum concentrations are therefore not always indicative of hepatobiliary disease. Greater specificity can be derived from isoenzyme-5 fractions of the enzymes, such as LDH.[189]

In cases of biliary obstruction or irritation, alkaline phosphatase enzymes may be released from the cells of bile ducts. Increases in serum concentrations of these enzymes also help differentiate hepatic dysfunction caused by parenchymal disease from that

BOX **19-18**

Physiologic Functions of the Hepatobiliary System

Bilirubin Formation and Excretion
- Conjugation of free bilirubin and secretion into bile

Carbohydrate Metabolism
- Glycogenesis
- Gluconeogenesis
- Glycogenolysis

Fat Metabolism
- Lipogenesis
- Lipolysis

Protein Metabolism
- Formation of proteins, such as albumin, prothrombin, transferrin, and glycoprotein
- Synthesis of plasma cholinesterase
- Deamination of proteins, such as hormones, into ammonia and urea

Hormone Metabolism Drug Detoxification
- Conversion of lipophilic drugs into inactive hydrophilic substances
- Hydrolysis of ester linkages by plasma cholinesterase

Vitamin Storage
- Storage of fat-soluble vitamins A, D, E, and K
- Storage of antipernicious anemia factor, vitamin B_{12}

Synthesis of Coagulation Factors and Inhibitors
- Synthesis of most clotting factors, including prothrombin, fibrinogen, factors V, VII, IX, and X
- Synthesis of antithrombin
- Mast-cell production of heparin

Phagocytosis
- Filtration and destruction of bacteria and debris in blood circulating through hepatic sinusoids by Kupffer cells

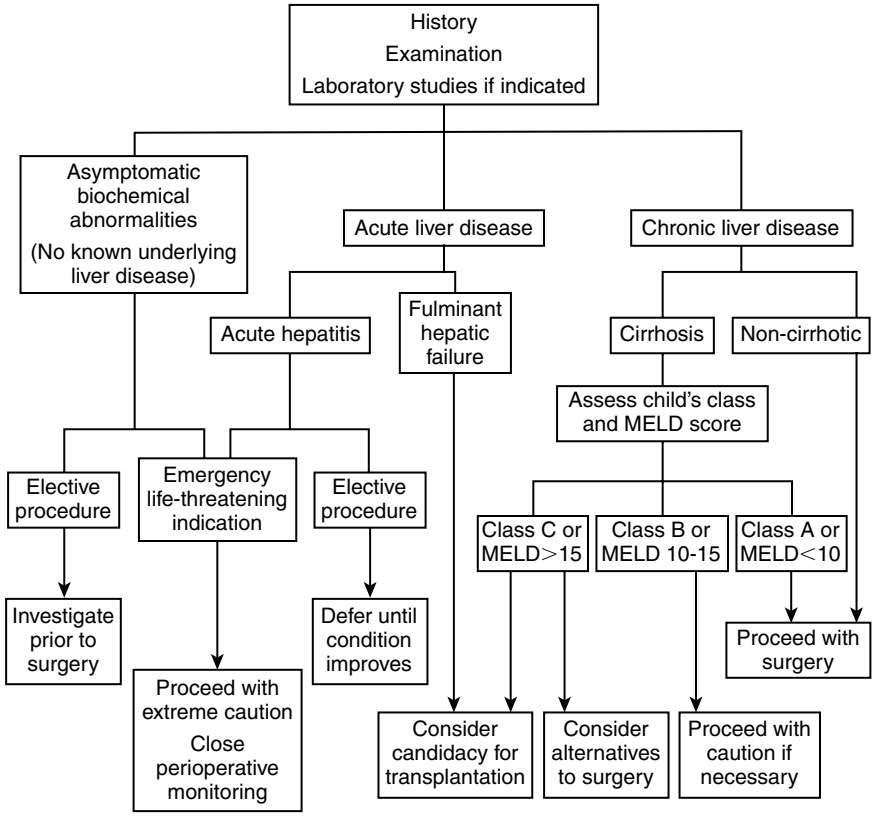

FIGURE **19-6** Suggested algorithm for assessing the patient with known or suspected liver disease—the MELD (Model for End-stage Liver Disease) scoring system to objectively assess liver disease severity. (From Keegan MT, Plevak DJ. Preoperative assessment of the patient with liver disease. *Am J Gastroenterol.* 2005;100:2116-2127.)

caused by cholestasis. The interpretation of these results is again limited by the presence of extrahepatic stores of alkaline phosphatase. In this situation, cholestatic liver disease can be confirmed by high serum levels of conjugated (direct) bilirubin.[190] Causative factors are then determined from discussions with a gastroenterologist and the results of ultrasound, CT, and endoscopic retrograde cholangiopancreatographic scans.

When acute parenchymal injury is evident, prolongation of prothrombin time offers the most rapid and reliable hallmark of liver dysfunction and is shown to have prognostic significance. It reflects the inability of the acutely damaged liver to synthesize clotting factors. Although the production of albumin is also affected, its plasma half-life exceeds that of prothrombin. Hypoalbuminemia may then be inapparent for days after an acute hepatocellular insult.[191]

Once a functional impairment of the liver has been established, the cause is investigated as part of the preoperative evaluation. Cirrhosis and hepatitis, for example, are frequently associated with long-standing alcohol abuse. The increasing consumption of alcohol in the United States parallels the rising incidence of liver disease. Exposure to hepatotoxic agents in the workplace, such as carbon tetrachloride or vinyl chloride, should be ruled out. Hepatotoxic drugs may then be discontinued or avoided before surgery. These drugs commonly include acetaminophen and other nonsteroidal antiinflammatory drugs, aspirin, methyldopa, isoniazid, and rifampin.[192,193] Finally, a diagnosis of infectious hepatitis should be pursued in patients with hepatobiliary disease of unknown cause and in patients considered to be at high risk, which includes those with a history of hemodialysis, multiple blood transfusions, or intravenous drug abuse. Because of the virulent nature of the hepatitis viruses, care of an infected patient also poses an occupational hazard for anesthesia providers.[194] Maximum precautions must be consistently exercised, and vaccination with the hepatitis B virus, as recommended by the Centers for Disease Control and Prevention, should be performed.[195]

The Child-Pugh score was developed to predict surgical mortality in patients with cirrhosis. It assigns points for five variables: total bilirubin level, serum albumin level, international normalized ratio (INR), ascites, and hepatic encephalopathy. Patients are categorized into Child-Pugh class A, B, or C. The predicted perioperative mortality for intraabdominal surgery in these patient groups is Class A (10%), Class B (30%), and Class C (80%). Patients in Child-Pugh classes A and B are suitable candidates for surgery with preoperative optimization. Patients in Child-Pugh class C are usually treated medically. Surgery, if necessary, is delayed until liver function improves.[190]

TABLE 19-10 Common Renal Function Tests

Test	Reference Range
Urea nitrogen	5-25 mg/dL
Creatinine	0.5-1.5 mg/dL
Sodium	133-147 mmol/L
Potassium	3.2-5.2 mmol/L
Chloride	94-110 mmol/L
CO_2	22-32 mmol/L
Uric acid	2.5-7.5 mg/dL
Calcium	8.5-10.5 mg/dL
Phosphorus	2.2-4.2 mg/dL
Urinalysis, routine	
Color	Straw-amber
Appearance	Clear-hazy
Protein	0 mg/dL
Blood	Negative
Glucose	0 mg/dL
Ketone	0 mg/dL
pH	4.5-8
Specific gravity	1.002-1.030
Bilirubin	Negative
Urinalysis, micro	
Red blood cells	0-3/high-power field
White blood cells	0-5/high-power field
Casts	0-2/low-power field

Modified from Brenner BM, et al, eds. *Brenner and Rector's The Kidney*. 9th ed. Philadelphia: Saunders; 2012.

Renal System

Evaluation of the kidneys and urinary tract includes preoperative determination of the patient's volume status and presence of polyuria; urinary incontinence or retention; microscopic or frank hematuria; recurrent infections in the form of glomerulonephritis, pyelonephritis, or cystitis; dysuria; and oliguria or anuria. Fluid balance is calculated from the patient's intake and output during the hospital stay. Preoperative dehydration may be evident, for example, in a patient receiving long-term diuretic therapy. Polyuria, when not attributed to diuretics, may reflect glycosuria or, rarely, inadequate secretion of antidiuretic hormone (diabetes insipidus). Urinary retention and other signs of neurogenic bladder may be caused by a spinal cord injury or long-standing diabetes mellitus. Frequent catheterizations are often necessary in such situations, increasing the patient's risk for developing chronic urinary tract infections. Preoperative urinalysis and culture are therefore required so infection can be ruled out. Treatment and resolution should be accomplished before elective surgery is performed, especially for procedures involving the placement of a prosthetic graft for a mitral valve or total hip replacement. Problems with intraoperative bladder catheterization can be anticipated in patients with dysuria or voiding difficulties. In older men, these problems are frequently attributed to chronic prostatism. Untreated prostatic hypertrophy, as well as renal calculi and congenital malformations of the ureters, results in obstructed urinary outflow. Over time these conditions may lead to a state of chronic renal insufficiency or failure.

Any suspicion of renal dysfunction should be investigated before surgery. Unfortunately, clinical evidence of renal insufficiency may not be apparent until at least 70% of nephrons are nonfunctional. Accurate diagnosis of renal insufficiency is further limited by the insensitivity of laboratory tests (Table 19-10).[196] Blood urea nitrogen (BUN) concentrations, for example, do not accurately reflect glomerular filtration rate (GFR). Although urea is freely filtered at the glomerulus, it is reabsorbed to a large and variable extent through the tubules. BUN levels are also affected by the amount of protein ingested in the gastrointestinal tract and the amount of urea metabolized by the liver, as well as by the catabolic state of the patient. Because tubular reabsorption of creatinine does not occur, creatinine levels correlate more with the rate of glomerular filtration than do BUN concentrations. The serum levels of creatinine, a by-product of skeletal muscle metabolism, can reflect the muscle mass and catabolic state of each patient. This characteristic limits its precision in determining the magnitude of nephron loss. Normal serum creatinine levels may be higher, for example, in a muscular man than in a woman. Conversely, serum creatinine levels can remain within the normal range in the elderly patient, despite a progressive decline in glomerular function,[197] because of the decrease in muscle mass associated with aging.

The most accurate reflection of renal reserve or GFR is creatinine clearance, which reflects the ability of glomeruli to excrete creatinine into the urine at a given blood concentration.[4] The drawbacks of this assessment lie in the cost and time required for the collection of urine samples. As a general principle, urine is collected over a 24-hour period and the creatinine clearance rate is measured by the following equation:

$$\text{GFR (mL/min)} = \text{UV} \div \text{P}$$

where U is the urinary concentration of creatinine (mg/dL), V is the volume of urine (mL/min), and P is the plasma concentration of creatinine (mg/dL).

Accurate measures of GFR also can be calculated from a 2-hour specimen.[198] Creatinine clearance or GFR values between 50 and

80 mL/min are indicative of mild renal dysfunction. Renal failure is otherwise evident when creatinine clearance levels decrease to less than 10 mL/min.

Practically all surgical patients with chronic renal failure are undergoing dialysis, usually hemodialysis performed at the hospital or renal facility. Others undergo continuous ambulatory peritoneal dialysis. The goal of dialysis therapy is to maintain a reasonable degree of homeostasis, although BUN and creatinine concentrations remain abnormal. The preoperative evaluation and preparation of the patient with chronic renal failure should therefore focus on fluid and electrolyte balance, as well as on the extent of concomitant diseases.[199] Estimates of volume status are derived from the amount of weight gained between periods of dialysis. Fluid overload may also be evidenced by jugular vein distention, peripheral and periorbital edema, and bibasilar rales.

Preoperative measurement of serum potassium concentration is recommended within 6 to 8 hours of surgery, regardless of whether dialysis is performed, because unexpected hyperkalemia, with its adverse cardiac effects, is known to occur rapidly. In cases in which the serum potassium level exceeds 5.5 mEq/L and congestive heart failure is apparent, elective surgery should be delayed until after dialysis. When postponement is not feasible, as with emergency surgery to relieve a pericardial effusion or procedures to revise a hemodialysis shunt, measures to reduce the serum potassium concentration are then instituted (see Table 20-6).

Although hemoglobin ranges from 5 to 8 mg/dL are not unusual in patients with chronic renal failure, a hemoglobin level should also be obtained as part of the preoperative evaluation. Chronic anemia is predominantly caused by decreases in renal erythropoietin production and enhanced fragility of red blood cells in the presence of uremia. It is further exacerbated by blood loss experienced with hemodialysis and chronic gastrointestinal bleeding. When extreme fatigue and pallor, limited exercise tolerance, and persistent tachycardia are evident before major surgery, the transfusion of packed red blood cells may be necessary. Because repeat transfusion and immunosuppression therapy are often required during the course of chronic renal failure, the patient is at greater risk for being infected with the hepatitis virus, human immunodeficiency virus (HIV), or both. Coagulopathies are also suspected. The most likely cause is a decrease in platelet adhesiveness secondary to the chronic state of metabolic acidemia. Hemodialysis can be effectively used for the correction of prolonged bleeding times before surgery in this situation.

Throughout the perioperative period, most therapeutic regimens for patients with chronic renal failure can be continued, including the administration of antihypertensives, digitalis preparations, corticosteroids, and insulin.[200] Requirements for preoperative sedation may be less than anticipated, and medications with prolonged durations, such as diazepam, are avoided.[201] Peripheral arteriovenous shunts should be assessed for patency and infection. Measurement of noninvasive blood pressures and application of intravenous lines are avoided in the limb of the graft. Administration of gastrointestinal preparations (e.g., antacids and gastrokinetic agents) and drainage of peritoneal dialysate, aimed at reducing the risks of regurgitation and pulmonary aspiration, are instituted when preparing the patient with chronic renal failure for anesthesia and surgery.

Endocrine System

Endocrine diseases of concern in the preoperative evaluation include diabetes mellitus, thyroid gland disorders, and adrenocortical dysfunctions. End-organ effects of each of these diseases increase perioperative risk substantially. For example, morbidity and mortality rates are 5 to 10 times greater in diabetic patients with renal and autonomic nervous system involvement.[202]

TABLE 19-11 Distinguishing Features of Diabetes Mellitus

	Type 1	Type 2
Previous name	Insulin-dependent diabetes	Non–insulin-dependent diabetes
Age of onset	Childhood	Middle age or elderly
Timing of onset	Abrupt	Gradual
Predisposing factors	Genetic	Obesity, pregnancy, drugs
Prevalence	0.2%-0.3%	2%-4%
Insulin requirement	Always	Infrequent
Ketoacidosis	Common	Rare
Systemic complications	Frequent	Frequent

Modified from Inzucchi SE, Sherwin RS. Type 1 diabetes mellitus. In: Goldman L, Schafer AI, eds. *Cecil Textbook of Medicine*. 24th ed. vol 2. Philadelphia: Saunders; 2012.

Diabetes

Diabetes mellitus is the most common of endocrine disorders, affecting more than 20.8 million people—8.3% of the population—in the United States. Twenty-seven percent of people ages 65 years or older report having diabetes.[203] It represents a dysfunction in glucose metabolism caused by impaired synthesis, secretion, or insulin resistance.

Most patients with diabetes (90% to 95%) are not dependent on exogenous insulin for the regulation of blood glucose levels. As shown in Table 19-11, the patient with non–insulin-dependent (also known as adult onset or type 2) diabetes often benefits from diet modification, weight control, and exercise alone. An oral hypoglycemic agent (Table 19-12) may also be added to the patient's therapeutic regimen.[204] The remaining 5% to 10% of patients with diabetes are dependent on insulin preparations listed in Table 19-13 and are therefore classified as having insulin-dependent, or type 1, diabetes mellitus.[205,206] These patients are susceptible to periods of hyperglycemia and ketoacidosis. Patients may be on a transitional continuum between the two types. As a result of microvascular changes, they are also prone to the development of severe end-organ complications, including diabetic retinopathy and cataract formation, somatic and autonomic insufficiency (e.g., orthostatic hypotension, bradycardia, gastroparesis), and nephropathy. Because of acquired abnormalities in the macrovasculature, patients with type 2 diabetes are more likely to have hypertension, coronary artery disease (which frequently is asymptomatic), and peripheral vascular disease. Death in the majority of patients with diabetes is secondary to complications of atherosclerosis (MI, stroke).[207]

The aim of an evaluation of a patient with diabetes, notably one with type 1 diabetes mellitus, is ascertaining the degree of preoperative blood glucose control and the presence of major organ system dysfunction. Renal and cardiovascular complications of diabetes substantially heighten perioperative morbidity and mortality. Particular attention should be paid to the following:

- *Diabetes*: Type of disease, method of home monitoring and usual metabolic control
- *Drugs*: Antidiabetic medication, medication for associated diseases

TABLE 19-12 Oral Hypoglycemic Therapy

Drug Class	Drug Name	Onset	Duration of Action
Second-generation sulfonylureas	Glyburide	30 min	24 hr
	Glipizide	IR 30 min	IR 24 hr
		ER 2-4 hr	ER 24 hr
	Glimepiride	2-3 hr	24 hr
DPP-4 Inhibitors	Sitagliptan	1 hr	8 hr
	Saxagliptan	1 hr	8 hr
	Linagliptan	1 hr	8 hr
GLP-1 Analogs	Exenatide	1-2 hr	24 hr
	Liraglutide	1-2 hr	24 hr
Biguanides	Metformin	1-3 hr	17 hr
Thiazolidinediones	Rosiglitazone	1-3 hr	4 hr
	Pioglitazone	2 hr	N/A
Non-sulfonylurea secratogues (glinides)	Repaglinide	30-90 min	4 hr
	Nateglinide	30-60 min	4 hr
Alpha-glucosidase inhibitors	Acarbose	2 hr	4 hr
	Miglitol	1 hr	4 hr

From Drugs for type 2 diabetes. *Treat Guidel Med Lett.* Aug 1 2011;(108); Inzucchi SE, Sherwin RS. Type 1 diabetes mellitus. In: Goldman L, Schafter AI, eds. *Cecil Textbook of Medicine*. 24th ed. vol 2. Philadelphia: Saunders; 2012; Inzucchi SE, Sherwin RS. Type 2 diabetes mellitus. In: Goldman L, Schafer AI, eds. *Cecil Textbook of Medicine*. 24th ed. vol 2. Philadelphia: Saunders; 2012.
ER, Extended release; *IR*, immediate release; *N/A*, not available; *DPP-4*, dipeptidyl peptidase-4; *GLP-I*, glucagon-like peptide 1.

- *Cardiovascular disease*: Including an assessment of exercise tolerance
- *Renal disease*: Electrolyte assessment, hemodialysis regimen if applicable
- *Neuropathy*: Peripheral and autonomic, in particular gastric paresis
- *Airway*: diabetics with stiff joint syndrome (due to glycosylation) often have limited mobility of the upper cervical spine and are more likely to have a poor view on direct laryngoscopy, and they may therefore present difficulties with tracheal intubation.[208] Patients with a long-standing history of diabetes require a close look at the airway to assess for potential difficulties.[4]

Early preoperative evaluation and workup of diabetic patients are important. This is especially true in patients who are noncompliant, patients whose blood glucose level is poorly controlled, and patients with newly diagnosed diabetes, because modifications in their care may be necessary before surgery. Early assessment of a patient allows for consultation with a medical internist to optimize the patient's preoperative condition before anesthesia and surgery. Elective surgery is also postponed in cases of extreme hyperglycemia and ketoacidosis. Aggressive fluid, electrolyte, and insulin therapy are initiated, and the cause of ketoacidosis must be investigated before surgery.

Consultation with a cardiologist may also help a practitioner evaluate and improve the preoperative cardiac status of a patient with diabetes, especially if the patient is undergoing a procedure associated with a greater risk of perioperative myocardial ischemia, such as a carotid endarterectomy or an abdominal aortic aneurysm resection. Because of the high incidence of ischemic heart disease in this population, exercise stress testing and a 12-lead ECG may be performed. Orthostatic hypotension, resting tachycardia, and lack of respiratory variability in cardiac rhythm may reflect

TABLE 19-13 Insulin Preparations and Guidelines

Insulin Type	Onset	Peak (hr)	Duration (hr)	Comments
Very Rapid				
Lispro; Aspart	IV immediate; subcut 5-15 min	Subcut 0.5-1.5	Subcut 3-4	Usually administered immediately prior to a meal; use subcut or via an insulin pump, but not recommended for continuous infusion
Short-Acting				
Regular	IV immediate; subcut 30-60 min	Subcut 2-3	Subcut 3-6	Usually administered 30-60 min before meals; most common in continuous IV infusions
Intermediate-Acting				
NPH	Subcut 2-4 hr	Subcut 6-10	Subcut 10-16	Often combined with regular insulin
Lente	Subcut 3-4 hr	Subcut 6-12	Subcut 12-18	
Long-Acting				
Ultralente	Subcut 6-10 hr	Subcut 10-16	Subcut 18-20	Perioperative use uncommon
Glargine	Subcut 4 hr	Minimal peak activity	Subcut 24	May be administered as usual to provide basal insulin levels during surgery
Combinations				
75/25 (75% protamine lispro, 25% insulin lispro)	Subcut 30-60 min	Dual	10-14	
70/30 (70% NPH, 30% regular)	Subcut 30-60 min	Dual	10-16	Usually given before breakfast
50/50 (50% NPH, 50% regular)	Subcut 30-60 min	Dual	10-16	Usually given before dinner

From Connery LE, Coursin DB. Assessment and therapy of selected endocrine disorders. *Anesthesiol Clin North America*. 2004(1);22:93-123; Powers AC. Diabetes mellitus. In: Longo DL, et al, eds. *Harrison's Principles of Internal Medicine*. 18th ed. New York: McGraw-Hill; 2012:2275-2304; Inzucchi SE, Sherwin RS. Type 1 diabetes mellitus. In: Goldman L, Schafer AI, eds. *Cecil Textbook of Medicine*. 24th ed. vol 2. Philadelphia: Saunders; 2012.
IV, Intravenous; *subcut*, subcutaneous.

autonomic neuropathy. Abnormalities in autonomic function may also result in bladder atrophy and delayed gastric emptying times in nearly 50% of diabetic patients.[209] A gastrokinetic agent, such as metoclopramide, should be considered before surgery to reduce the incidence of regurgitation and pulmonary aspiration during general anesthesia.

It is best to schedule surgery as early in the day as possible to minimize the fasting period. Just before surgery, diabetic patients who require insulin or oral hypoglycemic agents should have blood glucose checked. Depending on the type and length of surgery and the lability of diabetes, blood glucose levels are checked intraoperatively and in the postanesthesia care unit at 1-hour intervals. There continues to be discussion as to optimal levels; however, a safe goal of perioperative insulin therapy is to maintain the serum glucose level at less than 180 mg/dL while avoiding hypoglycemia.[210] Efforts to reduce the $HbA1_c$ to as close to normal as possible are desirable. Levels less than 5.7% are normal, 5.7 to 6.4 are high risk, and 6.5% or more are diabetic.

Preoperative management of antidiabetic medications is based on the principle that therapies aimed at providing basal insulin can, with careful management, be continued in the fasting patient. Therapy includes adjustment of routine dosing regimens and provision and careful monitoring of blood glucose. Correction therapy (i.e., sliding scale insulin) may be needed, but should not be relied upon as the sole therapy for long periods. Prandial therapies should be held in the fasting patient. Specific recommendations for preoperative management generally call for a reduction in the dose of insulin the evening before surgery and the omission of insulin or administration of a decreased dose the morning of surgery.

The insulin analog glargine warrants special attention. Glargine has a prolonged duration of 20 to 24 hours, but is unique in that its activity is without a significant peak. Because of an absence of peak activity, some experts believe that glargine is well suited for the perioperative period although a reduction in dose may be warranted. Recommendations for management of patients on insulin pumps include decreasing the insulin dose delivered to the patient the evening before and the morning of surgery with the patient being converted to an IV insulin drip for glycemic control during the procedure. If the patient is undergoing a short, simple case under local anesthesia, continuation of the insulin pump is safe.[8]

Several different regimens are available for the treatment of diabetic patients undergoing surgery and anesthesia. Consultation with the physician responsible for managing the diabetes is helpful in determining an acceptable range of serum glucose and when and what type of insulin therapy may be appropriate. Considerations for managing the diabetic patient are as follows[1,8,96]:

Night before the procedure:

- Continue usual dose of PM (afternoon/evening) glargine/NPH (neutral protamine Hagedorn) or mixture (can recommend two-thirds usual dose if tightly controlled) as long as patient allowed usual diet.
- Insulin pumps should continue at usual basal rate.

Morning of procedure:

- Patients undergoing short, simple procedures early in the morning can be managed by delaying the patient's normal diabetes treatments until the patient is ingesting food in the early postoperative period. It should be noted that procedures requiring a patient with diabetes to fast are customarily scheduled early in the morning to minimize disruption of routine diabetic treatments.
- The biguanide metformin is associated with increased risk of lactic acidosis, especially in settings in which glomerular filtration rate is decreased (as in surgery or radiologic procedures involving the injection of iodinated dyes). Published recommendations for the discontinuation of metformin vary. Some experts advise holding the medication for as long as 48 hours prior to surgery, whereas others suggest holding metformin only on the day of surgery.[8]
- Patients taking oral hypoglycemic agents should withhold the short half-life agents (e.g., repaglinide) on the day of surgery and withhold the longer-lasting agents (e.g., chlorpropamide and glimepiride) for up to 48 hours.
- Fasting patients who are receiving insulin should have intravenous access established. A crystalloid solution containing 5% glucose should be available to infuse for maintenance of optimal blood glucose levels. The intravenous route still has the risk of making the patient hyperglycemic or hypoglycemic if the glucose or insulin infusions become unbalanced. The tighter the control of glucose levels, the more frequent the glucose monitoring. The subcutaneous route of insulin administration has been criticized as being too unpredictable in its absorption, especially perioperatively, with alterations in blood pressure and cutaneous blood flow.[211]
- Patient should not take short-acting insulin bolus the morning of procedure unless blood glucose level is greater than 200 mg/dL and more than 3 hours preoperatively.
- In the patient with type 1 diabetes, a common approach, especially for brief procedures, is to subcutaneously administer a fraction (50% of usual dose) of the patient's usual morning dose of intermediate- or long-acting insulin and institute continuous 5% glucose infusion.
- Insulin pumps should be continued, but only to provide basal insulin coverage, and institute continuous 5% glucose infusion.
- For patients with either insulin-dependent or non–insulin-dependent diabetes, the most important goal of perioperative management is the prevention of hyperglycemia and especially hypoglycemia, as well as their adverse consequences, during surgical stress.

Thyroid Gland Disorders

Although disorders of the thyroid gland are relatively uncommon, the anesthesia provider may still encounter patients with hyperthyroidism or hypothyroidism who require surgery. Most have undergone adequate medical therapy before anesthesia and surgery are performed. Nevertheless, the anesthesia provider should be aware of the clinical manifestations of thyroid gland dysfunctions (Table 19-14).[95,212]

Hyperthyroidism. Hyperthyroidism is caused by an excess secretion of thyroid hormones, 3,5,3′-triiodothyronine (T_3) and tetraiodothyronine (thyroxine or T_4). It is evident in such conditions as Graves' disease, toxic goiter (multinodular, single), thyroid carcinoma, and pituitary tumors that oversecrete thyroid-stimulating hormone (TSH). Signs and symptoms reflect a hypermetabolic state with sympathetic overactivity (e.g., tachycardia, atrial fibrillation, fever, tremor) resulting from the primary effects of thyroid hormones on the adenylate cyclase system.[96]

The preoperative preparation of the hyperthyroid patient is aimed at attaining a euthyroid state. This may be accomplished through administration of antithyroid drugs such as methimazole or propylthiouracil for 6 to 8 weeks, followed by iodine for 7 to 14

TABLE 19-14 Clinical Features of Thyroid Gland Disorders

	Hyperthyroidism	Hypothyroidism
General	Heat intolerance; weight loss; tremor; sweating; warm, moist skin	Cold intolerance, thinning hair, arthralgia, alopecia, "strawberries and cream" complexion, gruff voice
Cardiovascular	Tachycardia, cardiac arrhythmias, wide pulse pressure, elevated systolic blood pressure, decreased diastolic blood pressure, increased left ventricular contractility and ejection fraction, atrial fibrillation and heart failure in elderly	Bradycardia, cardiomegaly, cardiac failure, increased peripheral resistance, pericardial effusions
Respiratory	Dyspnea	Hypoventilation, sleep apnea
Gastrointestinal	Diarrhea, nausea, vomiting	Decreased gastrointestinal motility, constipation
Neurologic	Anxiety, irritability, hyperactive reflexes, insomnia; depression, withdrawal, and apathy in elderly	Fatigue, lethargy, slow mental function, hypoactive reflexes, myxedema coma
Musculoskeletal	Goiter, weight loss, proximal myopathy, bone resorption	Goiter, lethargy, large tongue, amyloidosis, peripheral neuropathy, muscle stiffness
Ophthalmic	Exophthalmos, lid lag, lid retraction, reduced blinking	
Renal		Impaired free water clearance
Hematologic	Hypercalcemia, thrombocytopenia, mild anemia	Anemia, coagulopathy

Modified from Connery LE, Coursin DB. Assessment and therapy of selected endocrine disorders. *Anesthesiol Clin North America*. 2004; 22(1):93-123; Barash PG, et al, eds. *Clinical Anesthesia*. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2009; Elisha S, et al. Anesthesia case management for thyroidectomy. *AANA J*. 2010;78(2):151-160.

days.[212] Not only does propylthiouracil decrease the overall synthesis of thyroxine, it also lessens its conversion into the more potent T_3. Reversible agranulocytosis is infrequently seen with long-term therapy.[213] A complete blood cell and platelet count should be determined preoperatively. Beta-antagonist drugs, such as propranolol and esmolol, are also useful adjuncts in the management of hyperthyroidism. They ameliorate signs of sympathetic nervous system overstimulation such as tachycardia, diaphoresis, and tremors.

All drugs used to manage hyperthyroidism, including propylthiouracil and propranolol, should be continued perioperatively, including the morning of surgery, and elective surgery is postponed until the patient is rendered euthyroid. If emergency surgery cannot be delayed for a patient with symptomatic hyperthyroidism, a continuous infusion of esmolol (100 to 300 mcg/kg/min) may be initiated to control unwanted tachycardia (goal heart rate less than 90 beats/minute).[214] Higher doses of preoperative anxiolytics and sedatives, such as benzodiazepines, may also be required. Anticholinergics are avoided because of their interference with normal heat-regulating mechanisms and their potentiation of tachyarrhythmias.

Hypothyroidism. Hypothyroidism represents several conditions, such as chronic thyroiditis or Hashimoto disease, in which tissues are exposed to decreased circulating concentrations of T_3 and T_4. The cause of hypothyroidism may be primary, resulting from the destruction or hypofunction of the thyroid gland, or secondary, resulting from insufficient TSH production. The diagnosis of hypothyroidism is confirmed by decreased serum concentrations of T_3 and T_4, with or without secondary increases in TSH levels.[215]

The treatment of hypothyroidism consists of administration of T_4, levothyroxine sodium (Synthroid) replacement therapy, with the restoration of intravascular volume and electrolyte status. Elective surgery need not be delayed for patients with mild to moderate hypothyroidism. No difference in perioperative outcome has been noted between untreated hypothyroid patients and patients who are euthyroid.[95]

Adrenocortical Disorders. Disorders of the adrenal cortex, ranging from hyperadrenocorticism to hypoadrenocorticism, are the result of primary disease of the adrenal cortex or pituitary gland, ectopic production of adrenocortical hormones by malignant tissue, or most commonly treatment with exogenous corticosteroids. Steroids are commonly used to treat bronchial asthma, autoimmune diseases, and connective tissue disorders such as rheumatoid arthritis. Their high-dose administration for prolonged periods or their excess levels in circulating glucocorticoid hormones characteristically results in a syndrome referred to as *Cushing syndrome*. This syndrome is clinically manifested as hypertension and hypovolemia, truncal obesity with an accumulation of interscapular fat ("buffalo hump"), abdominal and gluteal striae, plethoric facial appearance ("moon facies"), easy bruising, osteoporosis, personality changes, and menstrual irregularities and hirsutism. Hyperaldosteronism—an excess of mineralocorticoid hormones—may be manifested as hypertension in association with marked hypokalemia (plasma potassium [K] less than 3 mmol/L). Its major alterations involve sodium and water retention, potassium depletion, and metabolic alkalosis.

Adrenocortical insufficiency may be of a primary origin (Addison disease) or caused by the secondary inhibition of adrenocortical function by prolonged exogenous steroid therapy. Clinical signs are less obvious than those of Cushing disease and include skin hyperpigmentation, weight loss, muscle wasting, hypotension, intravascular volume depletion, hypoglycemia, hyponatremia, and hyperkalemia.[216]

The preoperative preparation of a patient with adrenocortical dysfunction includes the correction of fluid and electrolyte disturbances and the treatment of coexisting disorders, such as hypertension and diabetes mellitus. Glucocorticoid or mineralocorticoid replacement therapy is also continued perioperatively. Patients are at risk for depression of the hypothalamic-pituitary-adrenal (HPA) axis if they have (1) received 20 mg or more of prednisone, or equivalent, for 5 or more days, or (2) have been treated for 1 month or more. HPA axis suppression may persist for 6 to 12 months after discontinuation of treatment.[96] A reliable test to assess adrenocortical function, the short adrenocorticotropic hormone (ACTH) stimulation test, may be performed to evaluate the need for supplemental steroid.[217] If the patient presenting for surgery is at risk for HPA axis depression, or if findings (i.e., hyponatremia, hyperkalemia, hypotension, eosinophilia) are consistent with adrenal insufficiency, then need for exogenous corticosteroid

supplementation should be assessed (see Table 19-4).[96,218] For patients currently receiving high-dose steroid therapy, such as those with chronic hypoadrenocorticism or Addison disease, further supplementation of the daily maintenance doses may be required based on the surgical stress. This recommendation, although controversial regarding the need for additional supplementation,[219,220] is based on concerns that additional cortisol may not be released from the adrenal cortex as a result of its primary hypofunction or secondary suppression in response to surgical stress. Unexplained hypotension in spite of intravenous fluid repletion or cardiovascular collapse may then ensue during major surgical procedures.

DIAGNOSTIC TESTING

Appropriate laboratory evaluations and diagnostic procedures should be obtained and the results considered to determine the patient's surgical and anesthetic risk, as well as the need for appropriate healthcare modifications. The controversy lies in which tests are necessary and appropriate for specific settings. The rationale for performing "routine" tests has been under intense scrutiny, primarily because of recent and ongoing changes in healthcare economics. A protocol that delineates the indications for testing should be established by each surgical facility and approved by the medical staff. When protocols are followed for ordering preoperative laboratory tests, the total number of tests performed has been reduced 50% to 60%, and the appropriateness of the tests has improved.[221] A necessary step in the implementation process for preoperative testing guidelines is the education of the medical staff. Centralizing the test-ordering process, such as in the preoperative assessment clinic, makes standardization and compliance more attainable.

Routine Diagnostic Testing

It has been traditional practice, even within the past decade, to order a "battery" of routine evaluative tests before a patient undergoes surgery and anesthesia. Routine ordering of preoperative diagnostic tests remains a common practice in many institutions. Until the early 1990s, the rationale for obtaining preoperative diagnostic tests was rarely questioned. Tests were frequently ordered for a variety of reasons but were often unrelated to findings based specifically on the patient's history and physical examination. Reasons cited for ordering the standard battery of preoperative tests included the following[222-224]:

- To follow customary practice at an institution
- To adhere to institutional or legislative mandates that dictate the tests be performed
- To further evaluate and determine the progress of a known disease or condition, because preexisting medical conditions have a greater risk for intraoperative and postoperative complications
- To detect asymptomatic yet modifiable conditions that could alter anesthetic and surgical care
- To detect asymptomatic but unmodifiable conditions that could alter anesthetic and surgical risk
- To screen for conditions unrelated to the planned surgery
- To acquire baseline results that might be useful in the perioperative period
- To protect against medicolegal involvement

When considering the value of preoperative tests, the following must be considered:

1. The diagnostic procedure should be cost-effective—that is, the costs saved from knowing the results exceed the expense of performing the test.
2. The diagnostic procedure should have a positive benefit-risk ratio—that is, the benefit derived from conducting the test outweighs the harm that might ensue from a false-positive result.
3. Test results are available for interpretation and recuperative intervention before surgery.
4. Test results will yield information that could not be obtained from the history and physical examination.
5. Abnormal test results in an asymptomatic patient would influence the patient care, the surgery, or the anesthesia management.

Without any clinical sign, the likelihood of observing a significant anomaly is very small for diagnostic procedures such as ECG,[223] chest radiography,[223,225,226] or laboratory tests.[223,227] Asymptomatic disease is rarely of clinical concern in perioperative surgical care. In addition, unexpected abnormal findings from preoperative testing tend not to affect the upcoming surgery.[228] When a battery of routine preoperative tests are conducted, abnormal test results potentially alter patient care only 0.22% to 0.56% of the time.[223,227] A consistent conclusion of most studies is that routine preoperative laboratory screening is not cost-effective or predictive of postoperative complications[222,229] and is unnecessary when an extensive history and physical examination do not suggest any patient abnormalities.[1,230-234]

Limitations to Routine Preoperative Diagnostic Testing

Studies estimate that at least 10% of the more than $30 billion spent on laboratory testing annually in the United States goes to preparing patients for surgery.[235] Although added healthcare costs are the most apparent limitation to performing the routine battery of preoperative tests, additional factors can negatively affect the patient and care providers. The indiscriminant ordering of tests for diagnostic evaluation increases the likelihood that at least one test will be abnormal in a healthy patient.[224] False-positive, or even false-negative, test results can lead to additional medical evaluation and the potential for increased morbidity. Abnormal laboratory tests for continuous data are defined in probabilistic terms and assume a normal patient population distribution.[223,224] The end points of the bell-shaped distribution curve are arbitrarily set at 2.5%; therefore 5% of test results in normal patients are reported as abnormal. False-positive test results may lead to additional follow-up tests, which can place the patient at risk of increased morbidity.[236] Abnormal test results that were not further pursued and lack of documentation of the rationale for not investigating abnormal test results have increased the medicolegal risk for physicians.[237]

Timing of Diagnostic Testing

In general, diagnostic testing results are deemed current within 6 months of the scheduled surgery if the test results are normal and if the patient's current health status indicates no change has occurred since the test was performed.[238] However, specific tests require more current data analysis. A serum potassium level should be obtained within 7 days of surgery for patients receiving diuretics or digitalis, and blood glucose level determinations should be obtained on the day of surgery for patients with diabetes controlled by medication. An electrocardiogram, when indicated, within 30 days prior to elective surgery is considered adequate for patients with stable disease.[107] Chest radiographs taken within 6 months are generally acceptable if the patient's pulmonary condition is stable.[239]

Indications for Diagnostic Testing

A continuing point of controversy relates to disagreement about which tests are appropriate for specific patients, surgeries, and

BOX **19-19**

Indications for Diagnostic Procedures

Chest Radiograph

- Previous abnormal results on chest radiography
- History of malignancy in which pulmonary metastasis might alter the surgical therapy
- History of tuberculosis (TB) or a positive skin test result for TB and no history of treatment
- History suggestive of pulmonary infection (e.g., new or chronic productive cough or blood-tinged or purulent-appearing sputum)
- Suspected intrathoracic pathologic condition (e.g., tumors, vascular ring)
- History of congenital heart disease
- History of prematurity associated with residual bronchopulmonary dysplasia
- Severe obstructive sleep apnea (patient may have cardiomegaly)
- Down syndrome (patient may have asymptomatic subluxation of the atlantoaxial junction)
- Symptomatic or debilitating asthma, chronic obstructive pulmonary disease, or cardiovascular disease

Electrocardiogram

- Patients at risk for cardiovascular disease (e.g., because of cocaine abuse, hypertension, chest pain, renal insufficiency, peripheral vascular disease, thyroid disease, diabetes mellitus [age 40 years or older], inability to exercise, significant pulmonary disease, smoking (more than 40 pack years), history of ischemic heart disease, history of compensated or prior heart failure, history of cerebrovascular disease
- History of previously unevaluated pathologic-sounding murmur or palpitation
- Family history reveals possibility of inherited prolonged QT syndrome
- Patients with history of morbid obesity, moderate to severe sleep apnea, or chronic anatomic airway obstruction (e.g., Pierre Robin syndrome) may be at risk for right-sided heart strain

Adapted from Zaglaniczny K, Aker J, eds. *Clinical Guide to Pediatric Anesthesia*. Philadelphia: Saunders; 1999; Institute for Clinical Systems Improvement. *Health Care Guidelines: Preoperative Evaluation*. 9th ed, June 2010. Accessed June 21, 2012 at http://www.icsi.org/preoperative_evaluation/preoperative_evaluation_2328.html.

conditions. Difference of opinion exists among and within medical specialties regarding which tests are appropriate. Suggested guidelines for ordering various diagnostic tests based on results of the patient's history and physical examination have been offered for ordering diagnostic procedures (Box 19-19) and laboratory tests (Box 19-20).

Pregnancy Testing

Routine preoperative pregnancy testing in women of childbearing age remains controversial. If a patient is concerned about possible pregnancy, uncertain of her pregnancy status, or if the physical examination or medical history suggests the possibility of pregnancy (e.g., because of information regarding sexually active status, time of last menstrual period, presence or absence of birth control methods), a preoperative pregnancy test should be performed with the patient's consent on the evening prior to or morning of the surgery.[1,240] A serum human chorionic gonadotropin (hCG) measurement performed either the day prior to surgery or on the morning of surgery (realizing the potential for delay while awaiting the hCG result) should be considered for patients less than 1 month past the expected date for their initial missed period. Currently available urine pregnancy tests may yield falsely negative results until week 5 of the pregnancy.[241] Issues to address when deciding whether to test include the following:

- Policies of the hospital or healthcare facility based on medical staff bylaws. The medical facility should have established guidelines, supported on ethical, legal, financial, and scientific relevance that delineate when testing for pregnancy is appropriate.[242]
- All women should be advised of the potential fetal risk (e.g., premature labor, spontaneous abortion) secondary to the underlying surgical condition and surgical uterine stimulation that is unrelated to anesthesia.[240] The incidence of congenital abnormalities is no greater in pregnant women who undergo surgery, however, than it is in those with a surgery-free pregnancy.[243,244] Despite this finding, patients are advised to postpone elective surgery until postpartum or at the least well after the first trimester, when fetal organogenesis is complete.
- Patients should be privately questioned about the possibility of pregnancy. Female staff should interview adolescent patients in the absence of family members.
- Patients should be offered pregnancy testing despite history, except in patients with a history of hysterectomy or bilateral salpingo-oophorectomy.[245]

Chest Radiography

A preoperative chest radiograph is of minimal predictive importance and is not cost-effective as a screening test for postoperative respiratory problems, so it is not to be recommended without specific indications, that is, new or unstable cardiopulmonary disease, from the medical history and physical examination.[1,4,246,247] The risk of performing a routine preoperative chest radiograph in asymptomatic patients less than 75 years of age is greater than the benefit.[237]

Electrocardiography

A routine preoperative electrocardiogram is not necessary unless a specific indication is present.[1,233] Many medical facilities continue to use an age-specific criterion for acquiring a preoperative ECG, regardless of indications—or lack of indications—based on the patient's medical history and physical examination. The recommended minimum age for routinely conducting a baseline ECG, if deemed necessary by the facility, has gradually increased to 65 years or older and is considered current if tested within I year of the procedure provided no changes in the patient's condition have occurred.[107,248] Inquiry has even been raised regarding the appropriateness of an age-only basis for preoperative ECG testing, especially since the Centers for Medicare and Medicaid Services (CMS) no longer reimburse for routine, age-based testing.[233]

The value of obtaining a routine preoperative 12-lead ECG in asymptomatic, low-risk patients, that is, having cataract surgery,[249]

BOX **19-20**

Indications for Laboratory Testing

Complete Blood Count
- Hematologic disorder
- Vascular procedure
- Chemotherapy
- Unknown sickle cell syndrome status

Hemoglobin and Hematocrit
- Age less than 6 months (less than 1 year if born prematurely)
- Hematologic malignancy
- Recent radiation or chemotherapy
- Renal disease
- Anticoagulant therapy
- Procedure with moderate to high blood loss potential
- Coexisting systemic disorders (e.g., cystic fibrosis, prematurity, severe malnutrition, renal failure, liver disease, congenital heart disease)

White Blood Cell Count
- Leukemia and lymphomas
- Recent radiation or chemotherapy
- Suspected infection that would lead to cancellation of surgery
- Aplastic anemia
- Hypersplenism
- Autoimmune collagen vascular disease

Blood Glucose Level
- Diabetes mellitus
- Current corticosteroid use
- History of hypoglycemia
- Adrenal disease
- Cystic fibrosis

Serum Chemistry
- Renal disease
- Adrenal or thyroid disease
- Chemotherapy
- Pituitary or hypothalamic disease
- Body fluid loss or shifts (e.g., dehydration, bowel prep)
- Central nervous system disease

Potassium
- Digoxin therapy
- Diuretic therapy
- ACE inhibitors or angiotensin receptor blockers

Creatinine and Blood Urea Nitrogen
- Cardiovascular disease (e.g., hypertension)
- Renal disease
- Adrenal disease
- Diabetes mellitus
- Diuretic therapy
- Digoxin therapy
- Body fluid loss or shifts (e.g., dehydration, bowel prep)
- Procedure requiring radiocontrast

Liver Function Tests
- Hepatic disease
- Exposure to hepatitis
- Therapy with hepatotoxic agents

Coagulation Studies
INR, Prothrombin Time, and Partial Thromboplastin Time
- Leukemia
- Hepatic disease
- Bleeding disorder
- Anticoagulant therapy
- Severe malnutrition or malabsorption
- Postoperative anticoagulation to establish a baseline

Platelet Count and Bleeding Time
- Bleeding disorder
- Abnormal hemorrhage, purpura, history of easy bruising

Urinalysis
- Not indicated as a routine screening test

Pregnancy Test
- Possibility of pregnancy

Medication Levels
- Monitor for medications (e.g., theophylline, phenytoin, digoxin, carbamazepine) if patient exhibits signs of ineffective therapy, potential drug side effects, or poor drug compliance or has recently changed medication therapy without documentation of the drug level

ACE, Angiotensin-converting enzyme; *INR*, international normalized ratio (prothrombin time).

has been questioned.[250,251] This rethinking of indications for when to order a preoperative ECG has been challenged for the following reasons:

- It has not been shown to be cost-effective.[228,252,253]
- It is a poor predictor of perioperative complications.[251,253,254]
- It is of limited value in detection of ischemia in asymptomatic individuals.[255,256]
- Abnormal preoperative ECGs rarely lead to alteration in patient care.[228,252,257]
- No evidence supports the value of a "baseline" ECG.[250,251,258]

FASTING CONSIDERATIONS

Part of the anesthesia provider's role in patient preparation involves establishing an appropriate fasting interval for the patient. This requires knowledge of risk factors for pulmonary aspiration of gastric contents weighed against the consequences of prolonged fasting. The risk of perioperative pulmonary aspiration of gastric contents that results in morbidity or mortality is relatively low, so the recommendations for withholding oral feeding before elective surgery have recently become much more liberal. When studies were conducted challenging the traditional fasting times (7 hours or greater) for clear liquids, the results appeared to show that a reduced fasting interval does not increase the risk of pulmonary aspiration in normal, healthy individuals.[259]

The traditional policy of fasting after midnight fails to address three variables that influence gastric emptying for surgery: (1) the time of the scheduled surgery, (2) the time at which the patient retired for the night, and (3) the variability in gastric emptying for solids and fluids among individuals. Prolonged fasting, especially in children, can be highly distressing in addition to causing physiologic alterations. Periods of long preoperative fasting have been shown to contribute to the following:

- Dehydration[260]
- Hypoglycemia (in smaller children)[261]

BOX 19-21

Conditions That Increase the Risk of Regurgitation and Pulmonary Aspiration During Anesthesia

- Age extremes (less than 1 yr or older than 70 yr)
- Anxiety
- Ascites
- Collagen vascular disease (e.g., scleroderma)
- Depression
- Esophageal surgery
- Exogenous medications (e.g., opioids, premedication)
- Failed intubation or difficult airway history
- Gastroesophageal junction dysfunction (e.g., hiatal hernia)
- Mechanical obstruction (e.g., pyloric stenosis, duodenal ulcer)
- Metabolic disorders (e.g., hypothyroidism, chronic diabetes, hepatic failure, hyperglycemia, obesity, renal failure, uremia)
- Neurologic sequelae (e.g., those of developmental delays, head injury, hypotonia, seizures)
- Pain
- Pregnancy
- Prematurity with respiratory problems
- Smoking
- Type and composition of gastric contents (e.g., solid foods and milk products)

- Hypovolemia
- Increased irritability[261]
- Enhanced preoperative anxiety[262]
- Reduced compliance with preoperative fasting orders[260]
- Thirst[263] and related discomforts (e.g., hunger, headache, unhappiness)

Pulmonary Aspiration Risk

Recent ingestion of food and liquid before surgery does contribute to an increased risk of pulmonary aspiration. Solid foods must be digested to a bolus diameter of less than 2 mm before the food can pass through the pylorus.[264] This process normally takes several hours for solids, whereas liquids pass through the pylorus in 1 to 2 hours. Historically, patients have been required to fast for extended periods in an attempt to ensure an empty stomach. However, sustained fasting does not guarantee that the stomach will be empty at the time of surgery.[265]

Part of the preoperative evaluation process identifies patients who are at risk for aspirating gastric contents into the lungs and developing aspiration pneumonitis. Factors associated with an increased risk of pulmonary aspiration of gastric contents are listed in Box 19-21.[266-277]

Fasting Interval

When the fasting interval is minimized, patients (especially children) are reported to be less irritable, less thirsty, and less hungry; to have fewer headaches; to be more comfortable; and generally to tolerate the preoperative phase better than patients who have fasted for longer periods of time. Modest amounts of clear liquids taken orally 2 hours[278-280] to 3 hours[281,282] preoperatively, when compared with a conventional fasting interval of "7 to 8 hours" or "after midnight," are acceptable and have been shown to lower residual gastric volume (stimulation of the gastric emptying reflex) and raise gastric pH in a majority of patients. Acceptable clear fluids (e.g., water, apple juice, black coffee, black tea, clear juice drinks, clear Jell-O, clear broth, ice, Popsicles, Pedialyte) may be given to healthy, unpremedicated patients. Chewing gum or sucking on candy does not warrant delay or cancellation of the operation.[283] In light of these findings, recommended fasting guidelines for otherwise healthy individuals have been liberalized (Box 19-22).[277,283,284]

BOX 19-22

Fasting Guidelines for Healthy Patients (All Ages) Undergoing Elective Surgery

- No chewing gum (nicotine gum allowed with patient counseling) or candy after midnight (foreign body aspiration concern)
- Clear liquids up to 2 hours before surgery*
- Breast milk until 4 hours before surgery
- No infant formula, nonhuman milk,† or light meal‡ for at least 6 hours before surgery
- Prescribed medications (e.g., premedication) administered with a sip of water or prescribed liquid mixture (up to 150 mL for adult; up to 75 mL for children) up to 1 hour before anesthesia

From American Society of Anesthesiologists Committee. Practice guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration: application to healthy patients undergoing elective procedures: an updated report by the American Society of Anesthesiologists Committee on Standards and Practice Parameters, *Anesthesiology.* 2011;114(3):495-511.

*Consider the possibility that the case may proceed earlier than scheduled.

†Because nonhuman milk is similar to solids in gastric emptying time, the amount ingested must be considered when determining an appropriate fasting period.

‡A light meal typically consists of toast and clear liquids. Meals that include fried or fatty foods or meat may prolong gastric emptying time. Both the amount and type of foods ingested must be considered when determining an appropriate fasting period.

AMERICAN SOCIETY OF ANESTHESIOLOGISTS PHYSICAL STATUS CLASSIFICATION SYSTEM

With the conclusion of the preanesthesia assessment, assignment of an ASA physical status classification is made for each patient. The classification ideally represents a reflection of the patient's preoperative status and is not an estimate of anesthetic risk. For greater accuracy to be attained from its interpretation, the ASA status should also remain independent of the proposed surgical procedure.[285-288]

Advent and Purpose

In 1940 the ASA developed a system "to classify the physical condition of a patient requiring anesthesia and surgery." This six-category classification was then revised by the ASA in 1961 to the current system of five categories (Table 19-15).[289] The purpose of the ASA classification, then and now, is to provide a consistent means of communication to anesthesia staff, within and among institutions, about the physical status of a patient.[289] Furthermore, it allows for a standardized interpretation of anesthesia outcome based on one criterion.

Despite rough correlations between patient physical status and postoperative outcome, *the ASA classification system does not represent an estimate of anesthesia risk.*[285-288] Although a patient in poor physical health is known to be at greater risk for negative outcome, this does not account for other factors that influence perioperative morbidity and mortality. These factors include the duration and involvement of the surgical procedure, the degree of perioperative monitoring, and unfortunate circumstances, such as human error or equipment failure.

TABLE 19-15 American Society of Anesthesiologists Physical Status Classification

Classification	Physical Status
ASA Class I	No organic, physiologic, biochemical, or psychiatric disturbance
	Example: Healthy patient
ASA Class II	Mild to moderate systemic disturbance
	Examples: Heart disease that slightly limits physical activity, essential hypertension, diabetes mellitus, chronic bronchitis, anemia, morbid obesity, age extremes
ASA Class III	Severe systemic disturbance that limits activity
	Examples: Heart or chronic pulmonary disease that limits activity, poorly controlled essential hypertension, diabetes mellitus with vascular complications, angina pectoris, history of previous myocardial infarction
ASA Class IV	Severe systemic disturbance that is life threatening
	Examples: Congestive heart failure; persistent angina pectoris; advanced pulmonary, renal, or hepatic dysfunction
ASA Class V	Moribund patient undergoing surgery as a resuscitative effort, despite a minimal chance for survival
	Example: Uncontrolled hemorrhage from a ruptured abdominal artery aneurysm
ASA Class E	Emergency surgery is required
	Example: An otherwise healthy 30-year-old woman who requires a dilation and curettage for moderate but persistent hemorrhage is classified as ASA IE

Modified from American Society of Anesthesiologists. New classification of physical status. *Anesthesiology.* 1963;24:111.
ASA, American Society of Anesthesiologists.

Definition

The current ASA classification system ranges from class I through V, with E denoting an emergent procedure. At some institutions, a classification of ASA status VI also may be assigned to postmortem patients undergoing organ procurement procedures. By definition, a patient classified as ASA status I is a healthy individual except for the condition that has necessitated surgery. A healthy young woman about to undergo an emergency dilation and curettage for vaginal bleeding, for example, is classified as ASA status IE. At the other end of the spectrum, a 74-year-old man with hypertension, uncontrolled diabetes, and unstable angina who is scheduled for a coronary artery bypass graft procedure is classified as ASA status IV.[289]

Limitations of the Current System

Despite the numerous benefits of the ASA classification system, it has its shortcomings. Namely, the current system is not explicit enough in its categorization to account for every patient, and this can result in patient misclassification.[290] If the physical status classification system is used for statistical or reimbursement purposes within a department, overclassification is often the consequence. Overclassification of a patient also occurs when the proposed surgical procedure is incorporated into the assignment of ASA physical status. This improper classification, or overclassification, of patient status thereby limits the degree of accuracy attained from its original interpretation. As a result, correlations between preoperative status and postoperative outcome are skewed. Despite the shortcomings of the system, ASA physical status continues to be assigned to each patient as a summary of the preoperative evaluation.

PREVENTING OPERATIVE ERRORS

The Joint Commission has endorsed a universal protocol for eliminating wrong site, wrong procedure, wrong patient surgeries. It has been endorsed by more than 40 of the leading medical, nursing, and healthcare leadership organizations. The guidelines are to be used in all hospitals, ambulatory care surgery centers, and office-based surgery sites, as shown in Box 19-23.

BOX 19-23

Guidelines for Implementing the Universal Protocol for Preventing Wrong Site, Wrong Procedure, and Wrong Person Surgery

Conduct a Pre-Procedure Verification Process

Address missing information or discrepancies before starting the procedure.

- Verify the correct procedure, for the correct patient, at the correct site.
- When possible, involve the patient in the verification process.
- Identify the items that must be available for the procedure.
- Use a standardized list to verify the availability of items for the procedure. (It is not necessary to document that the list was used for each patient.) At a minimum, these items include:
  - Relevant documentation. Examples: History and physical, signed consent form, preanesthesia assessment
  - Labeled diagnostic and radiology test results that are properly displayed. Examples: Radiology images and scans, pathology reports, biopsy reports
  - Any required blood products, implants, devices, special equipment
- Match the items that are to be available in the procedure area to the patient.

Mark the Procedure Site

At a minimum, mark the site when there is more than one possible location for the procedure and when performing the procedure in a different location could harm the patient.

- The site does not need to be marked for bilateral structures. Examples: tonsils, ovaries
- For spinal procedures: Mark the general spinal region on the skin. Special intraoperative imaging techniques may be used to locate and mark the exact vertebral level.
- Mark the site before the procedure is performed.
- If possible, involve the patient in the site marking process.
- The site is marked by a licensed independent practitioner who is ultimately accountable for the procedure and will be present when the procedure is performed.*
- Ultimately, the licensed independent practitioner is accountable for the procedure – even when delegating site marking.
- The mark is unambiguous and is used consistently throughout the organization.
- The mark is made at or near the procedure site.

Continued

BOX **19-23—cont'd**

Guidelines for Implementing the Universal Protocol for Preventing Wrong Site, Wrong Procedure, and Wrong Person Surgery

- The mark is sufficiently permanent to be visible after skin preparation and draping.
- Adhesive markers are not the sole means of marking the site.
- For patients who refuse site marking or when it is technically or anatomically impossible or impractical to mark the site (see examples below): Use your organization's written, alternative process to ensure that the correct site is operated on. Examples of situations that involve alternative processes:
  - Mucosal surfaces or perineum
  - Minimal access procedures treating a lateralized internal organ, whether percutaneous or through a natural orifice
  - Teeth
  - Premature infants, for whom the mark may cause a permanent tattoo

Perform a Time-Out

The procedure is not started until all questions or concerns are resolved.

- Conduct a time-out immediately before starting the invasive procedure or making the incision.
- A designated member of the team starts the time-out.
- The time-out is standardized.
- The time-out involves the immediate members of the procedure team: the individual performing the procedure, anesthesia providers, circulating nurse, operating room technician, and other active participants who will be participating in the procedure from the beginning.
- All relevant members of the procedure team actively communicate during the time-out.
- During the time-out, the team members agree, at a minimum, on the following:
  - Correct patient identity
  - Correct site
  - Procedure to be done
- When the same patient has two or more procedures: If the person performing the procedure changes, another time-out needs to be performed before starting each procedure.
- Document the completion of the time-out. The organization determines the amount and type of documentation.

*In limited circumstances, site marking may be delegated to some medical residents, physician assistants (PA), or advanced practice registered nurses (APRN).

SUMMARY

An important feature of patient care is a timely and thorough preoperative assessment to identify factors that increase the risk of anesthesia and surgery. The preoperative evaluation and preparation of the patient involve integration of information obtained from the patient interview, chart review, physical examination, and interpretation of the results of necessary diagnostic tests. The anesthesia provider can then assimilate the assessment data and devise and implement the most appropriate anesthetic plan for the patient.

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CHAPTER 20

Fluids, Electrolytes, and Blood Component Therapy

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In the clinical practice of anesthesia, an important priority in patients experiencing the stresses of surgery and anesthesia is maintenance of homeostasis. Maintaining a physiologic balance of body fluids in both volume and composition is critical to maintaining overall homeostasis. The following discussion focuses on factors of fluid and electrolyte management and transfusion therapy that are of greatest consequence to patients in the perioperative period.

FLUID COMPARTMENTS

A prerequisite to understanding clinical fluid management is an appreciation of the role of fluids in the human body and the distribution of fluids and electrolytes among the fluid compartments. The body is in large part composed of fluid, ranging between 46% and 80%, depending on the age and gender of the individual and the body's composition of fat relative to muscle. Compared with muscle, fat contains less fluid as a percentage of weight. Total body fluid as a percent of body weight is the highest in newborns (70%-80%) and declines with age to approximately 50% at age 50.

Total body water is partitioned into two principal compartments: the intracellular fluid (ICF) and the extracellular fluid (ECF). The extracellular compartment is further subdivided into intravascular fluid (IVF) and interstitial fluid (ISF) spaces. The fluid compartments are divided by water-permeable membranes[1]; the intracellular space is separated from the extracellular space by the cell membrane, and the extracellular space is divided into intravascular and interstitial spaces by the capillary membrane.

The ICF compartment contains approximately two thirds of the body's total fluid volume[2] and is characterized by high concentrations of potassium, phosphate, and magnesium. The adenosine triphosphatase (ATPase)–driven sodium-potassium pump (Na-K–ATPase pump) located in the cell membrane maintains the high concentration of potassium found in ICF[3] (Figure 20-1 and Table 20-1). The Na-K–ATPase pump exchanges three sodium ions for two potassium ions and offsets the tendency for sodium to diffuse into the intracellular space.

The ECF compartment contains approximately one third of the body's fluid volume[2] and contains high concentrations of sodium and chloride compared with the ICF compartment. The IVF (also known as *plasma*) space contains approximately one quarter of the ECF volume and has essentially the same composition and concentration of electrolytes as the ISF. The presence in the IVF of relatively high concentrations of osmotically active plasma proteins, of which albumin is most important, is a significant difference distinguishing ISF from IVF.[4] The capillary membrane is relatively impermeable to the plasma proteins contained within the vascular space, unless a disease state such as trauma or sepsis alters the capillary permeability.

The properties of the membranes that separate the fluid compartments, as well as the relative concentration of osmotically active substances within each compartment, are the factors primarily responsible for the movement of fluid (water and electrolytes) among compartments in the body. Because the intravascular space is the fluid compartment accessible to the clinician and the chief focus of fluid therapy, it is useful to understand the motion of fluid from the IVF space to the ISF space across the capillary membrane. Four forces known commonly as *Starling forces* determine the motion of fluids across the capillary membrane. The four forces that govern fluid dynamics in the microcirculation are capillary pressure, ISF pressure, ISF colloid osmotic pressure, and plasma colloid osmotic pressure.[2]

The plasma colloid osmotic pressure is significant because this force is determined primarily by plasma protein concentration and serves to maintain the circulating fluid volume within the intravascular space. Plasma protein concentrations can be increased or decreased, depending on the types and volumes of intravenous (IV) fluids administered.

INFLUENCES OF SURGERY AND ANESTHESIA ON FLUID BALANCE

Illness, surgery, and anesthetics can profoundly alter the fluid and electrolyte balance of patients during the perioperative period.

Preoperatively, patients can become volume depleted and experience alterations of electrolyte balance due to several processes. Burns, vomiting, diarrhea, fever, and gastric suction can lead to hypovolemia before surgery.[5] If a large volume of fluid is lost from the gastrointestinal (GI) tract, careful evaluation of electrolytes and appropriate replacement is indicated.[4] Quite often, preoperative hypovolemia is at least in part an iatrogenic phenomenon secondary to bowel preparation and preoperative fasting. Unless surgery is of the greatest urgency, to reduce the risk of hypotension and complications resulting from electrolyte imbalances, preoperative fluid deficits and electrolyte abnormalities should be corrected before anesthetic induction.[6]

During the intraoperative period, the effects of surgery and anesthesia combine to challenge fluid and electrolyte homeostasis. Surgery can lead to hemorrhage and a need to replace fluids or blood. Surgery can also lead to evaporative loss; loss from exposed viscera is composed entirely of water (without electrolytes) and is most appropriately replaced with free water (water available for dissolving substances). Manipulation of tissues during surgery can lead to "third spacing," which is the redistribution of fluid from the intravascular space to the interstitial space. Replacement of fluid lost from the intravascular space in the phenomenon of third spacing is best carried out by balanced salt solutions that have an electrolyte composition similar to ECF.[1,6] Absorption of electrolyte-free irrigation solutions during transurethral prostate surgery

or endometrial ablation can result in a life-threatening hypo-osmolar state that must be addressed appropriately by the clinician.[7]

Anesthesia in and of itself can lead to derangements of fluid balance in surgical patients. The vasodilatory effects of both regional and general anesthesia can result in a relative hypovolemia, which may lead to hypotension on induction. General anesthesia increases the release of antidiuretic hormone, causing increased retention of water,[1,8] which can predispose the patient to hyponatremia.[9] Mechanical ventilation can increase evaporative loss of water and decrease the release of atrial natriuretic peptide, leading to renal conservation of sodium.[1]

The effects of surgery on fluid balance can persist into the postoperative period. Third-spaced fluids are typically mobilized (returned to the intravascular space) on the third postoperative day. The increased circulating volume may be poorly tolerated by patients with marginal renal or cardiovascular performance and can result in congestive heart failure or pulmonary edema.[4,10]

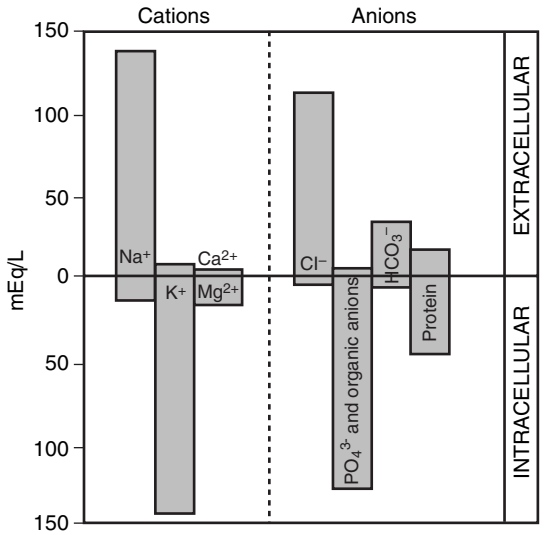

FIGURE **20-1** Major cations and anions of the intracellular and extracellular fluids. The concentrations of calcium and magnesium represent the sum of these two ions. The concentrations shown represent the total of free ions and complexed ions. (From Hall JE. *Guyton and Hall Textbook of Medical Physiology*. 12th ed. Philadelphia: Saunders; 2011:288.)

FLUID VOLUME DISORDERS

Fluid volume disorders, particularly hypovolemia, are often encountered in patients undergoing surgery. Discussion of disorders of concentration and volume of body fluids is facilitated by careful consideration of the concepts of osmolarity, osmolality, and tonicity. Osmolarity is an expression of the number of osmoles of solute in a liter of solution, whereas osmolality expresses the number of osmoles of solute in a kilogram of solvent. Because of the dilute nature of body fluids, the difference between osmolarity and osmolality is minimal. Tonicity, a concept related to osmolarity and osmolality, describes how a solution affects cell volume. Isotonic solutions have an effective osmolality close to that of body fluids (approximately 285 mOsm/L)[3]; therefore cells placed in an isotonic solution are not expected to swell or shrink.

Volume depletion, or *hypovolemia*, refers to the loss of ECF and is not to be confused with *dehydration*, which refers to a concentration disorder in which insufficient water is present relative to sodium levels.[3] Hypovolemia can result from an absolute loss of fluid from the body or a relative loss of bodily fluids in which water is redistributed within the body, leading to a reduced circulating volume. Causes of absolute fluid loss include loss of fluid from the GI tract, polyuria, and diaphoresis. Decreased intake of fluids is a common cause of absolute fluid deficit in surgical patients because

TABLE **20-1** Osmolar Substances in Extracellular and Intracellular Fluids

	Plasma (mOsm/L H_2O)	Interstitial Fluid (mOsm/L H_2O)	Intracellular Fluid (mOsm/L H_2O)
Na^+	142	139	14
K^+	4.2	4	140
Ca^{2+}	1.3	1.2	0
Mg^{2+}	0.8	0.7	20
Cl^-	108	108	4
HCO_3^-	24	28.3	10
HPO_4^-, $H_2PO_4^-$	2	2	11
SO_4^{2-}	0.5	0.5	1
Phosphocreatine	—	—	45
Carnosine	—	—	14
Amino acids	2	2	8
Creatine	0.2	0.2	9
Lactate	1.2	1.2	1.5
Adenosine triphosphate	—	—	5
Hexose monophosphate	—	—	3.7
Glucose	5.6	5.6	—
Protein	1.2	0.2	4
Urea	4	4	4
Others	4.8	3.9	10
Total mOsm/L	301.8	300.8	301.2
Corrected osmolar activity (mOsm/L)	282	281	281
Total osmotic pressure at 37° C (mmHg)	5443	5423	5423

From Hall JE. *Guyton and Hall Textbook of Medical Physiology*. 12th ed. Philadelphia: Saunders; 2011:288.

of intolerance to oral fluids and prolonged preoperative fasting. Relative fluid losses can be caused by conditions such as burns and third-space losses resulting from surgery. It should be noted that patient weight does not decrease in cases of relative fluid loss.

Because most cases of hypovolemia are caused by the loss of ECF, replacement with isotonic crystalloids (which have a composition similar to ECF) is appropriate.[3] Determining the appropriate volume of fluids to administer for maintenance and replacement needs is discussed later; however, in certain circumstances such as oliguria or hemodynamic instability, a fluid bolus (also known as *fluid challenge*) may be warranted. Four components of a fluid challenge are the type of fluid, rate of administration, critical end points, and safety factors. (Table 20-2). Estimated fluid and blood requirements based on the clinical presentation of a patient have been classified into four stages of shock (Table 20-3).

Hypervolemia is an excess of fluid volume in an isotonic concentration. Hypervolemia is not usually encountered in surgical patients but can be seen if diseases such as congestive heart failure, renal failure, or cirrhosis of the liver are present. Iatrogenic causes of fluid overload include administration of steroids and excessive IV administration of isotonic fluids. Excessive consumption of sodium in the diet or in medications can lead to retention of water and hypervolemia. Treatment of hypervolemia may include sodium restriction, diuretics, and in cases of renal failure, hemodialysis or ultrafiltration.

TABLE 20-2 Successful Fluid Challenge

Critical components of the fluid challenge: a hypothetical patient with hypotension mean arterial pressure (MAP) of 65 mmHg and a central venous pressure (CVP) of 15 mmHg

Example	Baseline	+10 Minutes	+20 Minutes
1. Type of fluid: Ringer's lactate			
2. Rate of infusion: 500 mL/30 minutes			
3. Clinical end points: MAP of 75 mmHg	MAP 65	MAP 70	MAP 75
4. Pressure safety limits: CVP of 15 mmHg	CVP 12	CVP 13	CVP 14

Adapted from Vincent JL, Weil MH. Fluid challenge revisited. *Crit Care Med*. 2006;34(5):1333-1337.

DISORDERS OF SODIUM BALANCE

Disorders of sodium balance may be encountered in anesthetic care and are of great clinical significance. Sodium is the most abundant electrolyte in the ECF; along with its accompanying chloride anion (NaCl), it is responsible for most of the osmotic activity of the ECF. The physiologic significance of sodium can be appreciated when one considers that gain or loss of sodium is accompanied by a gain or loss of water, respectively.[3] Because sodium concentration in the ECF is much higher than in the intracellular space (as a result of the action of the Na-K–ATPase pump in the cell membrane), alteration of sodium levels in the extracellular space greatly affects the osmotic relationship between intracellular and extracellular spaces, leading to movement of water across the cell membrane.

The clinical importance of sodium disorders is due largely to the influence of sodium on the water content in brain cells. The blood-brain barrier, unlike peripheral capillary beds, has only limited permeability to ionic solutes. The result of this limited permeability in the blood-brain barrier is the prevention of equilibration of osmotically active ionic solutes between intravascular and interstitial spaces. This lack of permeability to sodium (and consequent failure to equilibrate osmotically active solutes between the intravascular and interstitial spaces) changes the osmotic gradients between fluid compartments, leading to the precedence of sodium over plasma proteins as the most important osmotically active substance influencing the water content of the brain tissues.[10,11]

Because sodium imbalances reflect impaired concentration between water and sodium, evaluation of sodium imbalance should take into consideration both the volume of the solvent (water) and the amount of solute (sodium) present in the solution. Likewise, treatment of sodium imbalances can involve restriction or expansion of water volume and enhanced elimination or supplementation of sodium.

Hyponatremia may have multiple causes (Box 20-1). Of particular interest to anesthetists is hyponatremia resulting from the syndrome of inappropriate secretion of antidiuretic hormone (SIADH), which is discussed in Chapter 33. Water intoxication resulting from the absorption of electrolyte-free irrigation solution during procedures such as transurethral resection of the prostate and endometrial ablation is discussed in Chapter 29. Water intoxication and SIADH lead to hyponatremia from an excess of water, not loss of sodium.[1,12]

Hyponatremia results in a condition in which the intracellular environment is hyperosmolar relative to the ECF, leading to an

TABLE 20-3 Four Classes of Hemorrhagic Shock

	CLASS			
Parameter	**I**	**II**	**III**	**IV**
Blood loss (mL)	<750	750-1500	1500-2000	≥2000
Blood loss (%)	0-15	15-30	30-40	>40
Central nervous system	Slightly anxious	Mildly anxious	Anxious or confused	Confused or lethargic
Pulse (beats/min)	<100	>100	>120	>140
Blood pressure	Normal	Normal	Decreased	Decreased
Pulse pressure	Normal	Decreased	Decreased	Decreased
Respiratory rate	14-20/min	20-30/min	30-40/min	>35/min
Urine (mL/hr)	>30	20-30	5-15	Negligible
Fluid	Crystalloid	Crystalloid	Crystalloid + blood	Crystalloid + blood

Modified from Rhee P. Shock fluids and electrolytes. In: Townsend CM, et al, eds. *Sabiston Textbook of Surgery: The Biological Basis of Modern Surgical Practice*. 19th ed. Philadelphia: Saunders; 2012:72.

influx of water into the intracellular space. One of the most significant consequences of hyponatremia is cerebral edema. Because the brain is contained within the fixed confines of the skull, cerebral edema is poorly tolerated.[13] Compensatory mechanisms can forestall the development of symptomatic cerebral edema for a period of time.[14] Brain cells can maintain osmotic equilibrium by extruding intracellular solutes, thereby reducing intracellular osmolality.[9,13] However, if the extrusion of solute by brain cells is inadequate to compensate for the hypo-osmolar influence of the ECF, an intracellular influx of water may lead to symptomatic cerebral edema.[13]

Clinical studies have demonstrated that compared with men or postmenopausal women, menstruating women are at increased risk of brain damage resulting from hyponatremia.[3,13] It is believed that estrogen and progesterone inhibit the efficiency of the Na-K–ATPase pump, which is essential to the extrusion of intracellular solutes to maintain osmotic equilibrium in hyponatremia; female sex hormones may facilitate movement of water into the brain through the mediation of antidiuretic hormone (ADH).[13]

Hyponatremia is the most common electrolyte abnormality in hospitalized patients. The development of hypervolemic hyponatremia in patients with congestive heart failure (CHF) or cirrhosis is associated with an increased risk of death. Even mild stable euvolemic hyponatremia due to SIADH has been associated with cognitive defects and gait disturbances. Overly rapid correction of serum sodium, particularly in patients with chronic hyponatremia, can cause neurologic complications such as seizures, spastic quadriparesis, and coma due to osmotic demyelination.[15] There are two drugs available for the treatment of hypervolemic or euvolemic hyponatremia due to CHF, cirrhosis, or SIADH. Tolvaptan (Samsca) and conivaptan (Vaprisol) are vasopressin receptor antagonists. Tolvaptan is an oral preparation and conivaptan is available for intravenous use. Treatment of hyponatremia usually includes fluid restriction and diuresis. IV conivaptan has been used for short-term treatment of euvolemic hyponatremia. Oral treatment with tolvaptan can increase serum sodium concentrations in patients with hypervolemic or euvolemic hyponatremia due to cirrhosis, heart failure, or SIADH, but has not been shown to reduce mortality. Overly rapid correction of serum sodium, which can cause osmotic demyelination, has not been reported to date with tolvaptan.[15-17]

Controversy exists as to how aggressively hyponatremia should be treated (Figure 20-2). In chronically hyponatremic patients, rapid correction of serum sodium can lead to the neurologic disorder known as *myelinolysis*. Myelinolysis, originally known as *central pontine myelinolysis*, can lead to disorders of the upper neurons, spastic quadriparesis, pseudobulbar palsy, mental disorders, and in some cases death.[14] Patients at particular risk for myelinolysis are those who have been hyponatremic for more than 48 hours[9,14] and individuals who have had orthotopic liver transplantation or a history of alcohol abuse.[14] Optimal treatment of hyponatremia must balance the risks of cerebral edema against the risks of myelinolysis.[12]

The risk of myelinolysis can be reduced by correcting serum sodium levels in a deliberate manner. It has been suggested that serum sodium concentrations should be increased by no more than 1 to 2 mEq/L/hr. In symptomatic patients, this is accomplished by infusing 3% saline at a rate of 1 to 2 mL/kg/hr. Once the patient is clinically stable, sodium administration should be slowed to raise serum sodium not more than 10 to 15 mmol/L in 24 hours.[9,12,14]

Hypernatremia can result from several causes (Figure 20-3, Box 20-2, and Table 20-4) but is usually the result of impaired water intake.[12] Inadequate administration of free water to hospitalized patients can lead to an iatrogenic hypernatremia. Debilitated, mentally impaired, and intubated individuals are at particular risk for developing hypernatremia.[4,12] In cases of slow-onset hypernatremia, the brain can adapt by conserving intracellular solutes, which allows maintenance of normal intracellular volume. Rapidly occurring hypernatremia can be accompanied by rapid shrinking of the brain and concomitant traction on intracranial veins and venous sinuses, leading to intracranial hemorrhage.[7]

As with hyponatremia, overly aggressive treatment of chronic hypernatremia can lead to unwanted effects. In the case of hypernatremia, rapid correction of serum sodium with solutions containing large amounts of free water may lead to cerebral edema.[7]

Correction of hypernatremia is carried out by replacement of the water deficit, which can be calculated by the formula shown in Box 20-3. If the hypernatremia is acute (i.e., less than 24 hours' duration),

BOX 20-1

Hyponatremia*

Causative Factors and Classification

Isotonic Hyponatremia (Pseudohyponatremia)

Serum osmolality 275-295

Causes: Hyperlipidemia, hyperproteinemia, multiple myeloma, infusion of isotonic nonelectrolytic substances (e.g., glucose, mannitol glycine)

Hypertonic Hyponatremia

Serum osmolality greater than 295

Causes: Hyperglycemia, mannitol excess glycerol therapy

Hypotonic Hyponatremia

Serum osmolality less than 275

Hypovolemic hypotonic hyponatremia

Causes: Diuretics, salt-losing nephropathy, ketonuria, Addison's disease, vomiting, diarrhea, third spacing of fluids, excessive sweating

Isovolemic hypotonic hyponatremia

Causes: SIADH, renal failure, hypothyroidism, drugs, water intoxication, porphyria, pain, stress, positive pressure ventilation

Hypervolemic hypotonic hyponatremia

Causes: Nephrotic syndrome, cirrhosis, congestive heart failure, renal failure

Clinical Features

Seizure
Coma
Agitation
Confusion
Headache
Cerebral edema
Anorexia
Nausea and vomiting
Cramps
Weakness

*Serum sodium less than 135mEq/L.
SIADH, Syndrome of inappropriate secretion of antidiuretic hormone.

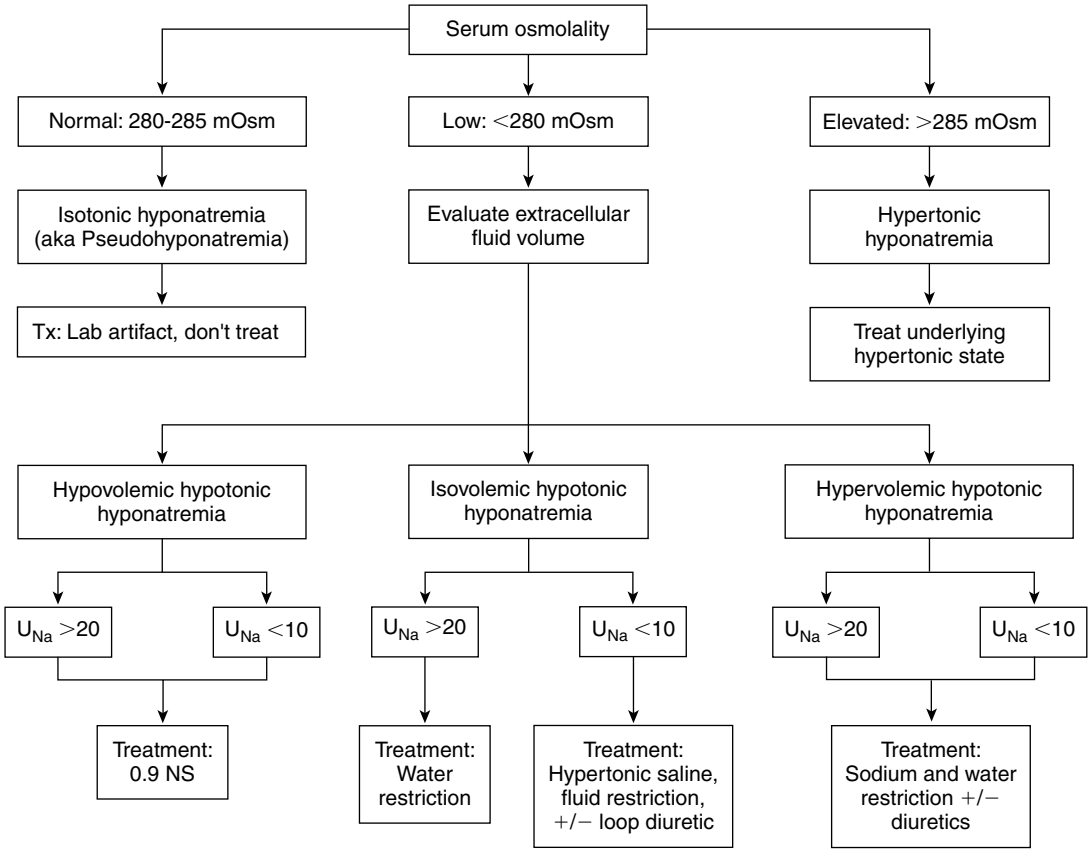

FIGURE **20-2** Treatment of hyponatremia. *Tx*, Treatment; U_{Na}, urinary sodium; *NS*, normal saline. (Modified from Ferri FF. *Practical Guide to the Care of the Medical Patient*. 8th ed. Philadelphia: Mosby; 2011.)

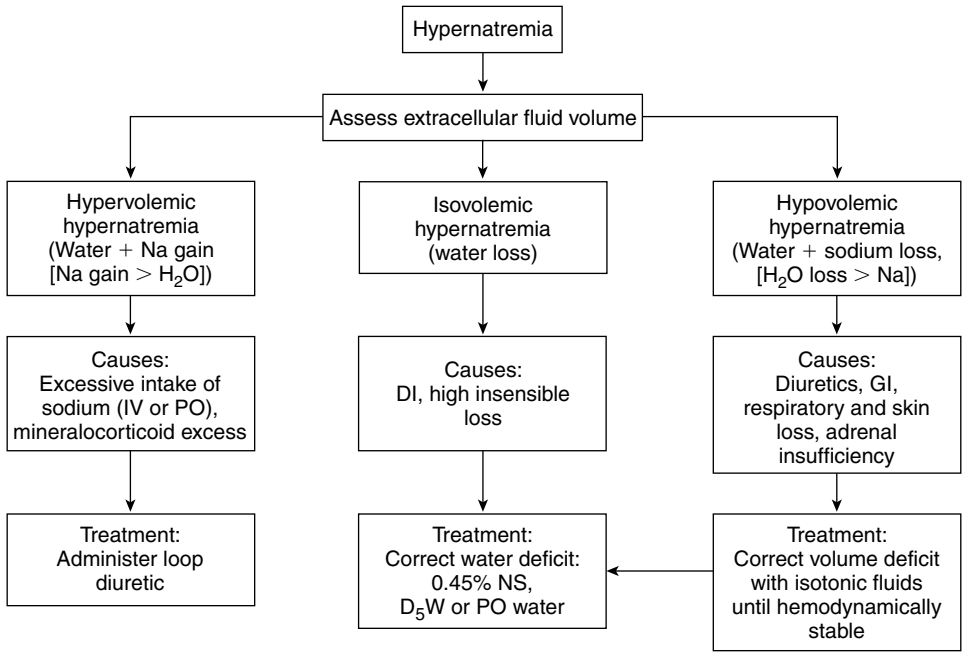

FIGURE **20-3** Hypernatremia (serum sodium [Na] greater than 145 mEq/L). *PO*, Oral; *NS*, normal saline; *DI*, diabetes insipidus. (Modified from Ferri FF. *Practical Guide to the Care of the Medical Patient*. 8th ed. Philadelphia: Mosby; 2011.)

BOX 20-2

Clinical Manifestations of Hypernatremia*

Neurologic Manifestations
- Thirst
- Weakness
- Seizure
- Coma
- Intracranial bleeding
- Disorientation
- Hallucinations
- Irritability
- Muscle twitching
- Cerebral edema

Cardiovascular Manifestations
- Hypovolemia

Renal Manifestations
- Polyuria or oliguria
- Renal insufficiency

**Serum sodium greater than 145 mEq/L.*

BOX 20-3

Sodium Equations for Clinical Use

Sodium Deficit
Sodium deficit (mEq) = ([Na] goal – [Na] plasma) × TBW
TBW = total body water = body weight × 60%

Free Water Deficit
Free water deficit = ([Na]/140) –1) × TBW

Corrected Sodium
Corrected sodium = ([Na] + 0.016) × (glucose – 100)

Serum Osmolality (Calculated)
(2 × [Na]) + (BUN/2.8) + (glucose/18)

Fractional Excretion of Sodium (Fr_{exc} Na)
Fr_{exc} Na = ([Na] urine) + (creatinine plasma/[Na] plasma) + (creatinine urine)
Less than 1% = prerenal (hypovolemia)
Greater than 2% = intrinsic renal disorder

From Rhee P. Shock fluids and electrolytes. In: Townsend CM, et al, eds. *Sabiston Textbook of Surgery*. 19th ed. Philadelphia: Saunders; 2012:109.
BUN, Blood urea nitrogen.

TABLE 20-4 Clinical Signs of Hypernatremia at Increasing Serum Osmolality

Osmolality (mOsm/kg)	Neurologic Symptoms
350-375	Confusion, restlessness, agitation, headache
375-400	Ataxia, tremors, weakness
400-430	Cramps, hyperreflexia, twitches, spasms
> 430	Coma, seizures, death

water deficits can be replaced relatively rapidly with hypotonic solutions. If chronic hypernatremia accompanied by volume depletion is present, the volume disorder is corrected first with isotonic crystalloids. Once the circulating volume has been restored, hypotonic solutions are used to correct the water deficit. Correction of chronic hypernatremia, like treatment of chronic hyponatremia, calls for prudence. Plasma sodium should be decreased by 1 to 2 mEq/hr until the patient is clinically stable, and correction of serum sodium to normal levels should gradually progress over the subsequent 24 hours.[12]

DISORDERS OF POTASSIUM BALANCE

Potassium is the principal electrolyte of the ICF, where 98% of the body's supply of potassium is located. The difference between intracellular and extracellular potassium concentration is in large part responsible for the resting membrane potential of the cell.[18] Potassium exists in a dynamic balance between the intracellular and extracellular compartments. Abnormal serum potassium levels may be the result of disturbances in the balance between intracellular and extracellular distribution of potassium or an abnormality in the total body store of potassium. Evaluation and treatment of disorders of potassium homeostasis should address factors that can shift potassium into the cell and total body levels of potassium. The symptoms associated with disorders of potassium homeostasis are largely a reflection of disorders of resting membrane potential.

Hypokalemia, defined as plasma potassium of less than 3.5 mEq/L, can result from an absolute deficiency caused by GI loss, renal loss, or from a poor intake of potassium (Box 20-4). Redistribution of potassium from the extracellular to the intracellular compartment can also lead to hypokalemia. β-Adrenergic stimulation, insulin, and alkalosis all promote movement of potassium into the intracellular space.[19]

Treatment of hypokalemia depends on the severity of the symptoms accompanying the potassium deficit. In the face of malignant dysrhythmias, aggressive IV administration of potassium is warranted.[18] IV replacement of potassium should be accomplished with the patient under continuous electrocardiographic (ECG) monitoring. Rates of IV administration as fast as 40 mEq/hr have been reported,[19] although a maximum rate of 10 to 20 mEq/hr is usually recommended to avoid an iatrogenic hyperkalemia.[4,7]

Once serious symptoms of hypokalemia such as respiratory muscle weakness or dysrhythmias have ceased, IV replacement can be discontinued in favor of oral supplementation.[19] It is recommended that IV potassium be replaced as a chloride, because the hypochloride state makes it difficult for the kidney to conserve potassium.[4] Furthermore, potassium chloride should be mixed in a dextrose-free solution to prevent stimulation of insulin, leading to increased redistribution of potassium to the intracellular space.[7,20]

Some clinicians have questioned whether surgery should be canceled because of low serum potassium. In a study of 447 patients scheduled for cardiovascular surgery, Hirsch and co-workers used continuous ECG monitoring to evaluate the preoperative and intraoperative incidence of ectopy. They found no significant difference in frequent or complex ventricular ectopy among patients with normal serum potassium and those with mild to severe hypokalemia. The authors concluded that cancellation of surgery based on low serum potassium was not warranted.[21]

Hyperkalemia is less common than hypokalemia if renal causes are excluded.[19] In addition to impaired renal excretion of potassium, causes of hyperkalemia include a high intake of potassium and a shift of potassium from the intracellular to the extracellular space. Movement of potassium from the intracellular to the extracellular compartment can result from lysis of cells, as well as from acidemia and the administration of β-adrenergic blockers, which inhibit the Na-K–ATPase pump and disrupt movement of potassium into the cell (Box 20-5). Electrocardiographic changes associated with increased levels of potassium are outlined in Table 20-5.

BOX **20-4**

Causes of Hypokalemia*

Decreased Intake
- Decreased dietary potassium
- Impaired absorption of potassium
- Clay ingestion
- Kayexalate

Increased Loss
Renal
- Hyperaldosteronism
  - Primary: Conn syndrome; adrenal hyperplasia
  - Secondary: Congestive heart failure; cirrhosis; nephrotic syndrome; dehydration
  - Bartter syndrome
- Glycyrrhizic acid (licorice, chewing tobacco)
- Excessive adrenocorticosteroids
  - Cushing syndrome
  - Steroid therapy
  - Adrenogenital syndrome
- Renal tubular defects
  - Renal tubular acidosis
  - Obstructive uropathy
  - Salt-wasting nephropathy
- Drugs
  - Diuretics
  - Aminoglycosides
  - Mannitol
  - Amphotericin B
  - Cisplatin
  - Carbenicillin

Gastrointestinal
- Vomiting
- Nasogastric suction
- Diarrhea
- Malabsorption
- Ileostomy
- Villous adenoma
- Laxative abuse

Increased Losses from Skin
- Excessive sweating
- Burns

Transcellular Shifts
Alkalosis
- Vomiting
- Diuretics
- Hyperventilation
- Bicarbonate therapy

Insulin
- Exogenous
- Endogenous response to glucose

Beta$_2$-agonists (albuterol, terbutaline, epinephrine)
Hypokalemic Periodic Paralysis
- Familial
- Thyrotoxic

Miscellaneous
- Anabolic state
- Intravenous hyperalimentation
- Treatment of megaloblastic anemia
- Acute mountain sickness

From Marx JA, et al. *Rosen's Emergency Medicine: Concepts and Clinical Practice*. 7th ed. Philadelphia: Mosby; 2010:1619.
*Serum potassium less than 3.5 mEq/L.

Treatment of hyperkalemia should be preceded by exclusion of pseudohyperkalemia, which is a laboratory artifact. Pseudohyperkalemia results from hemolysis of the blood sample, leukocytosis, thrombosis, or prolonged fist clenching during blood drawing. Treatment of hyperkalemia is based on the severity of the patient's presenting signs and symptoms (Table 20-6).

DISORDERS OF CALCIUM BALANCE

Calcium is a divalent cation, 99% of which is found in bones. Calcium has an important structural function, but perhaps most important to anesthetists is its role as a second messenger that couples cell membrane receptors to cellular responses. The action of calcium as a second messenger is critical to functions such as muscle contractions and release of hormones and neurotransmitters.[2,22] In addition to the second messenger function, calcium plays an important role in coagulation of blood and in muscle function.

Although most of the body's calcium is found in the bones, a small percentage is freely exchangeable with the ECF. Calcium in the ECF is found in three distinct fractions. Ionized calcium accounts for 50% of the calcium in the ECF and is the physiologically active portion of circulating calcium.[1] The remainder of the circulating calcium is bound either to anions (10%) or plasma proteins, primarily albumin (40%).[23] Changes in pH alter the extracellular distribution of calcium, with acidemia decreasing the protein-bound fraction and increasing the ionized fraction.[4]

Because the ionized fraction of calcium is the most clinically significant form, and total serum calcium levels are largely dependent on albumin levels, direct measurement of ionized calcium is the preferred method in critically ill patients.[3] Mathematical formulas to "correct" total calcium measurement for albumin concentration are available but have been characterized as inaccurate.[4,23]

Hypocalcemia has numerous causes (Box 20-6). In the intraoperative period, the most likely causes of hypocalcemia are hyperventilation and massive transfusion of citrated blood. Hyperventilation leads to an increased pH and an increased protein-bound fraction of calcium. Massive transfusion of citrated blood is discussed later in this chapter.

Treatment of acute hypocalcemia involves the infusion of calcium salts. Calcium chloride is the most bioavailable parenteral preparation of calcium and results in the most rapid correction of hypocalcemia; however, it is more irritating to the vein than calcium gluconate.[23] One technique for treatment of hypocalcemia calls for administration of 10 mL of 10% calcium gluconate (93 mg of elemental calcium) over 10 minutes, followed by an infusion of 0.3 to 2 mg/kg/hr of elemental calcium.[4]

Hypercalcemia typically results from a situation in which the movement of calcium from the bone to the ECF exceeds the ability

BOX **20-5**

Causes of Hyperkalemia*

Pseudohyperkalemia
- Hemolysis of sample
- Thrombocytosis
- Leukocytosis
- Laboratory error

Increased Potassium Intake and Absorption
- Potassium supplements (oral and parenteral)
- Dietary (salt substitutes)
- Stored blood
- Potassium-containing medications

Impaired Renal Excretion
- Acute renal failure
- Chronic renal failure
- Tubular defect in potassium secretion
  - Renal allograft
  - Analgesic nephropathy
  - Obstructive uropathy
  - Interstitial nephritis
  - Chronic pyelonephritis
  - Potassium-sparing diuretics
  - Miscellaneous (e.g., lead, systemic lupus erythematosus, pseudohypoaldosteronism)
- Hypoaldosteronism
  - Primary (Addison's disease)
  - Secondary
    - Hyporeninemic hypoaldosteronism (renal tubular acidosis type 4)
    - Congenital adrenal hyperplasia
    - Drug-induced (e.g., nonsteroidal antiinflammatory drugs; angiotensin-converting enzyme; heparin; cyclosporine)

Transcellular Shifts
- Acidosis
- Hypertonicity
- Insulin deficiency
- Drugs
  - Beta-blockers
  - Digitalis toxicity
  - Succinylcholine
- Exercise
- Hyperkalemic periodic paralysis

Cellular Injury
- Rhabdomyolysis
- Severe intravascular hemolysis
- Acute tumor lysis syndrome
- Burns and crush injuries

From Marx JA, Hockberger R, Walls R. *Rosen's Emergency Medicine: Concepts and Clinical Practice*. 7th ed. Philadelphia: Mosby; 2010:1621.
*Serum potassium greater than 5.0 mEq/L.

TABLE **20-5** ECG Changes with Hyperkalemia

Potassium mEq/L	ECG Change
6.0-7.5	Prolonged PR interval, peaked tall T waves, shortened QT interval
7.5-8	P wave flat, wide QRS, nodal and escape ventricular arrhythmias
>8.5	QRS complex degrades to sine wave pattern, ventricular fibrillation and cardiac arrest

ECG, Electrocardiogram.

of the kidney to excrete calcium (Box 20-7). Primary hyperparathyroidism accounts for more than half of all cases of hypercalcemia, with malignancy being the second most common cause.[23] Treatment of hypercalcemia involves volume expansion with normal saline (NS) (severely hypercalcemic patients are typically hypovolemic), which in and of itself increases renal excretion of calcium. The addition of a loop diuretic further enhances the renal excretion of calcium. Bisphosphonates, mithramycin, calcitonin, glucocorticoids, and phosphate salts also have been used in the treatment of hypercalcemia.[3]

DISORDERS OF MAGNESIUM BALANCE

Magnesium is the second most abundant intracellular cation, second only to potassium. The physiologic importance of magnesium lies in its role as a cofactor in more than 300 enzymatic reactions, including those involving energy metabolism and the function of the Na-K–ATPase pump.[22]

Hypomagnesemia is common in hospitalized patients, especially critically ill patients.[1,7] Magnesium deficiency is usually the result of increased renal or GI loss or poor intake of the electrolyte[3] (Box 20-8). Thirty percent of alcoholics admitted to the hospital are hypomagnesemic because of poor dietary intake.[7] Severe hypomagnesemia can be treated with administration of 1 to 2 g of magnesium sulfate over 5 minutes while the ECG is monitored, followed by administration of 1 to 2 g/hr of magnesium sulfate.[3]

Hypermagnesemia is most commonly the result of iatrogenesis (Box 20-9). Hypermagnesemia can result from the treatment of preeclampsia, preterm labor, ischemic heart disease, and cardiac dysrhythmias.[24] The symptoms of hypermagnesemia tend to reflect depression of the peripheral and central nervous systems and are dose related. Because magnesium potentiates the action of nondepolarizing neuromuscular relaxants, their use should be carefully monitored in patients with hypermagnesemia.[1] Treatment of hypermagnesemia involves discontinuing the administration of magnesium; in urgent situations such as bradycardia, heart block, and respiratory depression, calcium should be used as an antagonist.[7,25]

PARENTERAL FLUIDS

Intravenous fluids are the primary means to address a patient's need for fluid and electrolytes. Parenteral fluid therapy serves three principal purposes: provision of maintenance fluids, replacement of fluids lost as a result of surgery and anesthesia, and correction of electrolyte disturbances.[3] In anesthesia practice, IV fluids fall into two main categories: crystalloids (Table 20-7) and colloids.

Crystalloid solutions, which consist of fluids and electrolytes, are the most commonly used fluids in the surgical setting. Balanced salt solutions are crystalloids formulated to consist of an electrolyte concentration similar to ECF.[1] Two balanced salt solutions commonly administered to patients undergoing surgery include

TABLE 20-6 Guidelines for Treatment of Hyperkalemia

Clinical Feature	Therapy	Onset	Duration	Mechanism of Action
Electrocardiographic Evidence of Pending Arrest				
Loss of P wave and widening QRS; immediate effective therapy indicated	1. IV infusion of calcium salts*: 10 mL of 10% calcium chloride over 10-minute period *or* 10 mL of 10% calcium gluconate over 3-5 minutes	1-3 min 1-3 min	30-60 min 30-60 min	Membrane stabilization Membrane stabilization
	2. IV infusion of sodium bicarbonate: 50-100 mEq over 10- to 20-minute period	5-10 min	1-2 hr	Shifts potassium intracellularly
Electrocardiographic Evidence of Potassium Effect				
Peaked T waves; prompt therapy needed	1. Glucose and insulin infusion: IV infusion of 50 mL of $D_{50}W$ and 10 units of regular insulin; monitor glucose 2. Immediate hemodialysis	30 min	4-6 hr	Shifts potassium intracellularly
Biochemical Evidence of Hyperkalemia and No Electrocardographic Changes				
Effective therapy needed within hours	1. Potassium-binding resins in the gastrointestinal (GI) tract	1-2 hr	4-6 hr	GI excretion
	2. Promotion of renal potassium excretion: diuretic—Furosemide 40 mg IV	15-30 min	2-3 hr	Renal excretion

*Calcium chloride yields three times the ionized calcium as calcium gluconate; calcium chloride = 27 mg/mL; calcium gluconate = 9 mg/mL.
$D_{50}W$, 50% dextrose in water.

BOX 20-6

Causes and Clinical Features of Hypocalcemia*

Causes

Parathyroid Hormone Insufficiency

Primary hypoparathyroidism
- Congenital syndromes
- Maternal hyperparathyroidism

Secondary hypoparathyroidism
- Neck surgery
- Metastatic carcinoma
- Infiltrative disorders
- Hypomagnesemia, hypermagnesemia
- Sepsis
- Pancreatitis
- Burns
- Drugs (chemotherapeutics, ethanol, cimetidine)

Vitamin D Insufficiency

Congenital rickets
Malnutrition
Malabsorption
Liver disease
Renal disease
- Acute and chronic renal failure
- Nephrotic syndrome

Hypomagnesemia
Sepsis
Anticonvulsants (phenytoin, primidone)

Parathyroid Hormone Resistance States (Pseudohypoparathyroidism)

Calcium Chelation

Hyperphosphatemia
Citrate
Free fatty acids
Alkalosis
Fluoride poisoning

Clinical Features

Neuromuscular

Paresthesias
Muscle weakness
Muscle spasm
Tetany
Chvostek's and Trousseau signs
Hyperreflexia
Seizures

Cardiovascular

Bradycardia
Hypotension
Cardiac arrest
Digitalis insensitivity
QT prolongation

Pulmonary

Bronchospasm
Laryngeal spasm

Psychiatric

Anxiety
Depression
Irritability
Confusion
Psychosis
Dementia

From Marx JA, Hockberger R, Wall R. *Rosen's Emergency Medicine: Concepts and Clinical Practice*. 7th ed. Philadelphia: Mosby; 2010:1623-1624.
*Serum calcium less than 8.9 mg/dL; ionized calcium less than 4.6 mg/dL.

BOX **20-7**

Causes and Clinical Features of Hypercalcemia*

Causes

Primary Hyperparathyroidism

Malignant Disease
- Parathyroid hormone–related protein
- Ectopic production of 1,25-dihydroxyvitamin D
- Other bone-resorbing substances
- Osteolytic bone metastasis

Medications
- Thiazide diuretics
- Lithium
- Estrogens
- Vitamin D toxicity
- Vitamin A toxicity
- Calcium ingestion

Granulomatous Disorders
- Sarcoidosis
- Tuberculosis
- Coccidioidomycosis
- Berylliosis
- Histoplasmosis
- Leprosy

Nonparathyroid Endocrine Disorders
- Hyperthyroidism
- Adrenal insufficiency
- Pheochromocytoma
- Acromegaly
- Vasoactive intestinal polypeptide–producing tumor

Miscellaneous
- Milk-alkali syndrome
- Immobilization
- Idiopathic hypocalcemia of infancy
- Physiologic (in the newborn)

Clinical Features

Neurologic
- Fatigue, weakness
- Confusion, lethargy
- Ataxia
- Coma
- Hypotonia, diminished deep tendon reflexes

Cardiovascular
- Hypertension
- Sinus bradycardia, atrioventricular block
- ECG abnormalities (short QT, bundle branch block)
- Ventricular dysrhythmias
- Potentiation of digoxin toxicity

Renal
- Polyuria, polydipsia
- Dehydration
- Loss of electrolyte
- Prerenal azotemia
- Nephrolithiasis
- Nephrocalcinosis

Gastrointestinal
- Nausea, vomiting
- Anorexia
- Peptic ulcer disease
- Pancreatitis
- Constipation, ileus

From Marx JA, Hockberger R, Walls R. *Rosen's Emergency Medicine: Concepts and Clinical Practice*. 7th ed. Philadelphia: Mosby; 2010:1624-1625.
*Serum calcium greater than 10.5 mg/dL; ionized calcium greater than 5.6 mg/dL.
ECG, Electrocardiogram.

BOX **20-8**

Causes of Hypomagnesemia*

Alcohol abuse
Diuretic use
Renal losses
- Acute and chronic renal failure
- Postobstructive diuresis
- Acute tubular necrosis
- Chronic glomerulonephritis
- Chronic pyelonephritis
- Interstitial nephropathy
- Renal transplantation

Gastrointestinal losses
- Chronic diarrhea
- Nasogastric suctioning
- Short-bowel syndrome
- Protein-calorie malnutrition
- Bowel fistula
- Total parenteral nutrition
- Acute pancreatitis

Endocrine disorders
- Diabetes mellitus
- Hyperaldosteronism
- Hyperthyroidism
- Hyperparathyroidism
- Acute intermittent porphyria

Pregnancy
Drugs
- Aminoglycosides
- Amphotericin
- Beta-agonists
- Cisplatin
- Cyclosporine
- Diuretics
- Foscarnet
- Pentamidine
- Theophylline

Congenital disorders
- Familial hypomagnesemia
- Maternal diabetes
- Maternal hypothyroidism
- Maternal hyperparathyroidism

From Marx JA, Hockberger R, Walls R. *Rosen's Emergency Medicine: Concepts and Clinical Practice*. 7th ed. Philadelphia: Mosby; 2010:1627.
*Serum magnesium less than 1.7 mg/dL.

NS (also known as *0.9% normal saline* or *0.9% NS*) and lactated Ringer's (LR) solution.

Isotonic solutions such as NS and LR are commonly used to correct the hypovolemia resulting from surgery and anesthesia because the bulk of fluid lost is isotonic. Excessive volumes of NS have been associated with hyperchloremic metabolic acidosis.[26] A study by Scheingraber et al.[27] revealed that a significant acidosis was noted when NS but not LR was administered at a rate of 35 mL/kg/hr over a 2-hour period during the perioperative period. Although large-volume administration of LR may not result in acidosis, metabolic alkalosis may result when lactate is metabolized into bicarbonate by the liver[6]; furthermore, the potassium in LR can accumulate in patients with renal failure.

Hypertonic saline solutions (3% or 5% NaCl), or saline solutions containing Na concentrations exceeding 154 mEq/L, have been used as low-volume solutions for fluid resuscitation. Because of its hyperosmolar characteristics, hypertonic saline draws water from the interstitium into the vascular space. However, hypertonic saline carries with it a risk of unwanted hyperchloremia, hypernatremia, and cellular dehydration, as well as a limited intravascular duration. In the past, the principal role for hypertonic saline was the treatment of hyponatremia.[1] Current research suggests that isotonic saline solutions are preferred when treating hemorrhagic shock, in patients with traumatic brain injury (TBI).[28] Isotonic crystalloid solutions are the first choice for volume resuscitation of trauma patients with head injuries. Normal saline is a good choice because it is inexpensive, can be given with packed red blood cells, and is mildly hyperosmolar in comparison with normal plasma. A disadvantage is the development of hyperchloremic acidosis in large-volume resuscitation settings. Some trauma centers use other balanced salt solutions. Fluids to be avoided include hypotonic solutions such as 0.45% saline and any solution containing dextrose.[29]

Dextrose is often added to crystalloid parenteral solutions for a variety of reasons. Dextrose 5% in water (D_5W) is mildly hypotonic and is often used to provide free water that is available to the body once the dextrose has been metabolized. Dextrose also can be used as a metabolic substrate but is not usually administered intraoperatively because of the risk of hyperglycemia. Intraoperative dextrose administration is warranted in patients such as neonates, who have limited glycogen stores,[30] and diabetic patients who have received insulin and are at risk of hypoglycemia and protein catabolism.[1]

Colloids are solutions containing osmotically active substances of high molecular weight that do not easily cross the capillary membrane and therefore draw fluid into the intravascular space and expand circulating volume.[3] Colloids can be manufactured from human blood or synthesized from nonanimal substances.

Normal human serum albumin is manufactured from pooled donor plasma and is available in 5% and 25% (commonly called *salt-poor albumin*) solutions. Albumin 5% replaces plasma loss in a 1:1 ratio and remains in the vascular space for a prolonged time because of the presence of high-molecular-weight protein molecules. Albumin 25% can expand intravascular volume up to five times the volume infused, owing to its high osmotic pressure. Albumin 25% is well suited for use in patients with excessive ECF who need intravascular expansion.[1] Colloids formulated from human blood have at least a theoretical risk of disease transmission via pathogens such as prions,[31] and availability can be limited by donor supply.[32]

Synthetic colloids include dextran, gelatins, and hetastarch. Gelatins are generally not available for use in North America.[32] Dextrans are polysaccharides that are useful for volume expansion but are also associated with anticoagulation, which limits their application to settings such as vascular surgery, in which

BOX 20-9

Hypermagnesemia*

Causative Factors
- Renal failure
- Excessive magnesium administration
- Adrenal insufficiency

Clinical Manifestations
Serum Magnesium Levels
3-5 = Flushing, nausea, and vomiting
4-7 = Drowsiness, decreased deep tendon reflexes, weakness
5-10 = Hypotension, bradycardia
7-10 = Loss of patellar reflex
10 = Respiratory depression
10-15 = Respiratory paralysis, coma
15-20 = Cardiac arrest

Adapted from Ferri FF. *Practical Guide to the Care of the Medical Patient*. 8th ed. Philadelphia: Mosby; 2011:365-369.
*Serum magnesium greater than 2.5 mg/dL.

TABLE 20-7 Composition of Replacement Fluids

Fluid	Na^+ (mEq/L)	K^+ (mEq/L) (g/L)	Glucose (g/L)	Osm	pH	Other
5% Albumin	145 ± 15	<2.5	0	330	7.4	COP = 32-35 mmHg
Plasmanate	145 ± 15	<2.0	0	0	7.4	COP = 20 mmHg
10% Dextran 40	0	0	0	255	4.0	
HES 450/0.7	154	0	0	310	5.9	
0.9% NaCl	154	0	0	308	6.0	
Lactated Ringer's	130	4	0	273	6.5	Lactate = 28 mEq/L
5% Dextrose	0	0	50	252	4.5	
D_5LR	130	4	50	525	5.0	
$D_5$0.45% NaCl	77	0	50	406	4.0	
Normosol-R	140	5	0	294	6.6	Mg = 3, acetate = 27, gluconate = 23 mEq/L

From Kaye AD. Fluid management. In: Miller RD, Pardo MC, eds. *Basics of Anesthesia*. 6th ed. Philadelphia: Saunders; 2011:366.
COP, Colloid oncotic pressure; *D_5LR*, 5% dextrose in lactated Ringer's solution; *$D_5$0.45% NaCl*, 5% dextrose in 0.45% NaCl; *HES*, hydroxyethyl starch; *Osm*, osmolarity.

prevention of thrombosis is desired. Dextran is also associated with risk of anaphylaxis.[3]

Hetastarch is a synthetic colloid made from plant starch. It has fluid expansion properties similar to those of albumin[3] but is far less expensive than albumin. Use of hetastarch 6% in saline has been limited by its effect on coagulation. It can produce a dilutional dysfunction of coagulation like other colloids and crystalloids. Hetastarch also directly inhibits clot formation by movement into fibrin clots.[1] Because of the effect of this colloid on coagulation, it is generally not administered in volumes exceeding 20 mL/kg. Another formulation of hetastarch, Hextend, is a solution containing 6% hetastarch with balanced electrolytes, a lactate buffer, and physiologic glucose. A study by Gan et al.[32] evaluated hetastarch in saline versus the hetastarch in the buffered solution and found that patients with the newer formulation could receive the colloid in volumes exceeding 20 mL/kg without coagulopathy. Hydroxyethyl starch (HES) 130/0.4 (Voluven) is a new colloid solution indicated for the treatment and prophylaxis of hypovolemia. Because the Voluven molecule is smaller than those of other available hydroxyethyl starch products, it is associated with less plasma accumulation and may be safer for use in patients with renal impairment. Previous studies have demonstrated that Voluven has comparable effects on volume expansion and hemodynamics as other available HES products. Voluven is also associated with fewer effects on coagulation and may be an acceptable alternative to albumin for volume expansion in situations in which other starches are contraindicated secondary to risk of coagulopathy.[33] Several studies have been reported that questioned the use of Voluven for fluid resuscitation. They note that there is no convincing evidence that third-generation HES 130/0.4 is safe in surgical, emergency, or intensive care patients despite publication of numerous clinical studies.[34,35]

The amount of fluid replacement is an important clinical question. Traditional infusion concepts, also known as liberal, often aimed at keeping the patient "wet"; however, other studies indicate that a more restrictive infusion regimen of "dry" may be preferable. The terms *restrictive*, *conservative*, *standard*, or *liberal* have no clear definitions, and sometimes imply the same, sometimes contradictory approaches.[36] Current evidence suggests that the patient should be treated according to the principles of goal-directed therapies that compensate for individual needs. The primary objective of perioperative infusion therapy is maintenance of normovolemia. To achieve this target, it is crucial to discriminate between fluid substitution such as replacement of sensible and insensible fluid losses and volume therapy to replace intravascular volume losses, until individual transfusion triggers are met.[37]

In the past, patients undergoing major surgery were often administered large volumes of crystalloid, based on a preoperative dehydration from long fasting intervals and theoretical "third space" fluid loss. However, positive perioperative fluid balance, with postoperative fluid-based weight gain, is associated with increased major morbidity. The concept of "third space" fluid loss has been refuted, and preoperative dehydration has been minimized by reduced fasting times and the allowance of oral fluids up to 2 h before the operation. A "restrictive" intraoperative fluid regimen, avoiding hypovolemia but limiting infusion to the minimum necessary may improve outcomes after major surgery.[38]

Goal-directed therapy is based on the assumption that maximizing cardiac flow parameters as a surrogate for oxygen delivery improves outcome. The use of minimally invasive esophageal Doppler technology may assist in further individualizing fluid guidance from goal-directed fluid therapy. This technology may become routine practice in the years to come. Esophageal Doppler monitoring uses Doppler ultrasound technology to asses the blood flow in the descending aorta. A disposable probe is inserted into the esophagus and aligned with the blood flow to produce a flow velocity profile for each heartbeat. The stroke volume can be used to indicate volume responsiveness. Modern evidence-based practice suggests that intraoperative fluid therapy should be tailored to two broad clinical contexts: In healthy patients undergoing low-risk or ambulatory surgery, high-volume crystalloid infusions of the order of 20–30 ml/kg (e.g., 2 liters over 30 min to the average adult) improves ambulatory anesthesia outcomes such as pain, nausea, and dizziness, and increases street readiness. High-risk patients undergoing major surgery seem to benefit from a "restrictive" fluid regimen. This remains to be clearly defined, but in a patient with normal renal function the restrictive fluid amounts should maintain intraoperative urine output between 0.5 and 1.0 ml/kg/hour. Fluids given early in the case seem to improve outcome as compared to later administration.[37-39]

Estimation of intraoperative fluid requirements is an imperfect science and is based on an understanding of patient fluid needs as well as the dynamics of fluid compartments. Fluid therapy in surgical patients should include administration of fluids to compensate for preoperative fluid deficit, maintenance fluids to compensate for evaporative losses and provide solute for excretion of waste, and fluids to replace surgical fluid losses (e.g., third-space loss and blood loss).[30] Recently clinicians have questioned whether the classical third space exists. Instead they theorize that perioperative fluid shifting predominantly represents losses toward the interstitial space. Crystalloids should be suitable to replace extracellular losses through insensible perspiration and urinary output. Colloids are the therapy of choice to replace acute blood losses above the blood transfusion border. As far as possible, hypervolemia and hypovolemia should be avoided. If clinical signs of intravascular hypovolemia occur, despite sufficient replacement therapy of measured and estimated losses, two explanations are possible. Either blood loss has been underestimated or a pathologic protein-rich shift is accruing that is related to an alteration of the vascular barrier. In both cases, intravascular application of further isooncotic colloid, not of crystalloid, should be considered.[39]

Traditional hourly maintenance fluid requirements are estimated according to the 4-2-1-formula (Table 20-8). A shortcut for estimating hourly maintenance fluid requirements in patients who weigh more than 20 kg is to add weight in kilograms to 40 to arrive at an hourly infusion volume in milliliters. Fluid deficit is estimated by multiplying the hourly maintenance requirement by

TABLE 20-8 Maintenance Fluid Requirement Calculation

Weight	Rate
The first 10 kg	4 mL/kg/hr
The next 10-20 kg	Add 2 mL/kg/hr
For each kg above 20 kg	Add 1 mL/kg/hr
Sample calculation for a 45-kg patient: 10 kg × 4 mL/hr = 40 mL/kg 10 kg × 2 mL/hr = 20 mL/kg 25 kg × 1 ml/hr = 25 mL/kg	Total maintenance rate 85 mL/kg/hr
Sample calculation for a 75-kg patient: 10 kg × 4 mL/hr= 40 mL/kg 10 kg × 2 mL/hr = 20 mL/kg 55 kg × 1 mL/hr = 55 mL/kg	Total maintenance rate 115 mL/kg/hr

TABLE 20-9 Fluid Losses from Various Types of Surgical Cases

Invasiveness and Surgical Trauma	Additional Fluid Requirements
Minimal Short superficial procedure	0-2 mL/kg
Moderate Uncomplicated intraabdominal or orthopedic procedure	2-4 mL/kg
Severe Prolonged highly invasive procedure	4-8 mL/kg

the number of hours the patient has been without oral or parenteral fluids. Calculation of the fluid deficit also should account for fluids lost through preoperative events such as nasogastric suctioning and bowel preparation.

Surgical fluid loss consists of blood loss, evaporative loss resulting from an open wound, and possible third-space losses resulting from fluid redistribution. Estimation of third-space loss is based on the degree of tissue trauma expected during the surgical procedure (Table 20-9) and can be substantial (e.g., as in major abdominal surgery). Estimation of blood loss is discussed in the section on transfusion therapy; blood volume loss can be replaced by crystalloids in a 3:1 or 4:1 ratio of crystalloid to blood. The 3:1 or 4:1 ratio has come into question because of the understanding that as crystalloids are infused, plasma osmotic pressure decreases, which leads to an increased loss of fluid from the intravascular to the interstitial space. Traditional rules of thumb indicating the need for three to four times the amount of crystalloids for the plasma volume to be replaced are probably erroneous and might have contributed to association of overly aggressive crystalloid resuscitation with poor outcome. Significant progress has been made in the last few years with respect to the understanding of basic principles of volume resuscitation in the critically ill. Isotonic crystalloids are safe and effective for use and the amount of crystalloid required to restore circulating blood volume is substantially less than assumed in the past.[40] Replacement of blood with crystalloid or colloid solutions replaces volume only and does not replace lost oxygen-carrying capacity or coagulation factors.

The rate at which fluids are administered intraoperatively is determined after summation of fluid requirements for surgical loss, deficit, and maintenance. Typically, maintenance and replacement fluids are administered to meet the hourly needs of the patient, and the deficit is replaced within the first 3 hours after induction. In clinical practice, induction of anesthesia frequently requires a fluid bolus to maintain blood pressure and often results in an initial infusion of IV fluids that exceeds what might be suggested by calculations.

The subject of much discussion, selection of IV fluid for therapy is based in large part on the purpose of the fluid. Maintenance needs are ideally met by fluids such as 5% dextrose and ¼% NS (D_5-¼ NS), which provide free water to facilitate excretion of waste and replace evaporative loss.[30] IV therapy in the operating room is principally focused on replacement of fluids lost during surgery and uses balanced salt solutions such as NS or LR. Replacement needs can also be met by colloid solutions such as hetastarch.

The relative merits of LR versus NS as a replacement solution for trauma resuscitation were explored in an animal model by Healey et al.[41] They found that in cases of moderate hemorrhage, NS and LR were both acceptable solutions. However, in cases of massive hemorrhage, LR was found to be superior to NS because of an absence of hyperchloremic metabolic acidosis. The treatment of hypovolemia in patients with non-cerebral trauma should begin with Ringer's lactate solution. Normal saline (0.9% sodium chloride) is appropriate for patients with head injury, alkalosis, or hyponatremia, but in large volumes may lead to metabolic acidosis. Base deficit and lactate levels can be used to guide resuscitation.[42]

TABLE 20-10 Advantages and Disadvantages of Crystalloid and Colloid Solutions for Fluid Resuscitation

Crystalloid	Colloid
Advantages	
Inexpensive	Causes sustained increase in plasma volume
Promotes urinary flow	Requires smaller volume for resuscitation
Restores third-space loss	Causes less peripheral edema
Used for extracellular fluid replacement	Tends to remain intravascular after repletion
Used for initial resuscitation	Causes more rapid resuscitation
	Useful in conditions of altered vascular permeability
Disadvantages	
Dilutes plasma proteins	Expensive
Causes reduction of capillary osmotic pressure	Can cause coagulopathy (dextran > hetastarch > Hextend)
Causes peripheral edema	Can cause anaphylactic reaction (dextran)
Has transient effect	Decreases Ca^{2+} (albumin)
Has potential for pulmonary edema	Can cause renal failure (dextran)
Can cause osmotic diuresis	
Can cause impaired immune response (albumin)	

Whether crystalloids or colloids are superior as replacement fluids has been debated for decades. The relative merits and disadvantages of each fluid are well known (Table 20-10). Data to support the choice of either crystalloids or artificial and natural colloids in the critically ill are tipping the scales toward crystalloids for reasons of safety, side effects, and containment of costs.[40] The Saline versus Albumin Fluid Evaluation (SAFE) study, a multicenter, randomized, double-blind trial, compared the effect of fluid resuscitation with albumin or saline on mortality in a heterogeneous population of patients.[43] A subgroup analysis evaluated patients with traumatic brain injury (TBI).[44] Almost 7000 patients who had been admitted to the intensive care unit (ICU) were randomly assigned to receive either 4% albumin or normal saline for intravascular-fluid resuscitation. At 24 months, 33.2% in the albumin group compared to 20.4% of patients in the saline group had died. Patients with a history of TBI also showed an unfavorable effect of albumin. A recent Cochrane review noted that there is no evidence that resuscitation with colloids reduces the risk of death compared to resuscitation with crystalloids in patients with trauma, burns, or following surgery. Because colloids are not associated with an improvement in survival, and are more expensive than crystalloids, it is hard to see how their continued use in these patients can be justified.[45] Another recent review suggested that evidence from clinical studies shows that comparable resuscitation is achieved with

TABLE 20-11 Average Blood Volumes

Age	Blood Volume
Neonates	
Premature	90-100 mL/kg
Full-term	80-90 mL/kg
Infants	80 mL/kg
Adults	70 mL/kg

considerably less crystalloid volume than frequently suggested, namely, less than twofold the volume of colloids. The use of colloidal solutions for resuscitation of patients with acute hypovolemia is not supported by clinical evidence. Synthetic colloids are not superior in critically ill adults and children and may be harmful depending on the cumulative dose administered. Crystalloids are safe and equally effective as compared to colloids; therefore the use of synthetic colloids should be avoided.[46]

BLOOD COMPONENT THERAPY

For the purpose of volume replacement, perioperative blood loss can be replaced with crystalloids and/or colloids, but if hemorrhagic losses are significant, transfusion therapy involving the administration of blood or blood components may be necessary to increase oxygen-carrying capacity, increase intravascular volume, and restore hemostasis. Decisions regarding transfusion therapy must take into account several factors, including perioperative blood loss, the clinical condition of the patient, and access to the patient blood type.

Estimation of blood loss, patient-specific blood volume, and calculation of allowable blood loss for that patient are important factors to consider when making decisions about blood component therapy. Estimating blood volume (EBV) takes into account patient age and weight, and is summarized in Table 20-11.

Once blood volume has been estimated, a clinician can, by a simple calculation, determine the volume of blood loss that would decrease hematocrit to a target value. The formula for maximum allowable blood loss (MABL) is as follows:

$$\text{MABL} = \frac{\text{EBV} \times (\text{Starting hematocrit} - \text{Target hematocrit})}{\text{Starting hematocrit}}$$

Unfortunately, estimation of intraoperative blood loss is fraught with error because of a lack of practical objective measures. Rapid intraoperative measurement of hemoglobin and hematocrit has become widespread with the introduction of easy-to-use, point-of-care monitors.[47] They do not measure the amount of blood loss.[48] Measuring net suction volume (amount of fluid suctioned minus amount of irrigant) and counting or weighing sponges are common methods used to determine the volume of blood lost during surgery. A study by Orth et al.[49] examined the accuracy of conventional, subjective techniques for estimation of blood loss by comparing the results of conventional techniques to those derived from an objective technique (sodium fluorescein dye). The investigators found a significant difference between subjective and objective techniques; in general, blood loss was underestimated by an average of approximately 300 mL when subjective techniques were used.

In addition to estimating blood loss, patient response to intraoperative hemorrhage should be taken into consideration when making decisions regarding transfusion therapy. Tachycardia and decreased mixed venous oxygen saturation are suggestive of anemia, especially in the setting of intraoperative hemorrhage. A useful metric in decision making for transfusion therapy involves the measurement of systemic oxygen delivery (DO_2), which integrates cardiac index, oxyhemoglobin saturation, and hemoglobin concentration to produce a global measure of DO_2, rather than one isolated parameter such as hemoglobin. Survival in high-risk patients is associated with a DO_2 greater than or equal to 600 mL O_2/min/m^2.[10]

TABLE 20-12 Relationship Among Blood Groups, Antigens, Antibodies, and Blood Compatibility

Blood Group	Antigen on Red Blood Cell	Antibodies in Serum	Blood Group Compatibility
A	A	Anti-B	A, O
B	B	Anti-A	B, O
AB	A and B	—	AB, A, B, O
O	—	Anti-A and Anti-B	O only
Rh-positive	D	—	Rh-positive and Rh-negative
Rh-negative	—	Anti-D if sensitized	Rh-negative

A further prerequisite of blood component therapy is establishing blood compatibility. Because of the presence of antigens in red blood cell (RBC) membranes and circulating antibodies, a blood recipient can receive red cells only from a compatible donor (Table 20-12). Two blood groups deserve special attention. Individuals with group AB blood possess both A and B antigens on their RBCs and lack anti-A and anti-B antibodies; therefore such individuals can receive blood from any ABO group and are known as *universal recipients*. Individuals with type O blood are known as *universal donors* because their RBCs are devoid of any of the ABO antibodies.

The most important tests of blood compatibility are those used to determine ABO and Rh (also known as *type D*) blood groupings; transfusion of ABO- or Rh-incompatible blood can result in serious hemolysis. Patients at risk for needing a transfusion and the banked blood stored for transfusion are "typed" to determine ABO and Rh status. To further reduce the risk of a transfusion reaction, patients and banked blood are screened for clinically significant antibodies other than ABO and D. The ultimate test of blood compatibility is a type and crossmatch, during which donor blood and recipient blood are mixed together in what is essentially a trial transfusion. In contemporary clinical practice, patients are often prepared for surgery with only a type and screen, which predicts compatible transfusions 99.94% of the time. The addition of crossmatching increases the possibility of a compatible transfusion only one hundredth of 1%.[50]

In an emergency situation in which a patient's blood group is unknown, uncrossmatched type O, Rh-positive blood can be given to males or females of non-childbearing years who have never received a previous type O Rh-positive blood transfusion. Type O Rh-negative should be reserved for females of childbearing years, or when clinicians are unsure of the patient's previous blood transfusion history in order to avoid any hemolytic reaction. However, if two or more units of O-negative whole blood have been given, the patient may not be able to receive transfusions of his or her own type (A, B, or AB) because of the risk of hemolysis. It is preferred that type O Rh-negative uncrossmatched packed RBCs (PRBCs) should be used because packed erythrocytes have smaller plasma volumes and are almost free of hemolytic anti-A and anti-B antibodies. The patient may not be transfused with his or her respective blood type until the blood bank determines that the transfused anti-A and anti-B antibodies have decreased to levels that permit safe transfusion of type-specific blood.[50]

Currently in the United States, most donor blood is fractionated into its component parts (i.e., RBCs, plasma, platelets, and individual factor concentrates). Because of fractionation, blood component therapy can be targeted to a specific patient need (e.g., diminished oxygen-carrying capacity and/or hemostasis). Red blood cell transfusions are used to treat hemorrhage and to improve oxygen delivery to tissues. Indications for transfusion include symptomatic anemia in high-risk patients, acute blood loss of more than 30% of blood volume, or in hemodynamically unstable patients where blood loss continues. Fresh frozen plasma infusion can be used for reversal of anticoagulant effects. Platelet transfusion is indicated to prevent hemorrhage in patients with thrombocytopenia or platelet function defects. Cryoprecipitate is used in cases of hypofibrinogenemia, which most often occurs in the setting of massive hemorrhage or consumptive coagulopathy. Transfusion-related infections are less common than noninfectious complications. Acute complications occur within minutes to 24 hours of the transfusion, whereas delayed complications may develop days, months, or even years later.[51]

Storage of blood as components rather than as whole blood has distinct advantages[52]; however, banked blood does undergo undesirable changes during storage (Box 20-10). The deleterious effect of storage on RBCs in particular has been well known for some time and has been referred to as "the storage lesion." The clinical effects of the functional and morphologic changes observed in banked blood are not fully understood at present and continue to be the subject of intense investigation.[53] A recent observational study of almost 6000 cardiac surgery patients found an association between transfusion of blood stored longer than 14 days and increased postoperative morbidity and mortality when compared with patients receiving blood stored for less than 14 days.[54] Similar findings were noted in intensive care units.[55,56]

Deciding when to administer blood components is an important clinical judgment that should be based on sound evidence, not custom. In recent years, critical attention has been directed to transfusion practices because of concerns regarding the expense, availability, and risks of transfusions. In 1996 and 2006, the American Society of Anesthesiologists (ASA) convened task forces on blood component therapy to develop guidelines to help inform clinicians of the best practices in transfusion therapy.[57,58]

A single threshold for transfusion, a so-called *transfusion trigger*, has been the subject of much discussion and study. The literature, based largely on clinical experience with Jehovah Witnesses, records the survival of patients with hemoglobin values as low as 1.8 g/dL, although significant mortality is associated with hemoglobin values of less than 5 g/dL.[31] During anemic episodes, oxygen delivery to the tissues can be improved by increased cardiac output and improved microvascular blood flow resulting from the decreased viscosity of diluted blood.[59] The current consensus is that no single transfusion threshold exists and that decisions regarding RBC transfusions should be based on the specific clinical situation.

In practice, packed RBCs (PRBCs) are the component of choice for improving oxygen-carrying capacity. PRBC infusions are generally administered in a ratio of 1 mL for each 2 mL of blood loss (along with crystalloids or colloids for volume). The 1 to 2 ratio is due to the higher hematocrit of packed red blood. A commonly used rule of thumb states that each unit of PRBCs increases hemoglobin 1 g/dL and hematocrit 2% to 3%.[48]

The ASA Task Force concluded that transfusion is "usually unnecessary" in patients with hemoglobin greater than or equal to 10 g/dL and should "usually be administered" when hemoglobin is less than 6 g/dL.[58] Transfusing patients with a hemoglobin level of 6 to 10 g/dL is based on specific clinical factors. Factors that affect the selection of a transfusion threshold in individual patients include consideration of cardiopulmonary reserve, experienced and expected blood loss, O_2 consumption (reflected in indices such as arterial oxygen saturation and mixed venous oxygen saturation), and the presence or absence of atherosclerotic disease.[31,57,58]

BOX 20-10

Changes in Banked Blood

- Depletion of 2,3-diphosphoglycerate (DPG)
- Depletion of ATP (adenosine triphosphate)
- Oxidative damage
- Increased adhesion to human vascular endothelium
- Acidosis
- Altered morphology of red blood cells (change in shape, decreased flexibility, membrane loss)
- Accumulation of microaggregates
- Hyperkalemia (as high as 17.2 mEq/L)
- Absence of viable platelets (after 2 days of refrigerated storage)
- Absence of factors V and VIII
- Hemolysis
- Accumulation of proinflammatory metabolic and breakdown products such as lysophospholipids

From Corazza ML, Hranchook AM. Massive blood transfusion. *AANA J*. 2000;68(4):311-314; Tinmouth A, et al. ABLE Investigators Canadian Critical Care Trials Group: clinical consequences of red cell storage in the critically ill. *Transfusion*. 2006;46(11):2014-2027; Shander A, et al. Patient blood management in Europe. *Br J Anaesth*. 2012;109(1):55-68.

Outcomes in patients whose transfusions were guided by restrictive transfusion triggers have been studied. The Cochrane Injuries Group conducted a systematic review of 17 studies examining restrictive transfusion triggers and concluded that in patients without cardiovascular disease, renal failure, or hematologic disorders, withholding transfusions in those with hemoglobin as low as 7g/dL was a justifiable practice.[60]

The most common surgical procedures that require transfusion are orthopedic, especially hip and knee replacement, colorectal, cardiac, major vascular, liver transplant, and trauma. Because most of these procedures are elective, careful preoperative planning is possible. Patient Blood Management (PBM) has been adopted worldwide as a strategy to reduce unnecessary transfusions and maximize patient outcomes. PBM is a multidisciplinary, multimodality care strategy for timely use of safe, effective medical and surgical techniques designed to prevent anemia and decrease bleeding in an effort to improve outcomes.[61-63] Three strategies of PBM include optimizing the patient's own red blood cell mass, minimizing blood loss, and optimizing the patient's physiologic tolerance of anemia. Major goals for PBM are listed in Box 20-11. The Joint Commission has developed transfusion performance measures as accreditation goals (Table 20-13).[61]

The American Association of Blood Banks (AABB) has recently issued four recommendations for transfusions: (1) adhere to a restrictive transfusion strategy (7 to 8 g/dL) in hospitalized, stable patients; (2) adhere to a restrictive strategy in hospitalized patients with preexisting cardiovascular disease and consider transfusion for patients with symptoms or a hemoglobin level of 8 g/dL or less; (3) no recommendation for or against a liberal or restrictive transfusion threshold for hospitalized, hemodynamically stable patients with the acute coronary syndrome; and (4) transfusion decisions should be influenced by symptoms as well as hemoglobin concentration.[64] A common strategy for management of transfusions is given in Table 20-14. Restrictive triggers

BOX **20-11**

Patient Blood Management Strategies

Preoperative Suggestions

- Screen for and treat anemia. Manage any underlying disorders that may lead to anemia.
- Treat iron deficiency and administer erythropoiesis-stimulating agents as indicated.
- Identify and manage any bleeding risks such as medications or chronic diseases.
- Assess patient reserve and optimize patient-specific tolerable blood loss.
- Formulate management plan with evidence-based transfusion strategy.
- Preoperative autologous blood donation in select situations.
- May require preoperative visit up to 30 days prior to elective surgery to accommodate therapy.

Intraoperative Suggestions

- Perform elective surgery when hematologically optimized.
- Use meticulous blood-sparing surgical techniques.
- Continually measure and assess hemoglobin and hematocrit.
- Plan and optimize fluid management of nonblood products.
- Optimize cardiac output, oxygen delivery, and ventilation.
- Use blood salvage and autologous transfusion when possible.

Postoperative Suggestions

- Treat anemia with erythropoiesis-stimulating agents and iron deficiency as indicated.
- Vigilant monitoring and management of postoperative bleeding.
- Maintain normothermia to minimize oxygen consumption.
- Avoid and/or treat infections promptly.
- Carefully manage anticoagulant medications.

Adapted from Shander A, et al. Patient blood management in Europe. *Br J Anaesth*. 2012 Jul;109(1):55-68; Goodnough LT, Shander A. Patient blood management. *Anesthesiology*. 2012 Jun;116(6):1367-76; Shander A, Javidroozi M. Strategies to reduce the use of blood products: a US perspective. *Curr Opin Anaesthesiol*. 2012 Feb;25(1):50-8.

TABLE **20-13** Patient Blood Management

TJC* Performance Measures	Principles
Preoperative anemia screening	Formulate a plan of proactive management for avoiding and controlling blood loss tailored to the clinical management of individual patients, including anticipated procedures
Preoperative blood type and antibody screen (blood compatibility testing)	Employ a multidisciplinary treatment approach to blood management using a combination of interventions (e.g., pharmacologic therapy, point-of- care testing)
Transfusion consent	Promptly investigate and treat anemia
Blood administration	Exercising clinical judgment, be prepared to modify routine practices (e.g., transfusion triggers) when appropriate
RBC transfusion indication	Restrict blood drawing for unnecessary laboratory tests
Plasma transfusion indication	Decrease or avoid the perioperative use of anticoagulants and antiplatelet agents
Platelet transfusion indication	

From Goodnough LT, Shander A. Patient blood management. *Anesthesiology*. 2012;116(6):1367-1376.
*The Joint Commission.

may be harmful in patients with signs and symptoms of low blood volume or other risk factors such as in patients experiencing acute myocardial infarction or unstable angina. Most hospitals have developed general transfusion guidelines to assist decision making.

Massive transfusion of RBCs, variously defined as (1) replacement of estimated blood volume within 24 hours, (2) ≥ 10 units of RBCs over 24 hours, or (3) 50% of blood volume within 3 hours or less[65] presents special concerns to anesthetists. Replacement of lost blood volume by PRBCs, often accompanied by crystalloids and colloids, does not provide coagulation factors and can lead to a dilutional coagulopathy or dilutional thrombocytopenia. Banked blood is commonly anticoagulated by a solution containing sodium citrate, which binds calcium, thereby inhibiting coagulation. Very rapid infusion of blood can reduce the level of ionized calcium.[50] This phenomenon, sometimes referred to as *citrate intoxication*, presents as acute hypocalcemia. Fortunately, normothermic patients with normal kidney and liver function can metabolize the amount of citrate present in 20 units of banked blood per hour and are not likely to display citrate intoxication.[4]

Fresh-frozen plasma (FFP) contains all coagulation factors[66] and is administered to provide coagulation factors that may be inadequate because of dilution or dysfunctions of coagulation. Indications for administration of FFP include reversal of the effects of warfarin, correction of known coagulopathy, correction of microvascular bleeding in the presence of elevated prothrombin time (PT) or partial thromboplastin time (PTT) that is > 1.5 times normal, and correction of microvascular bleeding in patients suspected of dilutional coagulopathy. For the reversal of warfarin, FFP is usually administered in doses of 5 to 8 mL/kg; 10 to 20 mL/kg is the guideline for all other purposes and should increase coagulation levels 20-30%.[57,58,66] The majority of FFP is transfused for the management of acquired bleeding disorders. The PT and the international normalized ratio (INR) are the most common tests to detect these disorders. Studies have shown that the PT correlates poorly with clinical bleeding and that transfusion of plasma often achieves no measurable change in the INR and has no known clinical benefit. The use of FFP is being discouraged if the INR is less than 2.0 in the absence of active bleeding, and the use of vitamin K is encouraged if the patient is on warfarin.[67]

Platelets are essential for adequate hemostasis and may need to be transfused because of thrombocytopenia or abnormal function.[52] Platelets are available as platelet concentrates separated from one unit of whole blood or as apheresis platelets, which originate from a single donor and are the equivalent of approximately six platelet concentrates.[68] Transfusion of platelets is usually indicated when the count is less than $50 \times 10^3/\mu L$ but not more than $100 \times 10^3/\mu L$. Platelet transfusions in patients with platelet counts of $50 \times 10^3/\mu L$ to $100 \times 10^3/\mu L$ are indicated when the patient displays microvascular bleeding or if the patient is at risk for platelet dysfunction or continued bleeding. The usual dose of platelets is one platelet concentrate per 10 kg of body weight; transfusion raises the platelet count for 6 to 7 days.[52,57,58]

TABLE 20-14 Decision Criteria for Transfusion

Class of Hemorrhage	Reduction of Volume (%)	Blood Loss (mL)*	Hemoglobin	Indication for Transfusion of PRBC
Class I	<15%	<750	≥ 10 g/dL	Not necessary if no preexisting anemia
Class II	15-30%	750-1500	8-10 g/dL	Not necessary, unless preexisting anemia and/or cardiopulmonary disease
Class III	30-40%	1500-2000	6-8 g/dL	Probably necessary
Class IV	>40%	>2000	≤ 6 g/dL	Necessary

PRBC, Packed red blood cells.
From Liumbruno GM, et al. Recommendations for the transfusion management of patients in the peri-operative period. II. The intra-operative period. *Blood Transfus*. 2011;9(2):189-217.
*In an adult person weighing 70 kg and with a circulating blood volume of 5000 mL.

A less frequently used blood component, cryoprecipitate, contains factor VIII, von Willebrand factor, and fibrinogen.[52] Cryoprecipitate is recommended for treatment of patients with von Willebrand disease and in patients with probable or documented deficits in fibrinogen (e.g., fibrinogen less than 80 to 100 mg/dL).[57,58] Cryoprecipitate should be administered through a filter and as rapidly as possible. The rate of administration should be at least 200 mL/hr, and infusion should be completed within 6 hours of thawing.[50]

An adjuvant therapy that has been used in cases of massive transfusion is recombinant factor VIIa (rFVIIa). This therapy was approved in 1999 for the treatment of congenital or acquired hemophilia A or B, for inhibitors of coagulation, or for congenital factor VII deficiency. Currently, 90% of rFVIIa use is off-label, meaning that its usage is for treatment of conditions other than what was approved by the FDA. The exact mechanism of action is not fully understood; however, it is believed that rFVIIa induces coagulation by binding to platelets and exposed tissue factor at the site of injury, which initiates a thrombin burst. This thrombin-burst amplifies the activation of clotting factors and the generation of thrombin-enhancing hemostasis. According to two recent meta-analyses, there is limited evidence that demonstrates a mortality reduction when compared to the risk of thromboembolism with the use of rFVIIa.[68,69]

Benefits of transfusion include increased oxygen-carrying capacity and improved coagulation. Unfortunately, transfusion of blood and blood products is not without risk. Infectious and noninfectious complications are possible, and the risk of complications is increased by massive transfusion, as well as by transfusion of blood that has been stored for a prolonged period.

COMPLICATIONS OF BLOOD TRANSFUSION

Some of the most common serious complications of blood transfusion are due to incompatibility. In a survey of hematologists in the United Kingdom and Ireland (the Serious Hazards Of Transfusion [SHOT] initiative), reports of transfusion reactions have been assessed on an ongoing basis. The most recent report noted 300 serious transfusion reactions, 262 of which were "incorrect blood component transfused" incidents. (Incorrect transfusions in the SHOT study were typically the result of procedural errors that led to the misidentification of patients.[70,71]) The result of transfusion to an incompatible recipient is an immune reaction, with the risk of intravascular hemolysis because of an interaction between the circulating antibodies of the recipient and the RBCs of the donor. Approximately half of all deaths from acute hemolytic reactions are caused by ABO-incompatible transfusions resulting from procedural or administrative error. Volumes of donor blood as small as 10 mL may lead to hemolytic reactions that may result in death for 20% to 60% of patients.[50] The clinical picture is complicated by the fact that general anesthesia may obscure the symptoms associated with a hemolytic reaction.[57]

Other life-threatening complications seen in the context of transfusion include transfusion-associated graft-versus-host disease and transfusion-related acute lung injury (TRALI). Transfusion-associated graft-versus-host disease results when donor lymphocytes incorporate themselves into the tissues of the recipient, leading the recipient's immune system to attack the embedded recipient tissues. Rash, leukopenia, and thrombocytopenia occur, with sepsis and death usually ensuing.[50]

Since 2003, TRALI has been recognized by the U.S. Food and Drug Administration (FDA) as the leading cause of transfusion-related death in the United States and is believed to occur as frequently as once in every 432 units of platelets or as infrequently as one in every 7900 units of FFP.[72,73] It is likely that TRALI is underreported because the syndrome may be confused with other forms of acute lung injury (ALI) and was without a clear definition until 2005. TRALI has been defined as ALI occurring within 6 hours of transfusion in individuals who were previously free of ALI and without other risk factors for ALI.[72]

The etiology of TRALI has not been fully explained, but two theories have been proposed to describe the syndrome. One explanation proposes that antibodies in donor plasma activate recipient neutrophils, leading to pulmonary capillary leakage. An alternative explanation puts forward a two-event model in which a physiologic stressor such as sepsis leads to sequestration of neutrophils in the lungs, then the transfusion of biologically active mediators (the second event) leads to activation of the neutrophils and capillary leakage. Treatment of TRALI is supportive and should include notifying the blood bank that a transfusion reaction suspected to be TRALI has occurred.[72-74]

Several undesirable effects of transfusions have been linked to the presence of leukocytes in allogenic blood. Homologous transfusions, which invariably contain some leukocytes, have been implicated in immunosuppression of recipients, leading to unexpectedly early recurrences of cancer and higher than expected rates of postoperative infection—a condition known as *transfusion-related immunomodulation* (TRIM).[52,57,69]

Nonhemolytic transfusion reactions are relatively common, occurring in 1% to 5% of all transfusions, and are associated with symptoms such as fever, chills, and urticaria. Like hemolytic reactions, these reactions are difficult to detect during general anesthesia.[57] Although not usually life threatening, febrile nonhemolytic and allergic reactions can cause concern and may lead to interruption of the transfusion.[50] According to the FDA, the most common causes of transfusion-related deaths are TRALI followed by hemolytic transfusion reaction, transfusion-associated sepsis, transfusion-related circulatory overload, babesiosis, anaphylaxis, and graft-versus-host disease.[75]

Leukoreduction, the use of filters to reduce the level of white blood cells (WBCs), is one technique used to reduce the incidence of certain adverse events related to transfusion. Leukoreduction has proven

BOX 20-12

Clinical Benefits of Leukoreduction

Proven clinical relevance
- Reduced frequency and severity of NHFTRs
- Reduced risk of CMV transmission
- Reduced risk of HLA alloimmunization and platelet refractionness

Likely clinically relevant
- Reduced infectious risk associated with immunomodulation (TRIM)
- Reduced organ dysfunction and mortality
- Reduced direct risk of transfusion-transmission bacteria

Unproven clinical relevance
- Avoidance of vCJD transmission
- Avoidance of HTLV I/II, EBV, and similar viruses
- Reduced risk of GVHD

From Blajchman MA. The clinical benefits for the leukoreduction of blood products. *J Trauma*. 2006;60(suppl 6):S83-S90; Friese RS, et al. The use of leukoreduced red blood cell products is associated with fewer infectious complications in trauma patients. *Am J Surg*. 2008;196(1):56-61; Phelan HA, et al. Prestorage leukoreduction abrogates the detrimental effect of aging on packed red cells transfused after trauma: a prospective cohort study. *Am J Surg*. 2012;203(2):198-204.
CMV, Cytomegalovirus; *EBV*, Epstein-Barr virus; *GVHD*, graft-versus-host disease; *HLA*, human leukocyte antigen; *HTLV*, human T-lymphotrophic virus; *NHFTRs*, nonhemolytic febrile transfusion reactions; *TRIM*, transfusion-related immunomodulation; *vCJD*, variant Creutzfeldt-Jakob disease.

to be effective in reducing the incidence of nonhemolytic transfusion reactions and is likely to be effective in the reduction of TRIM. One hypothesis for the mechanism behind this storage lesion centers on the role of leukocytes in the donor units. Leukocytes exert a variety of immunomodulatory effects on the recipient in a magnitude that is proportional to the length of time the donor unit is stored. The effects of universal leukoreduction have been so promising (Box 20-12) that several nations, including Canada and France, have mandated universal leukoreduction for their nations' blood supply.[76-78]

Despite enhanced safety of the blood supply, infectious complications remain a real, although perhaps overemphasized, possibility (Table 20-15).[79-81] The current rates of transmission of viral illness by transfusion are so low that mathematical models are now used to estimate risk.[69] Even with improved testing, transmission of viral disease can still occur during a period of time commonly called the *window period*, during which the donor blood is infectious, but screening tests used by blood banks are insensitive. Polymerase chain reaction (PCR) assays have improved testing for antibodies and shortened the window period to approximately 11 days for human immunodeficiency virus (HIV) and 8 to 10 days for hepatitis C virus (HCV).[82] Although hepatitis and HIV continue to be the subjects of considerable attention, other newly emerging viral diseases in the United States threaten the safety of the blood supply. West Nile virus is one example of a newly recognized transfusion-related illness. Fortunately, rapidly developed testing procedures for the virus have greatly reduced the risk of transmission by transfusion.[83]

One of the most recently identified transfusion-related diseases is variant Creutzfeldt-Jakob disease (vCJD). Theories suggest that this disease is contracted by blood donors through the ingestion of beef from cattle infected with bovine spongiform encephalopathy (BSE). The infectious agent responsible for BSE—believed to be an abnormal prion protein—can be passed from blood donor to transfusion recipient and become manifest in the recipient as vCJD,

TABLE 20-15 Risks and Side Effects of Allogenic RBC Transfusion

Type of Risk	Incidence (per Unit Transfused)
Infections	
Viruses	
Human immunodeficiency virus (HIV)	1:1,468,000 – 1:4,700,000
Hepatitis B virus (HBV)	1:31,000 – 1:205,000
Hepatitis C virus (HCV)	1:1,935,000 – 1:3,100,000
Bacteria	
All	1:28,000 – 1:143,000
Parasites	
Malaria	1:4,000,000
Prions	
New variant Creutzfeldt-Jakob disease	Possible
Immunologic Reactions	
Hemolytic Transfusion Reactions	
Acute hemolytic TR	1:13,000
Delayed hemolytic TR	1:9000
Alloimmunization	1:1600
Immunosuppression	1:1
Transfusion-related acute lung injury	1:70,000
Mistransfusion	
All RBC mistransfusions	1:14,000 – 1:18,000
Increased mortality	
Increased length of hospital stay	

From Spahn DR, Kocian R. Artificial 0_2 carriers: status in 2005. *Curr Pharm Des*. 2005;11(31):4099-4114; Spahn DR, et al. More on transfusion and adverse outcome: it's time to change. *Anesthesiology*. 2011;114(2):234-6; Glance LG, et al. Association between intraoperative blood transfusion and mortality and morbidity in patients undergoing noncardiac surgery. *Anesthesiology*. 2011;114(2):283-92.
RBC, Red blood cell; *TR*, transfusion reaction.

leading to degeneration of the central nervous system. Fortunately, vCJD remains a rare disease, with the majority of cases confined to the United Kingdom. Measures to protect the integrity of the blood supply include careful donor screening and leukodepletion.[84]

Bacterial contamination of blood remains a risk and increases with the length of time the blood is stored.[69] Contamination of platelets is of particular concern. Platelets are stored for a maximum of 5 days[85] at room temperature and carry a risk of bacterial contamination of 1 in 12,000.[69]

Concerns regarding cost, availability, and complications associated with blood and blood products have led to strategies to reduce the risk of intraoperative blood loss, such as careful preoperative evaluation of the patient focusing on conditions that place the patient at increased risk of hemorrhage. In the surgical setting, these factors generally include medications that affect coagulation and inherited and acquired defects of coagulation. An important tool to reduce the risk of significant intraoperative blood loss is the preoperative administration of agents to promote coagulation or reverse anticoagulants. The ASA transfusion practice guidelines recommend judicious preoperative administration of reversal agents such as vitamin K, prothrombin-complex concentrate, recombinant factor VII, and FFP. Antifibrinolytic agents should be considered in cases in which

large amounts of blood loss are anticipated. This may lead to the administration of agents such as tranexamic acid G.[58,86]

In the event that blood transfusion becomes unavoidable, alternatives to blood transfusion from anonymous donors have been developed in the hope of reducing patient risk. One option involves the use of directed donors. Donor-directed blood transfusions are homologous blood transfusions from a donor selected by the recipient and believed by some to decrease the risk of transmission of disease. Studies comparing the safety of donor-directed blood with blood from anonymous donors, however, fail to demonstrate any advantage to using donor-directed blood.[48,68]

A widely used alternative to allogenic blood transfusion is the use of autologous transfusion. Autologous transfusion techniques can be divided into three main categories: intraoperative and postoperative blood salvage, preoperative blood donation, and acute normovolemic hemodilution.[87] Autologous transfusion is a valuable tool when used in select patients.[88]

Intraoperative red-blood-cell (RBC) salvage involves the aspiration of blood shed into the surgical field into a specialized apparatus that concentrates the RBCs and washes the shed blood to remove debris, after which the RBCs are reinfused. Cell salvage may be used in surgical cases in which significant blood loss is likely, as well as in cases of unexpected massive blood loss (Table 20-16). Generally accepted contraindications to cell salvage include surgery involving wounds contaminated by bacteria, sepsis, bowel contents, amniotic fluid, or malignant cells, as shown in Table 20-16.[89] Cell-washing devices can provide a volume equivalent to 10 units of blood per hour for transfusion in cases of massive blood loss.[90] Prolonged use of cell salvage of large volume autotransfusion may be associated with dilution of clotting factors and thrombocytopenia, and regular laboratory or point of care monitoring is required. Cell salvage should be considered in all cases where significant blood loss (greater than 1000 mL) is expected or possible. The use of cell salvage in combination with a leukocyte depletion filter appears to be safe.[71]

Preoperative blood donation consists of the collection and storage of a potential recipient's own blood for possible reinfusion of the blood at a later date, the intraoperative period. Although this procedure may eliminate certain risks associated with transfusions, some risks remain, and other risks arise (Box 20-13).[87] The process of autologous preoperative blood donation and transfusion carries with it the risks of preoperative anemia and resultant myocardial ischemia, the risk of bacterial contamination, and the risk of clerical error leading to the administration of the wrong blood.[50] In addition to these patient risks, approximately half of autologously donated blood is discarded,[90] which contributes to waste. Other disadvantages include a possible reduction in preoperative hemoglobin and anemia tolerance, and the donated blood requires storage so the usual concerns with banked blood remain.[88]

Acute normovolemic hemodilution is a transfusion alternative involving the removal of whole blood from a patient immediately before or after the initiation of anesthesia and surgery and replacing volume with crystalloid or colloid solutions. Blood lost during surgery will have a low hematocrit. Reinfusion of the whole blood (with a normal hematocrit as well as clotting factors) is initiated when intraoperative loss of blood has stopped, or earlier if the patient's condition warrants it. Advocates of acute normovolemic hemodilution suggest that hemodilution, compared with autologous donation, eliminates the expense of testing, the risks of bacterial contamination, and opportunity for wrong unit transfusion because the whole blood remains in the operating room.[90]

The search for a "blood substitute" has evolved over time into efforts to develop "oxygen therapeutics," which involves the use of technology to increase the oxygen-carrying capacity of the circulating volume.[91] Main areas of concentration in this field include the development of cell-free hemoglobin solutions to carry oxygen and perfluorochemicals to carry dissolved oxygen in a manner similar to that of plasma.[80,86,90-92]

SUMMARY

Surgery and anesthesia challenge the body's ability to maintain the dynamic balance of fluids and electrolytes necessary for proper function. Skillful management of fluids and electrolytes in the perioperative period is one of the most challenging and important tasks of the anesthetist and requires knowledge of both basic sciences and clinical research.

A subject intimately related to fluid and electrolyte management is transfusion therapy. An expanding body of evidence addressing transfusion therapy is better informing the clinician, who must evaluate risks versus benefits in the process of clinical decision making.

TABLE 20-16 Cell Salvage

General Indications for Cell Salvage

Specialty	Surgical procedure	Comments
Cardiac	Valve replacement Redo bypass grafting	
Orthopedics	Major spine surgery Knee replacement Hip replacement	
Urology	Radical retropubic prostatectomy Cystectomy Nephrectomy	Individualized by surgeon Limited to patients with prior radiation therapy When tumor involves major vessels
Neurosurgery	Giant basilar aneurysm	
Vascular	Thoracoabdominal aortic Aneurysm repair Abdominal aortic aneurysm repair	Should be individualized by surgeon and patient's characteristics
Liver transplant		
Other	Jehovah Witnesses Unexpected massive blood loss Red cell antibodies	When accepted by patient

TABLE 20-16 Cell Salvage—cont'd

Relative Contraindications to Cell Salvage
Pharmacologic Agents
Clotting agents (e.g., Avitene, Surgicel, Gelfoam) Irrigating solutions of disinfectants for topical use (e.g., oxygenated water, betadine, distilled water, alcohol, antibiotics meant for topical use)
Anticoagulant drugs
Synthetic resins such as methylmethacrylate Catecholamines (pheochromocytoma) Oxymetazoline (Afrin) Papaverine
Contaminants in the Operating Field
Urine Bone chips Fat Bowel contents Infection Amniotic fluid
Malignant Tumors or Neoplastic Cells
Hematologic Disorders
Thalassemia Sickle cell disease
Miscellaneous
Carbon monoxide (electrocautery smoke)

Adapted from Esper SA, Waters JH. Intra-operative cells salvage: a fresh look at the indications and contraindications. *Blood Transfus*. 2011;9(2):139-147.

BOX 20-13

Autologous Blood Donation

Advantages

- Prevents transfusion-transmitted disease
- Prevents red-cell alloimmunization
- Supplements the blood supply
- Provides compatible blood for patients with alloantibodies
- Prevents some adverse transfusion reactions
- Provides reassurance to patients concerned about blood risks

Disadvantages

- Does not affect risk of bacterial contamination
- Does not affect risk of ABO incompatibility error
- More costly than allogeneic blood
- Results in wastage of blood not transfused
- Increased incidence of adverse reactions to autologous donation
- Subjects patient to perioperative anemia and increased likelihood of transfusion

From Goodnough LT. Autologous blood donation. *Anesthesiol Clin North America*. 2005;23(2):263-270.

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Positioning for Anesthesia and Surgery

CHAPTER 21

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The act of positioning a patient for surgery is a group endeavor that requires teamwork, timing, communication, and knowledge of measures that protect against injury. The goal of patient positioning is to allow optimal surgical access while minimizing potential risk to the patient. Every surgical position carries some degree of risk that is magnified once an anesthetic is administered, which renders the patient unable to make necessary changes in positioning as needed. To prevent patient injury, clinicians must be knowledgeable about possible hazards associated with various surgical positions.

PHYSIOLOGIC EFFECTS OF SURGICAL POSITIONS

Anesthesia providers are intimately involved in coordinating and directing patient positioning and are also continually monitoring and assessing the subsequent changes in the patient's physiologic status. Numerous factors have an effect on these changes: the surgical position; the length of time; the padding and positioning devices used; the type of anesthesia given; and the operative procedure. These changes most frequently involve (1) the cardiovascular system, (2) the respiratory system, (3) the nervous system, and (4) other vulnerable areas such as the skin, eyes, breasts, and genitalia.

Cardiovascular System

Cardiac output and blood pressure are generally decreased under general anesthesia in response to central nervous system and myocardial depression and vasodilation induced by volatile anesthetics. As a result, blood pools in dependent body areas, reducing preload and decreasing stroke volume. Administration of neuromuscular blocking agents also contributes to decreased venous return because normal muscle tone is abolished. Additionally, opioids and volatile agents slow the heart rate, further decreasing cardiac output and blood pressure. In healthy patients, mean arterial pressure (MAP) is maintained by compensatory increases in heart rate and systemic vascular resistance (SVR), but elderly patients and those with preexisting diseases can be less adaptive. Compensatory mechanisms to increase heart rate when hypotension occurs are blunted by general anesthetics, rendering cardiac output and blood pressure more susceptible to gravitational forces.

Hemodynamic changes are usually minimal in the supine and lateral positions.[1,2] However, cardiac output and blood pressure are often decreased in the sitting, prone, and flexed lateral positions, where the lower extremities are dependent.[1,3] Although central venous pressure (CVP) is increased in the prone position, left ventricular volume is reduced, probably due to decreased venous return and increased intrathoracic pressure.[4] Cardiac index (CI) may be decreased[5,6] or unchanged[5] in the prone position compared with the supine; the effect may be frame dependent.[6] In the lateral decubitus position with the kidney rest elevated, hypotension is likely because the legs are dependent, venous return is reduced by extreme flexion, and the kidney rest may compress the great vessels.[1,3] Conversely, blood pressure may appear normal or higher in the lithotomy position, in which elevation of the legs above the trunk provides an autotransfusion of 100 to 250 mL per leg.

Mean arterial pressure increases or decreases by approximately 2 mmHg per inch for each change in height between the heart and a body region.[7] Therefore regions elevated above the heart in the head-up, sitting, and lithotomy positions may be at risk for hypoperfusion and ischemia, particularly if hypotension occurs. The decrease in hemodynamic parameters depends on the degree of elevation of the torso. Hemodynamic changes are minimal if the patient is placed in a 45-degree, head-up sitting position, but cardiac output decreases 20% if the patient is raised to 90 degrees, because venous blood pools in the extremities. When the patient is in the seated position, as compared with supine, CI, CVP, and pulmonary capillary wedge pressure (PCWP) decrease significantly and SVR increases.[8] In procedures in which the head is elevated and cerebral perfusion is a concern, invasive arterial blood pressure monitoring should be instituted, with the transducer placed at the level of the circle of Willis.[9]

Positioning devices and mechanical ventilation may contribute to decreased cardiac output and hypotension. In the lateral decubitus position, elevation of the kidney rest under the flank may cause vena cava compression. When the patient is in the lateral decubitus position, the kidney rest should lie under the dependent iliac crest.[1] Extreme flexion of the hips in some variations of the prone or lithotomy positions may occlude the femoral vessels and contribute to decreased venous return. Large tidal volumes and positive end-expiratory pressure (PEEP) may generate high intrathoracic pressures, with a subsequent reduction in atrial filling and cardiac output.

A variety of methods have been suggested for attenuating the hemodynamic changes associated with surgical positioning. Slow assumption of the surgical position allows the cardiovascular system time to compensate for position-induced hemodynamic alterations. Because hemodynamic changes may be influenced by anesthetic technique, using a nitrous-narcotic technique or a lighter level of anesthesia (less than 0.5 minimum alveolar concentration) or gradually attaining a deeper level of anesthesia may attenuate position-induced hypotension.[3] Intravascular volume loading before positioning can reduce or eliminate hypotension.[1,6] However, volume replacement must be done judiciously because excessive fluid administration can lead to volume overload in susceptible individuals when the patient is returned to the supine position, or when the vasodilatory effects of general anesthetics are terminated.[3]

The Trendelenburg position is often used to treat hypotension, because it is assumed to increase venous return and MAP. When placed in a head-down position, normotensive individuals compensate for increases in CVP and pulmonary artery pressure (PAP) with vasodilation and a decrease in heart rate from stimulation of baroreceptor reflexes. However, hypotensive individuals may

not respond in the same manner. Investigators have demonstrated variable effects of the Trendelenburg position on cardiovascular parameters. Changes in intrathoracic blood volume of 2% to 3% in unanesthetized normovolemic individuals are reported with the Trendelenburg position.[10] CVP, mean PAP, and pulmonary artery occlusion pressure can be increased in the head-down position, but this increase may not reflect changes in CI, stroke volume, or MAP.[10,11] Others have shown no increase in MAP, an increase in SVR, and a decrease in CI in hypotensive patients placed in Trendelenburg position.[12]

Hypovolemia can be unrecognized in the lithotomy and Trendelenburg positions, because MAP can appear normal despite volume deficit. Volume replacement can be assessed as adequate until acute hypotension occurs when the patient is returned to the horizontal position. An additive effect can occur if the Trendelenburg position is used to supplement the lithotomy position.

Patients with comorbidities may be susceptible to the detrimental effects of various positions. The combination of the lithotomy position and a head-down tilt can have a detrimental effect on myocardial function in patients with coronary artery disease, because CVP, PAP, and PCWP are increased, whereas cardiac output is decreased.[13] The Trendelenburg position may increase myocardial work by increasing central blood volume, cardiac output, and stroke volume. Individuals with very poor cardiac function can have decreased cardiac output if the increased central blood volume moves them to a worse position on the Frank-Starling curve. The lower extremities of individuals with peripheral vascular disease may be at risk of ischemia in the lithotomy and Trendelenburg positions because a relative state of hypoperfusion exists when the lower extremities are elevated above the heart.

The prone and Trendelenburg positions may increase venous pressure in the head, with resultant swelling of facial, pharyngeal, and orbital structures. Intracranial pressure can be elevated when the head is dependent, because venous pressures are transmitted to the head and intracranial structures through the valveless jugular system. Cerebral blood flow can be decreased when inflow is limited by venous congestion in intracranial structures. Postoperative visual loss (POVL) may result from an increase in ocular venous pressures and concomitant decrease in ocular perfusion pressure. Facial edema, macroglossia, and airway edema are reported following the prone and head-down positions.[14] A 10-degree head-up tilt may prevent the development of facial edema.

Respiratory System

During spontaneous respiration in awake patients, contraction of the diaphragm and intercostal muscles causes expansion of the thoracic cavity in both an anterior-posterior and lateral direction. Downward displacement of the diaphragm generates a negative intrathoracic pressure and allows lung expansion as gas flows inward. Lung elastance and chest-wall compliance affect the amount of pressure necessary to expand the alveoli for a given change in volume. Gravitational factors affect the distribution of ventilation and perfusion within the lung, as well as the shape of the thoracic cavity and movement of the diaphragm and abdominal contents.

Postural changes may significantly alter compliance, lung volumes, and the distribution of ventilation and pulmonary blood flow. Positioning devices may cause mechanical interference with movement of the belly wall and abdominal contents, the chest wall, or the diaphragm.[15] Therefore anesthetic-induced depression of ventilation may be worsened by the majority of surgical positions. Individuals with preexisting diseases that alter respiratory function may be more susceptible to the deleterious ventilatory effects of surgical positions.

Effective respiratory gas exchange depends on a balance of ventilation and perfusion throughout the lungs. Traditionally, gravitational effects on gas and blood flow are thought to result in differences in ventilation and perfusion in different lung segments. In both awake and anesthetized patients, gravitational forces are theorized to create a gradient that favors perfusion in dependent portions of the lungs and ventilation in nondependent regions.[16,17] However, new imaging techniques have identified a concentric pattern of blood flow in the lungs, with central regions receiving a greater proportion of flow than the periphery.[18,19] The mechanism for this gradient has not been identified, but the diameters and branching patterns of pulmonary vessels and the distance blood must flow to reach a site are possible factors. Nongravitational factors such as cardiac output, pleural pressures, and lung volumes are also thought to play a factor in regional lung perfusion.[16,19]

Positional changes may result in redistribution of ventilation and perfusion. These changes are less in the sitting position and more evident in the prone and lateral positions. In the prone position, changes in ventilation-perfusion ($\dot{V}/\dot{Q}$) ratios have been postulated as the cause of improved oxygenation.[16] More lung volume is present posteriorly than anteriorly, where anterior mediastinal structures occupy significant space; as a consequence, posterior lung segments are better ventilated. Ventilation is more uniform and $\dot{V}/\dot{Q}$ matching is better in the prone position than in the supine position.[17] In the lateral decubitus position, ventilation and perfusion are greater in the dependent lung than in the nondependent lung in awake, spontaneously breathing patients.[19]

$\dot{V}/\dot{Q}$ mismatching in the lateral decubitus position may affect oxygenation, especially with procedures requiring one-lung ventilation. Hypoxic pulmonary vasoconstriction in the unventilated lung further redistributes blood flow to the dependent lung to improve oxygenation.[19] Patients are susceptible to atelectasis in the lateral position, because closing volumes occur above functional residual capacity (FRC), with closing occurring earlier in the dependent than in the nondependent lung. Tidal volumes of 10 to 12 mL/kg and an F_{IO_2} of 0.5 or higher have been suggested to compensate for $\dot{V}/\dot{Q}$ mismatch in the lateral position; however, excessive tidal volumes can cause barotrauma, decrease hypoxic vasoconstriction, and reduce oxygenation in patients in the lateral position. Tidal volumes of 5 to 7 mL/kg and higher respiratory rates cause smaller declines in oxygenation. Although the application of PEEP to the dependent lung is sometimes used in an attempt to recruit collapsed alveoli and increase compliance, controversy exists regarding its effectiveness in improving patient oxygenation. The administration of oxygen at 2 to 4 L/min to the nonventilated lung may improve hypoxia. Application of 5 to 10 cm H_2O of continuous positive airway pressure (CPAP) to the nondependent lung can significantly improve oxygenation during one-lung ventilation, but the re-expansion of lung tissue may impede surgical access.[19]

Changes in the elastance and resistance of the diaphragm and abdomen occur when shifting between positions. These changes have little effect on movement of the chest wall in healthy individuals but may have an effect in persons with conditions that predispose to abnormalities of lung function.[20] In the prone position, diaphragmatic excursion can be limited by the abdominal viscera if the abdomen is compressed by the weight of the body or positioning devices. If the abdomen hangs free, gravity allows the abdominal contents to shift, reducing interference with diaphragmatic movement.[21,22] In the anesthetized patient in the lateral position, abdominal contents shift cephalad, moving the

hemidiaphragm of the dependent lung upward, thereby decreasing ventilation in the dependent lung and reducing its compliance. In the nondependent lung of the anesthetized patient, ventilation is greater and compliance increased due to the caudal shift of the upper hemidiaphragm allowing unrestricted lung excursion (see Chapter 27). The lithotomy position has little effect on the compliance of the respiratory system in healthy, conscious volunteers.[15] However, extreme flexion of the thighs in the exaggerated lithotomy position compresses the abdomen, shifts the abdominal viscera cephalad, and limits diaphragmatic movement. As a result, compliance and tidal volume are reduced, and airway pressures and dead space–to–tidal volume ratios are increased.[23] This effect may be amplified in obese individuals.

Lung capacities are decreased with most position changes. In the supine position, FRC and total lung capacity are significantly decreased compared with the sitting position due to the cephalad shift of the diaphragm caused by pressure of the abdominal viscera.[15,20] Some investigators have found an increase in FRC with patients in the prone position, when the abdomen hangs free.[16,24] Theories pose that better matching of ventilation and perfusion, rather than changes in lung volumes or capacities, cause improvements in oxygenation in the prone position.[15]

In the awake patient in the lateral position, ventilation favors the dependent lung during spontaneous respiration. With the addition of anesthesia, positive pressure ventilation, and paralysis, the upper lung becomes easier to ventilate. Displacement of the relaxed diaphragm by abdominal viscera and the downward gravity force of the mediastinum result in decreased compliance of the lower lung.[19-21]

Ventilatory changes associated with the lithotomy position are dependent on the extent to which the legs are flexed on the abdomen and the concomitant use of the head-down position. In the normal lithotomy position without Trendelenburg, changes in FRC are similar to those associated with the supine position, and the diaphragm does not shift farther cephalad.[23] However, adding Trendelenburg position to lithotomy can cause an additional decrease in FRC.

The sitting position is more favorable for ventilation and has less effect on lung volumes than other positions. The more the torso is elevated, the smaller the effect on lung mechanics. Forced vital capacity and FRC are within normal parameters in the seated position.[21] The abdominal contents shift caudally and anteriorly, causing less interference with diaphragmatic movement and allowing greater expansion of dependent lung regions.[15] Compared with the supine position, in which the abdominal muscles are used for breathing, in the sitting position, the rib cage contributes more to ventilation.[21] However, respiratory benefits of the sitting position are attenuated when the sitting position is modified to minimize cardiovascular effects. Flexion of the lower extremities at the hip and elevation of the legs causes abdominal contents to shift cephalad against the diaphragm. The sitting position then more closely resembles the supine position, limiting diaphragmatic excursion and decreasing FRC and closing volumes.[9]

The Trendelenburg position exacerbates the deleterious ventilatory effects of the various positions. The diaphragm is displaced cephalad, and its excursion is limited by shifting of the abdominal contents, decreasing the FRC progressively as the degree of Trendelenburg position increases. Movement of the mediastinum toward the head may result in the endotracheal tube migrating into the right mainstem bronchus.[25,26] This complication may also occur upon establishment of the pneumoperitoneum, in which the diaphragm is displaced in a cephalad direction by pressurized gas.[26,27]

PATHOPHYSIOLOGY OF NERVE INJURY

Transection, compression, stretch, and kinking are the primary mechanisms responsible for nerve injuries.[28,29] Nerves may be transected by surgical maneuvers or by trauma. Compression can happen when a nerve is forced against a bony prominence or a hard surface such as an armboard or operating table. In the lateral position, for example, the weight of the superior leg pushes against the dependent extremity and may compress the common peroneal nerve of the dependent leg against the operating table. Stretch or traction injuries occur where nerves such as the sciatic nerve or brachial plexus have a long course across many structures. Peripheral nerves have some laxity that allows a limited amount of elongation. However, excessive elongation or stretch may cause conduction changes, axonal disruption, or interruption of the nerve's vascular supply.[30-32] Kinking injuries happen when a peripheral nerve is pinched between two immovable structures. For example, the femoral nerve can be kinked under the inguinal ligament when the thighs are flexed on the abdomen, as in the exaggerated lithotomy position.

A common component of all peripheral nerve injuries is ischemia. Intraneural blood flow may be compromised by stretch, compression, or disruption of the nerve tissue itself.[33] Other causes include occlusion of major vessels, emboli, tissue edema, or inhibition of perfusion at the capillary level. For example, pressure applied over a body surface may limit venous capillary outflow, causing a rise in venous capillary pressure and a decrease in the hydrostatic pressure gradient between interstitial tissues and the capillary.[34] Ultimately, tissue edema occurs as fluid is sequestered in the cells and interstitial space. As venous capillary pressure rises, the arterial-venous pressure gradient is reduced, decreasing flow to tissues along the capillary. As venous and tissue pressures continue to rise, arterial inflow is eventually obstructed and ischemia results. Low mean arterial blood pressure may augment the development of ischemic conditions.[31]

Tissue metabolism continues even in the absence of blood flow. When ischemia ensues, adenosine triphosphate (ATP) production is decreased, causing failure of the transmembrane sodium-potassium pump and accumulation of sodium within the cell. The resulting osmotic pressure gradient favors the movement of water into the cells. Intracellular volume is increased, and tissue edema occurs.[35] A vicious cycle of ischemia results as tissue pressures increase, preventing the movement of fluid and nutrients from the capillaries into the cells.

The susceptibility of peripheral nerves to ischemia may be partially due to their anatomic structure (Figure 21-1). Peripheral

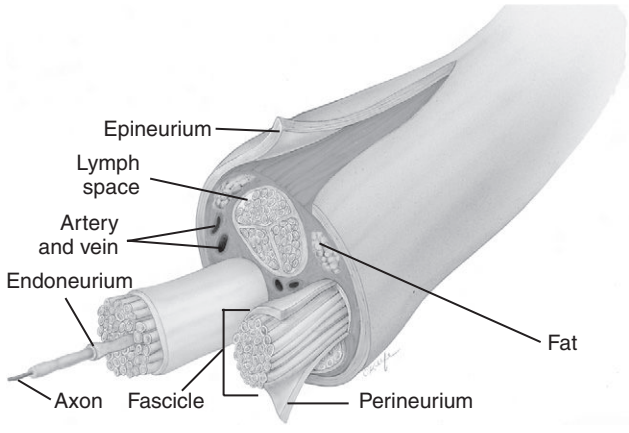

FIGURE 21-1 Cross section of a peripheral nerve trunk showing its components. (From Patton KT, Thibodeau GA. *Anatomy & Physiology*. 8th ed. St Louis: Mosby; 2013:392.)

nerves are composed of bundles of nerve fibers (fascicles) and their vascular supply is encased in protective connective-tissue coverings. Each nerve fiber is composed of one or more axons sheathed by Schwann cells (neurolemma) that are either myelinated or unmyelinated. The axons and neurolemma are covered by a loose connective tissue called the *endoneurium*. The *perineurium* is a tough connective tissue that binds the fascicles into identifiable structures. The *epineurium* consists of two layers: an inner epineurium that supports the fascicles and an outer epineurium that covers the external surface of the nerve.[31,36] The quantity of these protective tissues varies between nerves and even along the same nerve. The entire nerve trunk is covered by a loose layer of connective tissue that allows it to slide across joints and other tissues.[31]

Peripheral nerves have an extensive microvascular supply. Blood vessels in the epineurium run parallel to the nerve and form numerous anastomoses with the perineurium. Collateral connections between the perineurium and the endoneurial capillaries run obliquely between the layers and thus may be more susceptible to compression by increases in tissue pressure. In addition, the endoneurial space lacks lymphatic vessels, so edema and fluid accumulation in this region may obstruct the microcirculation.[31]

FACTORS CONTRIBUTING TO NERVE INJURIES

Postoperative peripheral nerve injuries are frequently attributed to incorrect surgical positioning; however, current evidence indicates that multiple factors are involved in postoperative peripheral neuropathies.[37,38] Perioperative factors that contribute to the development of nerve injuries include ancillary positioning devices, prolonged surgical procedures, and anesthetic technique. Patient-related factors include gender, age, body habitus, and preexisting medical conditions. However, the precise mechanism of nerve injury is often unclear, suggesting that further investigation is needed to identify causative factors.[37,39]

Positioning Devices

Controlled studies of complications related to specific positioning devices are largely nonexistent. Isolated case reports provide much of the evidence that is known about nerve injuries attributable to improper use of positioning devices. Ancillary positioning devices, such as straps used to restrain the patient or an extremity, may cause pressure and temporary injury if excessively tightened. For example, the lateral femoral cutaneous nerve in the thigh is susceptible to injury by tight table straps or the leg-holding device used for knee arthroscopy.[40] Common peroneal nerve injury has been attributed to the use of candy cane stirrups. Brachial plexus injury has been caused by a damaged armboard falling off the operating room (OR) table[41] or the use of shoulder braces with steep Trendelenburg position.[37] Compression injury of the radial nerve has been reported after the intraoperative use of tourniquets and blood pressure cuffs and by compression between the humerus and a firm surface, such as a positioning device.[42,43] Improper placement of an axillary roll may cause compartment syndrome and compression of neural and vascular structures.[44]

Length of Procedure

Prolonged surgical procedures contribute to postoperative positioning complications. Postoperative visual loss, nerve injuries, and compartment syndrome have been associated with a variety of procedures and positions in which the common denominator was a duration of more than 4 hours.[45-48] Rhabdomyolysis and acute renal failure also have been reported after lengthy procedures.[49,50] One possible explanation is that during long procedures, the weight of the body causes external compression of dependent tissues and states of low perfusion.[50] The longer this situation persists, the higher the potential for development of edema and ischemic injury.

Anesthetic Techniques

Anesthetic techniques may contribute to the development of position-related injuries.[51] Patients receiving general anesthesia cannot move in response to painful stimuli generated by uncomfortable body positions. The constraints of the procedure or surgeon may limit movement even when patients are sedated. Muscle relaxation due to neuromuscular blocking drugs or volatile anesthetics may contribute to stretch injuries by allowing increased mobility of joints.[30] For example, limited elbow extension from tight biceps muscles can be overcome by neuromuscular blockade, allowing the arms to be extended flat and subsequently stretching the median nerve.[31] The hypotensive effects of general anesthetics may lower perfusion pressures below acceptable levels in patients who are hypertensive or have other comorbidities. The use of hypotensive techniques to reduce blood loss should be balanced against the risk of possible complications resulting from decreased perfusion pressures, particularly during prolonged procedures and in the sitting, lithotomy, and Trendelenburg positions, in which gravity affects blood flow.

Although neuraxial and peripheral nerve blocks are associated with both permanent and temporary nerve injuries, the majority of injuries are not related to positioning but to block technique, hematoma formation, and needle trauma.[52] However, recognition of compartment syndrome may be delayed when providers attribute the patient's symptoms to the residual effects of regional blocks and local anesthetics.[53,54] Anesthetists must have a high index of suspicion when return of function is delayed beyond what is expected for a particular technique or local anesthetic and when patients complain of severe pain in the presence of a seemingly adequate block.

PATIENT-RELATED FACTORS CONTRIBUTING TO NERVE INJURIES

Body Habitus

Extremes of body habitus are correlated with an increased incidence of positioning complications.[47,49,50] Individuals who are underweight may develop decubiti or nerve damage due to lack of adequate adipose tissue over bony prominences.[47,55] For example, thin patients may be at higher risk for sciatic nerve damage when the opposite buttock is elevated,[28] and thinner women (body mass index [BMI] less than 22) are more likely to develop ulnar neuropathy.[52,55] Individuals with a muscular physique may also be at increased risk for compartment syndrome and ulnar nerve injury.

Obesity increases morbidity from positioning because large tissue masses place increased pressure on dependent body parts. Extreme abduction of the arms may cause stretch injuries to the lower roots of the brachial plexus, whereas the upper roots may be damaged by excessive rotation of the head to the opposite side. Ulnar neuropathy has been associated with an increased BMI.[56] Adipose tissue is poorly perfused and may contribute to this problem. For example, in the lateral position, a heavy superior extremity may interfere with perfusion by exerting substantial pressure on the inferior extremity.

Preexisting Conditions

Preexisting conditions appear to be associated with an increased risk of developing postoperative position-related injuries. Hypertension, diabetes mellitus, peripheral vascular disease, peripheral

BOX 21-1

Factors Associated with Position-Related Injuries

Positioning Devices
- Table straps
- Leg holders and stirrups
- Axillary roll
- Bolsters
- Fracture table post
- Shoulder braces
- Positioning frames
- Headrests
- Ether screen

Length of Procedure
- Longer than 4-5 hr

Body Habitus
- Obesity
- Malnutrition
- Bulky musculature

Preexisting Pathophysiology
- Anemia
- Diabetes mellitus
- Peripheral vascular disease
- Liver disease
- Peripheral neuropathies
- Alcoholism
- Limited joint mobility
- Smoking

Anesthetic Technique
- General anesthesia
- Hypotensive techniques
- Neuromuscular blockade

neuropathies, and alcoholism can exacerbate the physiologic effects of various positions. Nerve injury and preexisting neuropathies are more common in patients with diabetes,[28] and diabetes is the most common metabolic cause of spontaneous isolated femoral neuropathy.[57] A history of smoking within 1 month of the surgical procedure has been identified as a risk factor for nerve injury, as well as for delayed healing.[47,58] Individuals with subclinical ulnar nerve entrapment, which may not be apparent to the patient or anesthetist, are also at risk for nerve injuries.[59,60]

Box 21-1 highlights factors associated with position-related injuries.

PERIOPERATIVE NEUROPATHIES

In the awake patient, pain or discomfort from extreme body positioning would prompt optimization of position for the relief of symptoms. The induction of anesthesia renders a patient unable to make these changes and therefore susceptible to injury. The addition of muscle relaxants may allow body or extremity positioning that the awake patient would not otherwise tolerate, making the patient even more vulnerable to injury.[33] Table 21-1 and Box 21-2 identify specific nerve injuries associated with positioning and recommendations for prevention.

Ulnar Neuropathy

Ulnar neuropathy is one of the most frequently reported injuries after surgery and anesthesia, with a reported incidence ranging from 0.04% to 0.5%.[29,59,61] Ulnar neuropathy is a well-known complication of cardiac surgery, with a prevalence as high as 38%.[62] The American Society of Anesthesiologists (ASA) and American Association of Nurse Anesthetists Foundation (AANA-F) closed-claims studies found that the ulnar nerve was the first (28%) and second (16%) most commonly injured nerve.[61,63,64]

The ulnar nerve traverses the length of the upper extremity from its origins as a branch of the medial cord of the brachial plexus to its terminal branches in the hand. In the upper arm, the ulnar nerve passes along the anterior aspect of the medial head of the triceps muscle and posterior into the groove between the medial epicondyle of the humerus and the olecranon (Figure 21-2). In this region, the nerve is sheathed in the cubital tunnel before exiting and passing between the two heads of the flexor carpi ulnaris.

TABLE 21-1 Potential Position-Related Injuries

Body System or Anatomic Location	Potential Injury
Head, eyes, ears, nose, and throat	Postoperative vision loss Corneal abrasion Facial edema Vocal cord edema
Cardiovascular	Vascular occlusion Deep vein thrombosis Ischemic injuries
Respiratory	Atelectasis Endobronchial intubation
Neurologic	Peripheral neuropathy Quadriplegia Decreased cerebral blood flow Increased intracranial pressure
Genitourinary	Myoglobinuria Acute renal failure
Musculoskeletal	Amputation Backache Compartment syndrome Rhabdomyolysis
Integumentary	Abrasion Alopecia Decubiti

The cubital tunnel retinaculum (CTR) forms the roof of the cubital tunnel (see Figure 21-2), a potential area for nerve compression because fibrous tissue and the elbow capsule form a semirigid canal that changes shape with flexion and extension of the forearm.[47] When the elbow is flexed, the distance between the olecranon and medial epicondyle increases, stretching the CTR, decreasing the size of the tunnel, and increasing pressure on the nerve.[29]

Surgical positioning, age, preexisting diseases, and mechanical factors such as tourniquets and blood pressure cuffs have all been proposed as contributing to ulnar nerve injuries. However, ulnar neuropathy is more frequently associated with male gender,[33,55,59] the presence of a preexisting asymptomatic neuropathy,[59] prolonged hospital stays,[33,59] and extremes of body habitus.[33,52] Median sternotomy and sternal retraction are also proposed as a cause of ulnar nerve injury after cardiac surgery.[65] The incidence of ulnar neuropathy is higher in men—particularly those older than age 50—than in women.[37,55,61,66] Gender-related anatomic variations, such as a larger coronoid process and less subcutaneous tissue over the ulnar region are hypothesized to explain this difference.[55]

Although often blamed on intraoperative positioning, the prevalence of ulnar neuropathy is similar in medical and surgical patients, and prolonged hospital stays are significantly related to the development of ulnar neuropathy. Bedrest is suspected as contributing to ulnar neuropathy, because the initial presentation is often delayed 24 or more hours.[61,67] In addition, clasping the hands on the abdomen causes supination of the hands and rotation of the humerus, allowing the ulnar nerve in the postcondylar groove to be compressed against the bed.[67]

Recommendations for positioning to prevent ulnar nerve injury in anesthetized patients include the use of padding, placing the arms in a supinated position, and abducting the arms less than 90 degrees if armboards are used.[68,69] If the arms are secured on armboards, the forearm should be supinated (palm up), because pronation (palm down) increases pressure over the ulnar nerve.[70] When the patient's arms are tucked at the side of the body, they should be

BOX **21-2**

An Updated Report by the American Society of Anesthesiologists Task Force on Prevention of Perioperative Peripheral Neuropathies

I. Preoperative History and Physical Assessment

- When judged appropriate, it is helpful to ascertain that patients can comfortably tolerate the anticipated operative position.
- Body habitus, preexisting neurologic symptoms, diabetes mellitus, peripheral vascular disease, alcohol dependency, arthritis, and gender (e.g., male gender and its association with ulnar neuropathy) are important elements of a preoperative history.

II. Positioning Strategies for the Upper Extremities

Arm abduction in supine patients should be limited to 90 degrees. Patients who are positioned prone may comfortably tolerate arm abduction greater than 90 degrees.

- *Supine patient with arm on an armboard:* The upper extremity should be positioned to decrease pressure on the postcondylar groove of the humerus (ulnar groove). Either supination or the neutral forearm position facilitates this action.
- *Supine patient with arms tucked at side:* The forearm should be in a neutral position. Flexion of the elbow may increase the risk of ulnar neuropathy, but there is no consensus on an acceptable degree of flexion during the perioperative period. Prolonged pressure on the radial nerve in the spiral groove of the humerus should be avoided. Extension of the elbow beyond the range that is comfortable during the preoperative assessment may stretch the median nerve. Periodic perioperative assessments may ensure maintenance of the desired position.

III. Specific Positioning Strategies for the Lower Extremities

- *Stretching of the hamstring muscle group:* Positions that stretch the hamstring muscle group beyond the range that is comfortable during the preoperative assessment may stretch the sciatic nerve.
- *Limiting hip flexion:* Since the sciatic nerve or its branches cross both the hip and the knee joints, extension and flexion of these joints, respectively, should be considered when determining the degree of hip flexion. Neither extension nor flexion of the hip increases the risk of femoral neuropathy. Prolonged pressure on the peroneal nerve at the fibular head should be avoided.

IV. Protective Padding

- *Padded armboards:* Padded armboards may decrease the risk of upper extremity neuropathy.
- *Chest rolls:* The use of chest rolls in the laterally positioned patient may decrease the risk of upper extremity neuropathy.
- *Padding at the elbow:* Padding at the elbow may decrease the risk of upper extremity neuropathy.
- *Padding to protect the peroneal (fibular) nerve:* The use of specific padding to prevent pressure of a hard surface against the peroneal nerve at the fibular head may decrease the risk of peroneal neuropathy.
- *Complications from the use of padding:* The inappropriate use of padding (e.g., padding too tight) may increase the risk of perioperative neuropathy.

V. Equipment

The use of properly functioning automated blood pressure cuffs on the arm (i.e., placed above the antecubital fossa) does not change the risk of upper extremity neuropathy. The use of shoulder braces in a steep head-down position may increase the risk of perioperative neuropathies.

VI. Postoperative Assessment

A simple postoperative assessment of extremity nerve function may lead to early recognition of peripheral neuropathies.

VII. Documentation

Documentation of specific perioperative positioning actions may be useful for continuous improvement processes, and may result in improvements by helping practitioners focus attention on relevant aspects of patient positioning, and providing information on positioning strategies that eventually leads to improvements in patient care.

From Practice Advisory for the Prevention of Perioperative Peripheral Neuropathies: an updated report by the American Society of Anesthesiologists Task Force on prevention of perioperative peripheral neuropathies. *Anesthesiology.* 2011;114(4):741-754.

in a neutral position with the palms facing inward (Figure 21-3). Anatomic changes in the cubital tunnel with flexion and extension suggest that excessive flexion of the elbow should be avoided when the patient is in the lateral position or if the arms are secured across the chest. Evidence supports the conclusion that ulnar nerve palsy is not always a preventable complication despite the best efforts at careful positioning and padding.[68-70]

BRACHIAL PLEXUS INJURIES

The brachial plexus is vulnerable to injuries in almost every surgical position, particularly if the arms are abducted or the head is rotated (Figure 21-4). When the patient is supine, abduction of the arms greater than 90 degrees stretches the plexus around the humeral head. Turning the head to the side with the arms abducted can cause stretching and compression of the contralateral brachial plexus beneath the clavicle.[71] Even tucking the arms next to the body is not without risk if the head is turned laterally and the shoulders are depressed. When the patient is prone, inadequate support of the shoulders allows them to sag anteriorly, causing traction on the plexus. Also in the prone position, extending the arms over the head may compress the plexus between the clavicle and first rib.

In the lateral decubitus position, brachial plexus injury is most commonly the result of excessive stretching, usually because of arm abduction greater than 90 degrees, external rotation, extension and lateral flexion of the head, and posterior shoulder displacement.[28] In the lateral position, the weight of the chest can compress the lower shoulder and axilla putting pressure on the axillary neurovascular bundle. An "axillary roll" can be placed just caudal to the dependent axilla to relieve this pressure. If the nondependent arm is suspended on an arm holder or with traction, abduction of 45 to 60 degrees should be maintained and less than 10 pounds of traction applied.[72]

Brachial plexus injuries are also associated with positioning devices. Injuries have been caused by a damaged armboard falling off the OR table, causing excessive stretch of the plexus. Sometimes used during steep Trendelenburg position, shoulder braces placed too close to the base of the neck or along the midpoint of the clavicle can compress neurovascular structures and cause brachial plexus neuropathy. If used, shoulder braces are properly placed at the distal end of the clavicle.[41,73]

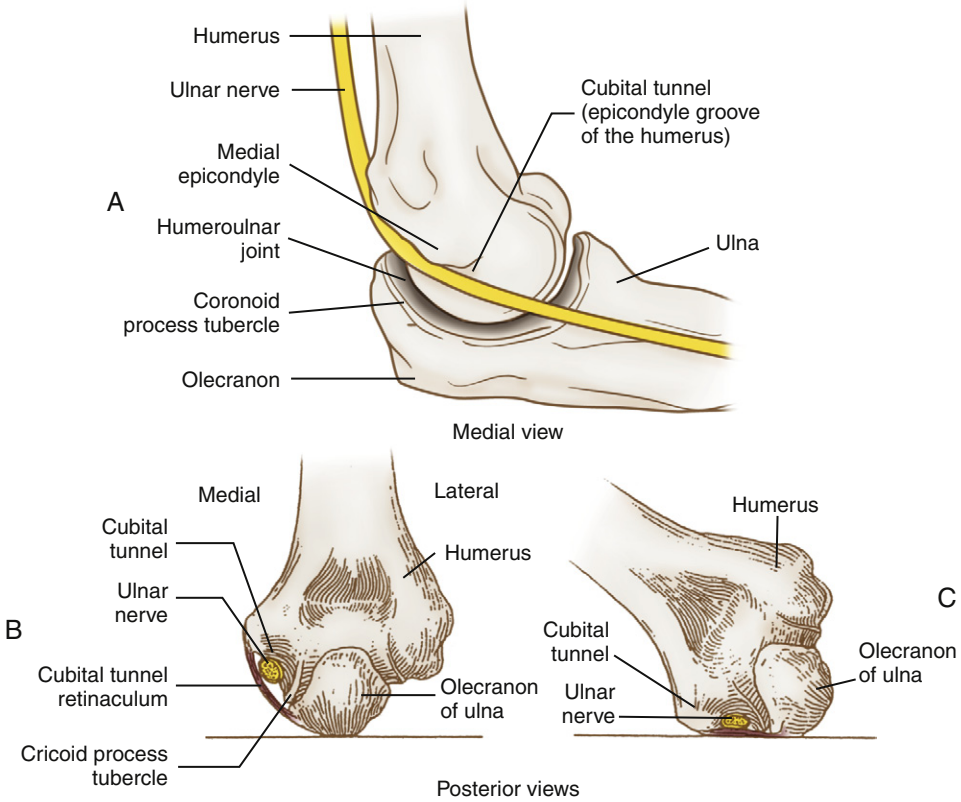

FIGURE **21-2** The ulnar nerve at the cubital tunnel. **A,** Medial view. **B,** Posterior view. Note cubital tunnel retinaculum over the ulnar nerve in the cubital tunnel. **C,** Posterior view with elbow tilted on medial side. Note the ulnar nerve compressed. (From Rothrock JC. *Alexander's Care of the Patient in Surgery*. 14th ed. St. Louis: Mosby; 2011:152.)

Spreading of the sternal retractor during cardiac surgery causes the clavicle to move posteriorly and the first rib to rotate upward, pinching the plexus between the two.[65] Dissection of the internal mammary artery requires wider, asymmetric chest retraction to allow adequate visualization and may predispose to brachial plexus neuropathy.[65,74] To prevent brachial plexus injury during cardiac surgical procedures, caudad placement of the sternal retractor and avoidance of excessive and prolonged asymmetric chest wall retraction are recommended.[65]

SPINAL CORD INJURY

Cheney et al.[37] compared claims documented since 1990 to the outcome claims in the pre-1990 ASA closed-claims database and found that spinal cord injury claims had surpassed ulnar nerve injury claims. However, spinal cord injury claims were primarily associated with neuraxial blocks in anticoagulated patients and with blocks for acute and chronic pain management. Although rare, hemiparesis and quadriplegia are associated with surgical procedures performed in the sitting and prone positions.[75-77] Mid-cervical flexion myelopathy with temporary or permanent quadriplegia may occur when the head is flexed on the neck in the sitting or prone positions. When the head is flexed, the spinal cord moves anteriorly and may be compressed against the posterior vertebral body. Ischemia may result from a combination of compression and stretch, because the spinal cord lengthens with flexion. Like a rubber band, the cord becomes thinner as it stretches, and the caliber of the vessels supplying the cord can be reduced.[77] Increased vertebral venous pressure is also proposed as leading to postoperative spinal cord injury. The absence of valves between the central venous and epidural venous systems allows direct transmission of increased abdominal or intrathoracic pressure to the vertebral venous systems.[78] Congestion in the veins draining the spinal cord, coupled with hypotension, may result in decreased spinal cord perfusion and the onset of new neurologic deficits.[77]

Somatosensory evoked potentials (SSEPs) have been suggested as being useful in identifying position-related changes in spinal cord function.[79] However, neurologic defects have emerged postoperatively despite normal intraoperative SSEP readings.[80-82] A study by Schwarts et al.[80] evaluated the role of transcranial electric motor-evoked potential (tceMEP) and its recommended use for the detection of not only spinal cord injury but also brachial plexus and ulnar nerve injury due to positioning. Hyperflexion of the head on the neck in any position may be avoided by allowing a minimum of two fingerbreadths between the sternum and mandible.[82]

POSTOPERATIVE VISUAL LOSS

Postoperative visual loss (POVL) is a rare but devastating complication of nonophthalmic surgery. It may occur in one or both eyes and refers to a variety of visual defects ranging from decreased visual acuity to total blindness.[83] Visual loss after nonophthalmic surgery is generally attributable to five causes: ischemic optic neuropathy (ION), central retinal artery occlusion (CRAO), central retinal vein occlusion, cortical blindness, and glycine toxicity.[84] In the ASA POVL registry, ION and CRAO accounted for 81% of all cases, with ION accounting for 89% of POVL after prone spinal procedures.[85]

As the name implies, ION is the result of ischemia in a portion of the optic nerve. The optic nerves may be susceptible to hypoperfusion. The central retinal and posterior ciliary arteries are end-arteries

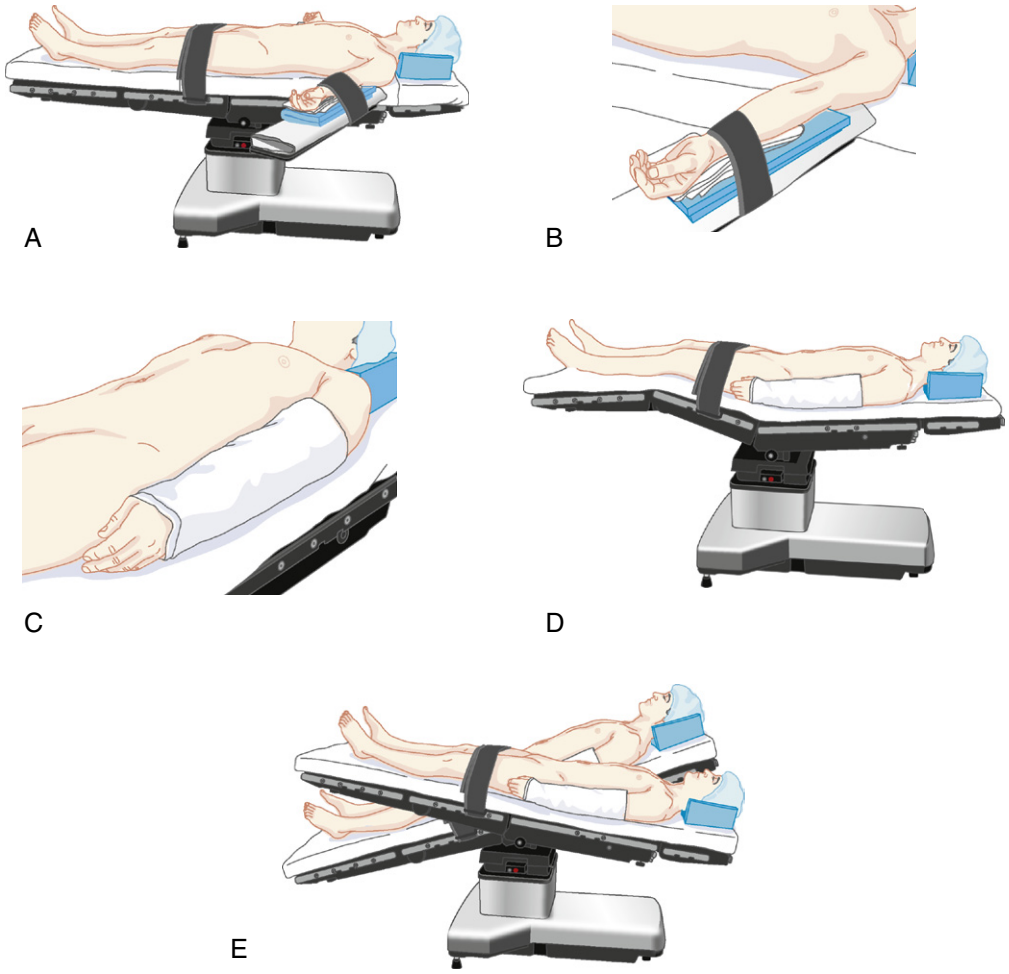

FIGURE **21-3** **A,** Supine. Note the asymmetry of the base of the table, placing the patient's center of gravity over the base if positioned in the usual direction. **B,** Arm position on the armboard. Abduction of the arm should be limited to less than 90 degrees whenever possible. The arm is supinated, and the elbow is padded. **C,** Arm tucked at patient's side. Arm in neutral position with palm to hip. The elbow is padded, and one needs to ensure that the arm is supported. **D,** Lawn-chair position. Flexion of the hips and knees decreases tension on the back. **E,** Trendelenburg position (head tilted down) and reverse Trendelenburg position (head tilted up). Shoulder braces should be avoided to prevent brachial plexus compression injuries. (From Miller RD, Pardo Jr MC. *Basics of Anesthesia*. 6th ed. Philadelphia: Saunders; 2011:302.)

and lack anastomoses with other arteries[86] (Figure 21-5). Thus the structures supplied by these vessels are in a "watershed" region, meaning that the region receives a dual blood supply from the most distal branches of two arteries. Watershed areas are reportedly vulnerable to ischemia if a portion of the blood supply is interrupted.[83,87] Although the ocular circulation lacks autonomic innervation, autoregulation does still occur in the ophthalmic and central retinal arteries.[86] The limits of autoregulation in the ocular circulation are unknown. Preexisting diseases such as diabetes and hypertension that disrupt autoregulatory mechanisms may contribute to ischemic episodes during periods of hypotension.[88]

A variety of patient factors are associated with postoperative ION, including male gender and the presence of coexisting diseases such as hypertension, vascular disease, obesity, and diabetes.[88] Intraoperative factors related to ION include spinal surgery, the prone position, prolonged surgical procedures, large blood loss, low hematocrit, and systolic blood pressure less than 100 mmHg.[88-90] However, ION has occurred in both healthy patients and in the absence of these intraoperative factors.[90,91]

The most common causes of ION are decreased perfusion and increased intraocular pressure.[83] Just as cerebral perfusion pressure equals mean arterial pressure (MAP) minus intracranial pressure, ocular perfusion pressure (OPP) is the difference between MAP and intraocular pressure (IOP).[92,93] Intraoperative and anesthetic events that decrease MAP and thus reduce OPP include general anesthetics, hypotension, hemorrhage, and hypovolemia. Venous pressure and the ratio of aqueous humor production to absorption affect IOP. An increase in venous pressure may impede aqueous humor outflow into the venous system, causing a rise in IOP.[93] As IOP approaches MAP, OPP will decrease. During surgery, ocular venous pressure can be increased by a head-down tilt, increased abdominal and right atrial pressure, and obstruction of jugular venous return.[87] Both steep Trendelenburg position and beds such as the Wilson frame, where the head is positioned much lower than the heart, may exacerbate venous congestion and increase IOP. Unlike CRAO, ION does not seem to be associated with pressure on the globe, because ION has occurred in patients whose heads were secured with pin-type headrests.[85]

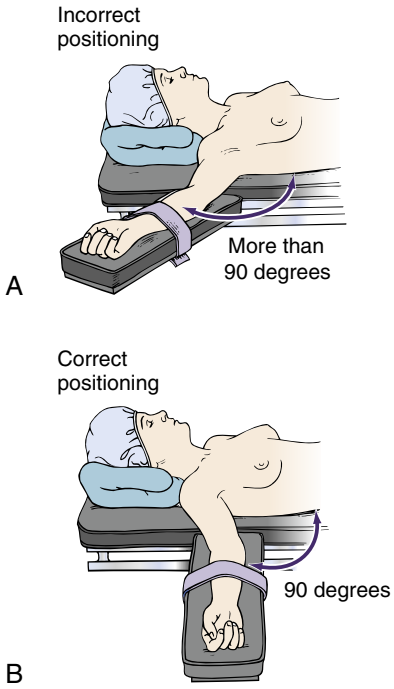

FIGURE **21-4** Position of arm on armboard should not exceed 90 degrees because otherwise injury to the brachial plexus may result. **A,** Incorrect positioning. **B,** Correct positioning. (From Phillips N. *Berry & Kohn's Operating Room Technique*. 12th ed. St. Louis: Mosby; 2013:499.)

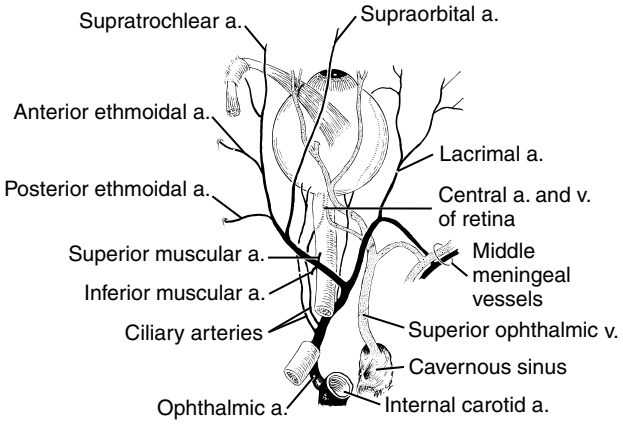

FIGURE **21-5** Superior view of the orbital arteries and veins. *a*, Artery; *v*, vein.

CRAO is a less common cause of POVL than ION. In 93 cases of POVL following prone spinal surgery, only 10 cases were attributed to CRAO.[85] The central retinal artery is one of the first branches of the internal carotid artery and nourishes the internal layer of the retina. Emboli from the ipsilateral carotid can migrate to the central retinal artery and cause unilateral blindness. Perioperative factors associated with CRAO are cardiopulmonary bypass, hypotension, and increased extraocular pressure. Some recovery of vision is possible if blood flow is restored within 4 hours. Although many treatments are recommended for CRAO, few have proven efficacy.[93]

General risk factors for central retinal vein obstruction syndrome include hypertension, cardiovascular disease, increased body mass index, open angle glaucoma, and sickle cell anemia. Because external pressure on the globe may cause central retinal vein obstruction, when the patient is placed prone for procedures on the head and neck, some suggest the use of three-pin headrests that securely immobilize the head rather than the horseshoe headrest.[84] Although the three-pin headrest avoids the potential for external ocular compression, POVL from ION has occurred despite its use.[85] Visual changes caused by central retinal vein obstruction can be subtle or marked, but in either situation, the prognosis for recovery of vision is poor.[84] No definitive treatment is available for central retinal vein obstruction.

Cortical blindness is the result of ischemia or trauma and a subsequent infarction of the visual pathways in the parietal or occipital lobes. Operative causes of cortical blindness include air and particulate emboli, cardiopulmonary bypass, and hypoperfusion resulting from hemorrhage or hypotension. No specific treatment is available for cortical blindness. Vision may improve over time.[84]

Glycine toxicity is a rare syndrome that occurs in patients with a deficiency of L-arginine, the enzyme needed to metabolize ammonia. Ammonia is a by-product of the metabolism of glycine, a nonessential amino acid, to glycolytic acid and ammonia. Temporary vision loss occurs in these patients as a consequence of high blood ammonia levels. Vision returns to normal as blood ammonia levels decrease.[94,95]

Much remains to be learned about POVL. Although factors such as hypertension, vascular disease, obesity, and smoking have been associated with POVL, specific methods for identifying at-risk patients are not available, and reasons that POVL occurs in patients without obvious risk factors are unknown. Patients at high risk of developing POVL include those undergoing lengthy procedures in the prone or steep Trendelenburg position, especially if surgery is accompanied by significant blood loss. During the preoperative interview, high-risk patients should be informed of the risk of POVL. Recently, research has been done regarding the use of intraoperative IOP monitoring, but presently there are no intraoperative monitoring methods that might detect the onset of POVL. Although periodic intraoperative monitoring of hemoglobin or hematocrit is suggested, safe lower limits for hematocrit are unknown. Deliberate hypotensive techniques to prevent blood loss during spine surgery should be avoided in individuals with chronic hypertension or other factors that place them at risk for POVL. Avoidance of direct pressure over the eye is recommended to avoid CRAO. The prone patient's head should be placed in a neutral position (avoid excessive flexion) and level with or slightly elevated above the heart (10-degree head-up tilt) when possible[96] (Figure 21-6). This prone position with the horseshoe adapter is the least preferred head support technique because of pressure on the eye and POVL (Figure 21-6, C and *D*). It should only be used for short procedures. The foam head pillows with cutouts are preferred (Figure 21-6, A). A complete discussion of POVL associated with prone positioning for orthopedic procedures can be found in Chapter 40.

OTHER POSITION-RELATED INJURIES

Position-related injuries range from minor skin abrasions and backache to events with serious morbidity (Table 21-2). Complications of these injuries can lead to tissue necrosis, infection, renal failure, paralysis, loss of limbs, and even loss of life. Although most individuals recover from minor position-related injuries without sequelae, more serious injuries may prolong a patient's hospital stay and recovery, cause psychological trauma, and perhaps even result in permanent disability. Anesthetists must not minimize the physical, psychological, social, and financial impact of transient injuries that resolve over hours, days, or months. Permanent, disabling injuries are even more devastating to patients and providers.

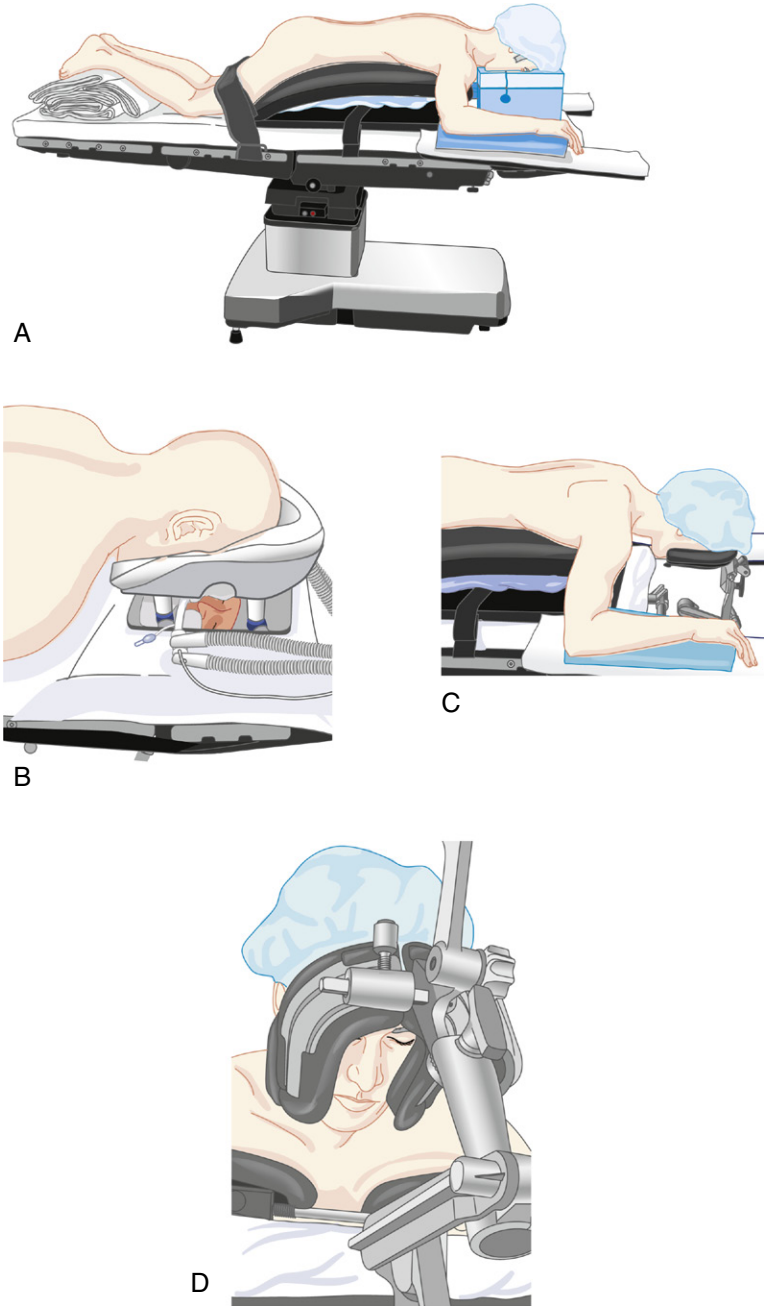

FIGURE **21-6** **A,** Prone position with Wilson frame. Arms are abducted less than 90 degrees whenever possible. Pressure points are padded, and chest and abdomen are supported away from the bed to minimize abdominal pressure and preserve pulmonary compliance. Foam head pillow has cutouts for eyes and nose and a slot to permit the endotracheal tube to exit. Eyes must be checked frequently. **B,** Mirror system for prone position. Bony structures of the head and face are supported, and monitoring of eyes and airway is facilitated with a plastic mirror. **C,** Prone position with horseshoe adapter. Head height is adjusted to position neck in a neutral position. **D,** Prone position, face seen from below. Horseshoe adapter permits superior access to airway and visualization of eyes. Width may be adjusted to ensure proper support by facial bones. (From Miller RD, Pardo Jr MC. *Basics of Anesthesia.* 6th ed. Philadelphia: Saunders; 2011:307.)

Compartment Syndrome

Compartment syndrome is a potentially life-threatening complication that causes damage to neural and vascular structures from tissue swelling as a result of increased pressures and decreased tissue perfusion in muscles with tight fascial borders. Because tissue swelling typically occurs when blood flow returns after a period of ischemia, the syndrome has also been dubbed a "reperfusion injury." Increased compartmental pressure compromises arteriolar supply and results in ischemia with subsequent muscle and nerve infarction.[44,97-99] Although compartment syndrome occurs most often in the extremities, abdominal compartment syndrome also occurs after tight wound closures.[100]

Compartment syndrome takes place as a result of a variety of reasons such as (1) systemic hypotension that falls below perfusion

TABLE 21-2 Common Nerve Injuries: Etiology and Prevention

Nerve/Nerve Group Injured	Potential Cause	Positioning Recommendation
Brachial plexus	*Supine, Trendelenburg, Lithotomy*	
	Arm abducted more than 90 degrees on armboard	Do not abduct arm more than 90 degrees
	Arm falls off table edge and is abducted and externally rotated	Ensure arms are adequately secured
	Arm abduction and lateral flexion of the head to the opposite side	Support head to maintain neutral alignment
	Trendelenburg	
	Shoulder braces placed too medial or lateral	Place well-padded shoulder brace over the acromioclavicular joint Avoid use if possible
	Lateral	
	Thorax pressure exertion on dependent shoulder and axilla	Place roll caudad to the axilla supporting the upper part of the thorax
	Prone	
	Arms abducted more than 90 degrees	Abduct arms minimally
Ulnar nerve	Arm pronated on armboard	Supinate forearm on padded armboard
	Arms folded across abdomen or chest with elbows flexed more than 90 degrees	Do not flex elbows more than 90 degrees
	Arms secured at side with inadequate padding at the elbow	Place sufficient padding around elbow
	Arms inadequately secured at side, elbows extend over table edge	Draw sheet should extend above the elbow and be tucked between the patient and the mattress
Radial nerve or circumflex nerve	Arm pressed against vertical positioning or retractor post or pole securing ether screen	Place adequate padding between or ensure arm is not pressing against vertical posts or pole
Suprascapular nerve	Patient in lateral position rolls semi-prone onto dependent arm with shoulder circumduction	Stabilize patient in lateral position
Sciatic nerve	Malnourished/emaciated patient supine or sitting on inadequately padded table	Generous soft padding under buttock
	Legs straight in sitting position	Flex table at knees
	Lithotomy	
	Legs externally rotated with knees extended	Minimal external rotation of legs; knees should be flexed
Common peroneal nerve	*Lithotomy*	
	Fibular neck rests against vertical bar of lithotomy stirrup	Adequate padding between leg and stirrup
	Knees extended, legs externally rotated	Knees flexed with minimal external rotation
	Lateral	
	Undue pressure on downside leg	Padding under the fibular head
Posterior tibial nerve	*Lithotomy*	
	"Knee crutch" stirrups supporting posterior aspect of knees	Generous padding under knees Avoid use of this stirrup for prolonged procedures
Saphenous nerve	*Lithotomy*	
	Foot suspended outside vertical bar, leg rests on bar	Sufficient padding between legs and vertical bar
	Excessive pressure on medial aspect of leg from "knee crutch" stirrups	Sufficient padding between stirrup and leg
Obturator nerve	*Lithotomy*	
	Excessive flexion of the thigh at hip	Minimal hip flexion
Pudendal nerve	Traction of legs against perineal post or orthopedic fracture table	Generous padding between perineum and post

Modified from Walsh J. AANA journal course: update for nurse anesthetists—patient positioning. *AANA J.* 1994; 62(3):289-298; Phillips N. *Berry & Kohn's Operating Room Technique*. 12th ed. St. Louis: Mosby; 2013:489-525; Heizenroth PA. Positioning the patient for surgery. In: Rothrock JC. *Alexander's Care of the Patient in Surgery,* 14th ed. St. Louis: Mosby; 2011:44-173.

pressure; (2) vascular obstruction of major extremity vessels by intrapelvic retractors, by excessive knee or hip flexion, or (3) external compression of the elevated extremity by a poorly padded positioning device or straps and wrapping that are too tight.[97,98] Other risk factors that might contribute to the development of compartment syndrome include lithotomy position, Trendelenburg position, advanced age, extremes of body habitus, patient history of nerve ischemia or neuropathy, connective tissue disease, anemia, prolonged operative duration, and vasoconstrictive drugs.[98-100] Compartment syndrome can be precipitated

by intraoperative hypotension in conjunction with leg elevation that causes low-flow states. Because blood pressure decreases by 0.75 mmHg per centimeter change in height, elevation of the legs puts the patient at greater risk.[97]

Unless the syndrome is promptly diagnosed and treated, permanent neuromuscular damage will occur. Fasciotomy is generally considered the definitive treatment because less aggressive therapies will not release the constricted compartments. If untreated, the syndrome progresses to tissue necrosis with myoglobinuria and acute renal failure (crush syndrome). Amputation and even death can occur.[100]

Although anesthetic technique has not been implicated as causing compartment syndrome, general and regional anesthesia can contribute to intraoperative hypotension and impaired blood flow. Controversy exists over whether regional anesthesia contributes to delayed diagnosis of the syndrome.[100-102]

Venous Air Embolism

Venous air embolism (VAE) is a well-known consequence of surgery performed in the sitting position. However, VAE may occur in any position where a negative pressure gradient exists between the right atrium and the veins at the operative site.[103-106] The precise incidence of VAE is unknown, but there is an increased incidence in surgeries performed in the sitting position.[107-109] Air that enters the right side of the heart can limit gas exchange in the lungs as it displaces blood in the pulmonary vasculature. Complications of VAE are dependent on both the rapidity and volume of air entrainment. Physiologic effects range from no effect for minimal amounts of air to hypotension, arrhythmias, cardiac arrest, and death with larger volumes.[106-109]

Paradoxical air embolism (PAE) can occur in the patient with a patent foramen ovale (PFO). Studies in vivo and in cadavers indicate that the incidence of PFO can be as high as 35% in the general population.[104,107,108] In the patient with PFO, air can enter the systemic circulation when right atrial pressure is greater than left atrial pressure, a reversal of the normal pressure gradient. Very small amounts of air in the arterial system can result in severe cardiovascular and neurologic complications.

Because VAE and PAE carry the potential for serious consequences, identifying individuals at risk for these complications is important. Preoperative transesophageal echocardiograph (TEE) with contrast is the gold standard for detection of PFO in patients scheduled for surgery in the sitting position.[105,109-111] The cost of TEE is thought to be justified because it is a low-risk, semi-invasive procedure and the sequelae of PAE are severe. However, PFO can be present and PAE can occur despite negative preoperative TEE.[109] Because echocardiography is uncomfortable for patients and has rare but serious complications, transcranial Doppler studies are recommended as an alternative, noninvasive approach for detection of PFO.[109,111]

In addition to the use of standard anesthetic monitoring techniques, patients who are susceptible to VAE should be monitored with devices that detect VAE and allow aspiration of entrained air. TEE, Doppler ultrasonography, capnography, and pulmonary artery catheterization vary in their ability to detect intraoperative VAE. TEE is the most sensitive, having the ability to identify emboli less than 0.2 mL/kg, but it is not specific for gas emboli.[108,111] Although TEE is the gold standard for VAE detection and can be used to position right atrial catheters, it also has its disadvantages. TEE requires specialized training, requires considerable time, comes with risk to the patient, and may not provide a continuous monitor of cardiovascular events.

The precordial Doppler is often used to monitor for VAE when patients are in the sitting position. The probe is placed over the third to sixth intercostal spaces to the right of the sternum. The Doppler is equally as sensitive as TEE and less expensive and cumbersome. However, it does not have the advantage of localizing entrained air within the cardiac chambers, it is sensitive to electrical interference from operating room equipment, and its effectiveness can be reduced by auditory fatigue in the anesthetist.[106,108,111] False positives can be generated by rapid infusion of fluid or flushing transducers. Most frequently used for sitting cases, Doppler devices have not traditionally been advocated for management of VAE during procedures performed in the prone position because of the excessive pressure that it may exert on the chest wall.

VAE increases dead space and contains nitrogen; monitoring capnography will reveal a drop in end-tidal CO_2 and the presence of end-tidal nitrogen. A "mill-wheel murmur" is a characteristic of VAE that can be heard through the esophageal or precordial stethoscope.[111] Air in the coronary arteries can cause ischemic electrocardiographic changes, and air in the pulmonary vessels can result in an increase in PAP and hypoxia. These signs occur later than changes detected by TEE, Doppler, or capnography and are indicative of PAE or large emboli.

Entrained air emboli can be removed from the circulation by aspiration through a multiorifice central venous catheter. For patients undergoing surgery in the sitting position, the catheter is placed in the right atrium at the junction of the superior vena cava.[105,111] Patients who are prone should have the CVP catheter positioned at the junction of the inferior vena cava (IVC) and right atrium because air emboli from spinal surgery enter the venous circulation through the lumbar epidural veins and IVC. The risks of central venous catheter placement, the potential for VAE, and the cardiopulmonary risks of the position must be weighed against the benefits of fluid volume management and air recovery with a CVP catheter. See Chapter 28, Neuroanatomy, Neurophysiology, and Neuroanesthesia for further discussion.

Airway Complications of Surgical Positions

Anesthetized patients in various surgical postures are vulnerable to endotracheal tube displacement, airway edema, and passive regurgitation. The endotracheal tube may become dislodged, kinked, or disconnected when the patient is moved or upon position change. A right mainstem intubation may occur as a result of flexion of the neck or when the patient is placed in steep Trendelenburg position. With neck flexion, the endotracheal tube moves downward and may inadvertently enter the right mainstem bronchus.[112,113] In the Trendelenburg position, pressure of the abdominal contents force the diaphragm cephalad and may cause a similar occurrence.[27] The endotracheal tube can become kinked with extreme degrees of flexion or may compress the arytenoids and epiglottis, resulting in postoperative supraglottic edema.

Extensive edema of the face, tongue, and oropharyngeal structures has been reported after procedures in the prone, head-down, and sitting positions.[114,115] In the prone and head-down positions, gravitational forces or increases in hydrostatic pressures may restrict venous return from the head and neck. Excessive flexion of the head on the neck with patients in the sitting position may obstruct jugular venous return, resulting in macroglossia and airway edema. Oral airways, endotracheal tubes, and esophageal stethoscopes may compress the base of the tongue and limit lymphatic drainage.[114] Macroglossia or upper airway edema may necessitate leaving the patient intubated after surgery until the edema subsides.[115] It may be prudent to verify an air leak around the endotracheal tube or examine the larynx via direct laryngoscopy before extubation in suspected patients.

SURGICAL POSITIONING

The Supine Position (Dorsal Decubitus)

The supine position is most frequently used for surgical procedures on the abdomen, head, neck, extremities, and chest, owing to the favorable exposure it allows. When positioning the patient supine, the head should be maintained in a neutral position on a small pillow or donut. The arms should be either comfortably positioned and secured alongside the trunk or positioned on padded arm boards.[32,82,113] If the patient has severe arthritis, decreased mobility of the head and neck, or neuropathy of the upper extremities, it is best to position the patient to his or her preference prior to the induction of anesthesia. During prolonged procedures, the head should be repositioned at intervals and the occiput massaged to prevent alopecia due to prolonged pressure. Gel-type donuts may more evenly distribute pressure.[38]

The ligaments of the vertebral column relax with anesthesia and can result in postoperative backache. A small support pad may be placed under the lumbar spine to prevent postoperative back pain due to abolition of the normal lumbosacral curve. Placing a pillow under the patient's knees or placing the table in a slight "lounge chair" position, with the patient's hips and knees flexed and the trunk slightly elevated increases patient comfort.[32,113] The legs must remain uncrossed to avoid pressure from the superior extremity damaging the superficial peroneal nerve in the dependent leg and the sural nerve in the superior leg. If prolonged surgery is anticipated, the heels should be elevated off the mattress to prevent pressure sores; however, using too large a support to elevate the heels can cause hyperextension of the knees and pain postoperatively. Gel pads or mattresses more evenly distribute the patient's body weight and prevent reddened areas after lengthy procedures.[32]

If the arms are tucked, the elbow must not be allowed to hang over the edge of the operating table because ulnar nerve damage may occur. When tucked, the hands should be placed in a neutral position, the elbow padded, with the palms facing the hip[66,67,70] (see Figure 21-3). If the arms are secured on armboards, the forearm should be supinated; pronation may result in compression of the ulnar nerve against the armboard. The arms should be abducted less than 90 degrees, and the head should be maintained in a neutral position to avoid brachial plexus stretch injuries.[67,70,71]

Trendelenburg/Reverse Trendelenburg Positions

Trendelenburg position (head-down position) is often used to increase venous return during episodes of hypotension and is also used to supplement the primary surgical position and improve surgical exposure. Physiologic alterations vary greatly depending on the degree of tilt and the primary position. An increase in central venous, intracranial, and intraocular pressures is observed with the Trendelenburg position and may contribute to edema of the face, tongue, oropharynx, and eyes.[10-13,116] Various complications have been observed as outcomes of the Trendelenburg position. Many are the result of devices. Improperly positioned shoulder braces designed to prevent the patient from sliding when in a steep Trendelenburg position can injure the brachial plexus. Placement of the shoulder brace in a position that is placed too medial can result in depression of underlying bony structures and compression of the plexus. Braces placed too lateral may result in a stretch injury of the brachial plexus. The brace should be placed over the acromioclavicular joint and should be avoided if at all possible because nerve injury can still occur despite proper placement.[11-13,70,117] The arms are vulnerable to injury in the Trendelenburg position, particularly if they are positioned on armboards and inadequately restrained. The arms can slip off, hyperextend, and abduct above the level of the shoulder, stretching the plexus.[11,70,82]

The reverse Trendelenburg position (head-up position), often used in laparoscopic surgeries, can also predispose patients to injury. The positioning of the head higher than the heart reduces perfusion pressure to the brain and should be monitored closely. When too tight, table straps used to prevent the patient from sliding in the reverse Trendelenburg position have resulted in lower-extremity neuropathies[70] (see Figure 21-3). The use of a foot board is preferable to the overzealous tightening of the table strap if a steep reverse Trendelenburg position is necessary.

The Lithotomy Position

The lithotomy position is used for surgical procedures that require access to any perineal structure. In the typical lithotomy position, the legs are held in flexion and abduction above the level of the torso by a leg-holding device (Figure 21-7).[38] Depending on the distance the legs are elevated above the torso, the position is identified as *low*, *standard*, *high*, or *exaggerated lithotomy* (Figure 21-8). In low lithotomy position, the legs are almost level with the torso, whereas in exaggerated lithotomy position, the legs are suspended with boots or stirrups so that the feet are well above the body. A hemilithotomy position, with one leg elevated, is also used for some orthopedic procedures.[38,70,113]

The arms are usually positioned either tucked at the sides or abducted on armboards. In the hemilithotomy position, one arm may be secured across the chest. The same cautions for positioning the upper extremity apply as in the supine position. Strict attention must be paid to the fingers, if the arms are tucked at the sides, to avoid a potentially disastrous crush injury or amputation if they become trapped when the foot section is raised.[70,82,113] Many neurovascular complications occur in the lithotomy position because of the position of the leg and hip. Both legs should be elevated and lowered simultaneously when they are placed in a leg-holding device; raising and lowering the legs separately can cause hip dislocation, spinal torsion, or postoperative back pain.[38,70] Acute abduction and external rotation of the hips can also cause femoral nerve or lumbosacral plexus stretch injuries. Flexion of the hips more than 90 degrees in the lithotomy position can cause neural damage by stretching the sciatic and obturator nerves or by direct pressure of femoral neurovascular structures under the inguinal ligament, with subsequent arterial or venous occlusion and nerve palsy.[38,70,117,118] Leg holders that support the leg under the knee can compromise vascular structures in the popliteal space.

Peroneal nerve injury is frequently associated with the lithotomy position because of its anatomic course.[28,30] The nerves crosses the knee joint laterally and wraps around the fibular head before traveling down the lower leg. Depending on the type of leg holder used, the nerve can be injured by compression against the upright bar or against the supporting cradle of the leg holder. The saphenous nerve courses down the medial aspect of the lower leg and is also at risk for compression in the leg holder. Care must be taken to adequately pad any points of potential compression.[70,116]

The Lateral Decubitus Position

The lateral decubitus position is often used for surgeries involving the thorax and kidneys when the supine position cannot provide sufficient exposure. Orthopedic procedures involving the hips, shoulders, or extremities can also require this position for better access to the surgical site. When a nephrectomy is performed using a lateral approach, exposure of the kidney can be facilitated by elevating the kidney rest beneath the dependent iliac crest and flexing the operating table so that the operative flank is higher than the upper torso or legs (Figure 21-9).[38,70,82]

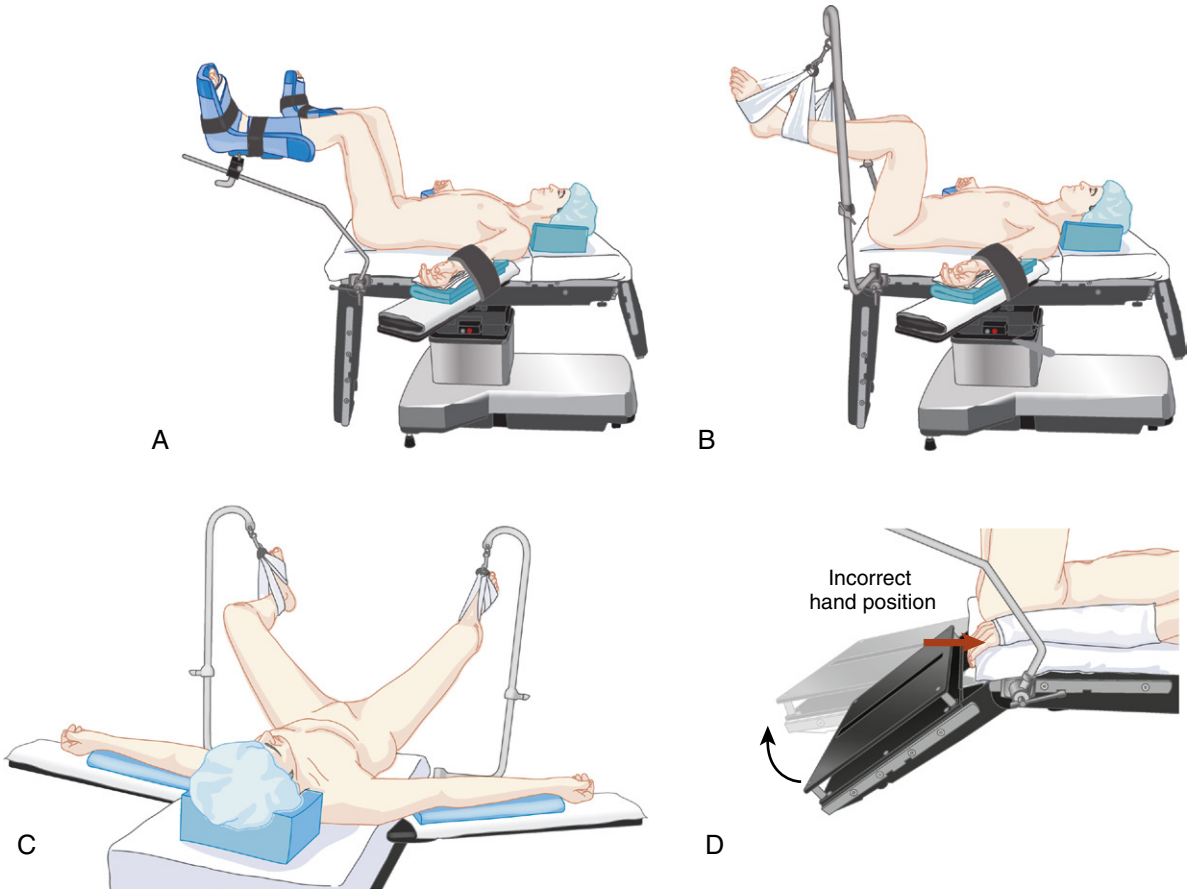

FIGURE **21-7** **A,** Lithotomy position. Hips are flexed 80 to 100 degrees with the lower leg parallel to the body. Arms are on armrests away from the hinge point of the foot section. **B,** Lithotomy position with "candy cane" supports. **C,** Lithotomy position with correct position of "candy cane" stirrups away from lateral fibular head. **D,** Improper position of arms in lithotomy position with fingers at risk for compression when the lower section of the bed is raised. (From Miller RD, Pardo Jr MC. *Basics of Anesthesia*. 6th ed. Philadelphia: Saunders; 2011:304.)

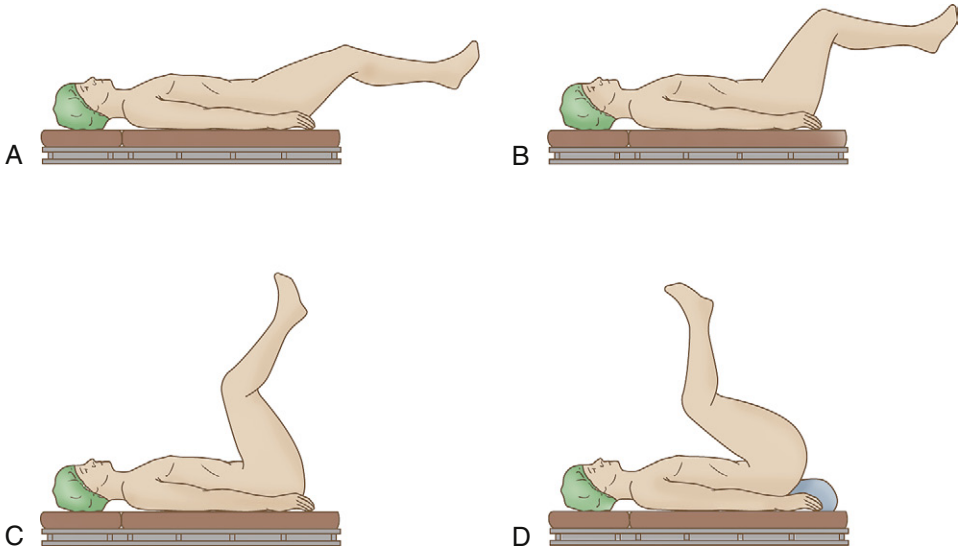

FIGURE **21-8** Four basic types of lithotomy position with progressively increasing leg elevation. **A,** Low. **B,** Standard. **C,** High. **D,** Exaggerated. (From Rothrock JC. *Alexander's Care of the Patient in Surgery*. 14th ed. St. Louis: Mosby; 2011:165.)

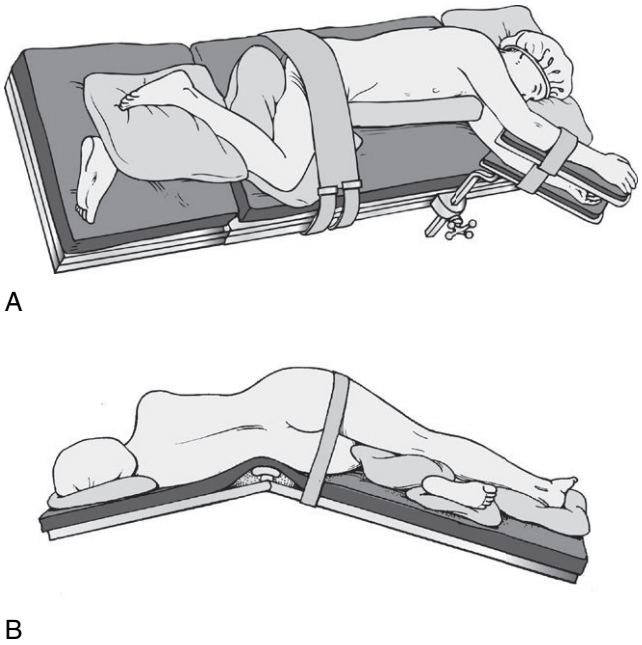

FIGURE **21-9** **A,** Standard left lateral decubitus position. **B,** Flexed lateral position with the kidney rest properly elevated under the iliac crest. (From Phillips N. *Berry & Kohn's Operating Room Technique*. 12th ed. St Louis: Mosby; 2013:507-508.)

Initially the patient is placed supine for induction of anesthesia and intubation. If a beanbag is used to support the torso, it is placed flat on the operating table prior to the patient's arrival in the OR. Before the patient is positioned, the endotracheal tube, breathing circuit, intravenous and monitoring lines, and any other devices should be secured so that none are beneath the body after the turn. The anesthetist should control the airway, head, and neck, as well as coordinate the turn.

Particular attention should be paid to body alignment in the lateral position. The shoulders, hips, head, and legs are maintained in the same plane and turned simultaneously to avoid stress and twisting of the torso and spine (Figure 21-10). The head and neck remain aligned with the spine in a neutral position. The head should be supported on pillows or a donut and not allowed to hang, tilt laterally, hyperflex, or hyperextend (see Figure 21-9). The dependent eye and ear must be free of pressure. A gel donut is useful for keeping the dependent ear suspended and pressure free.

Once the patient is in the lateral position, flexing the knee and hip of the dependent leg stabilizes the patient. The nondependent leg remains straight and is supported by a pillow placed between the lower extremities. Positioning the legs in this manner prevents bony prominences of the legs from resting on each other and reduces compression of the inferior leg by the superior extremity (see Figure 21-9, A). Padding should be placed along the lateral aspect of the dependent leg, extending from the knee to the heel to protect the peroneal nerve from external pressure against the table or beanbag.[28,68]

The dependent arm is positioned on a padded armboard perpendicular to the torso and flexed less than 90 degrees at the elbow.[28,68] The nondependent arm is placed to avoid interference with surgical exposure—usually parallel to the dependent arm and level with the shoulder on a well-padded arm-holding device. Alternatively, both arms may be positioned on a single armboard with adequate padding between them. Perfusion to the upper extremities, especially the dependent arm, should be periodically assessed by palpating the radial artery and checking capillary refill.[28,82]

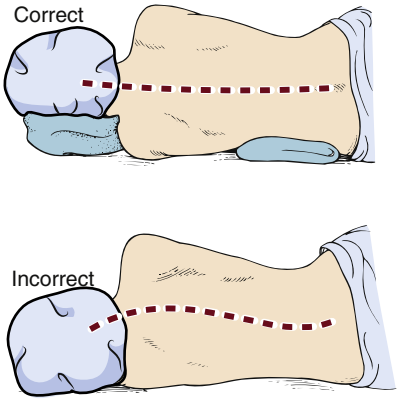

FIGURE **21-10** Proper alignment of spinal column in lateral position. (From Phillips N. *Berry & Kohn's Operating Room Technique*. 12th ed. St. Louis: Mosby; 2013: 507.)

The dependent shoulder and upper extremity are susceptible to compression in the lateral position. A small roll (axillary roll) is placed under the dependent side of the thorax, slightly caudad to, but not directly in the axilla, to lift the thorax and relieve pressure exerted on the shoulder, axillary vessels, and brachial plexus of the dependent arm.[82,119] It is useful to obtain blood pressures in the nondependent arm because of potential for neurovascular compression in the dependent arm from the blood pressure cuff.[82]

Ancillary positioning devices such as beanbags, pillows, sandbags, braces, and adhesive tape aid in securing the patient and preventing rotation of the trunk. If tape or straps are used to stabilize the torso, they should be placed just caudal to the axilla to reduce the risk of brachial plexus injury.[38] Placement across the ribs can impair ventilation. Soft tissue injury may occur if straps or tape is overly tight.

Rhabdomyolysis has been reported after use of the lateral decubitus position.[120,121] Prolonged operating time, hypotension, and pressure of the operating table against gluteal and flank muscles have been described as contributory factors. The anesthetist, as well as the entire operating team, should ensure that the operating table is well padded and that positioning devices are properly placed. Furthermore, prolonged or excessive hypotension should be avoided to ensure adequate tissue perfusion.

The Sitting Position

The term *sitting position* commonly refers to any position in which the torso is elevated from the supine position and is higher than the legs. A true sitting position in which the torso is elevated at 90 degrees to the legs is rarely used. The modified sitting position, in which the torso is elevated 45 degrees, the head is flexed, and the legs are elevated and flexed at heart level, is probably most commonly used. This position is variously described as the *lounging*, *lawn chair*, or *beach chair* position.[38] Although its use is reportedly decreasing in popularity, some neurosurgeons favor the sitting position for posterior fossa and cervical spine procedures because it allows excellent visualization of intracranial structures and facilitates drainage of blood and cerebral spinal fluid from the wound. During shoulder arthroplasty and arthroscopy, the sitting position reduces brachial plexus stretch and aids surgical exposure and manipulation of the arm and shoulder.[122]

Placement of the patient in the sitting position involves flexion of the operating room table, elevation of the backrest and legs, and head-down rotation. The degree of torso elevation desired

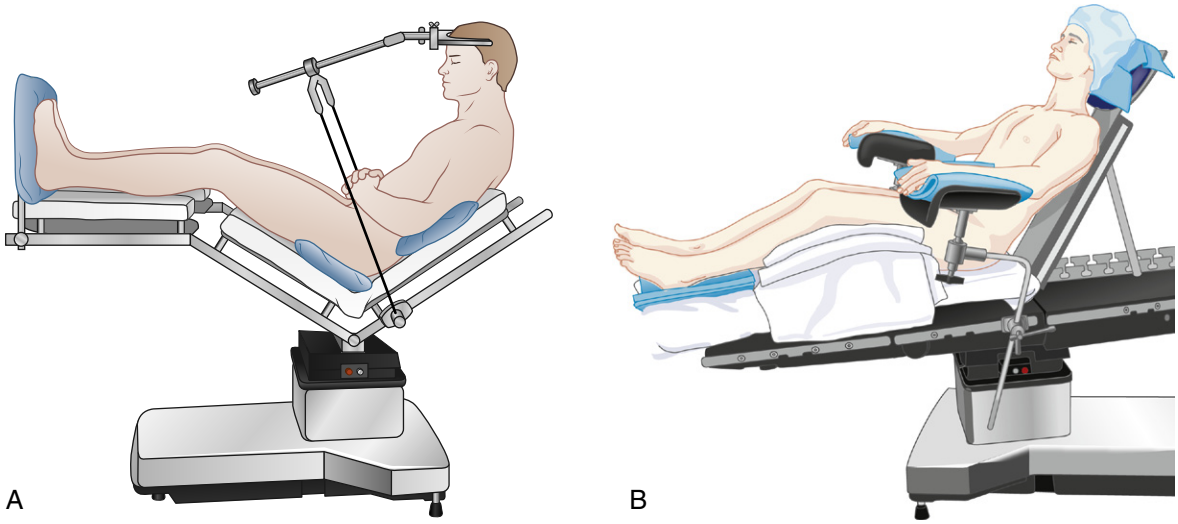

FIGURE **21-11** **A,** Sitting position with Mayfield head pins. The patient is typically semirecumbent rather than sitting because the legs are kept as high as possible to promote venous return. Arms must be supported to prevent shoulder traction. Note that the head holder support is preferably attached to the back section rather than the thigh section of the table so that the patient's back may be adjusted or lowered emergently without first detaching the head holder. **B,** Sitting position adapted for shoulder surgery. Note the absence of pressure over the ulnar area of the elbow. (From Miller RD, Pardo Jr MC. *Basics of Anesthesia*. 6th ed. Philadelphia: Saunders; 2011:309.)

determines the amount of operating table manipulation required. For neurosurgical procedures, a three-pin head holder is generally used to secure the head. The device provides better head stabilization compared with horseshoe-type headrests and avoids eye compression, but jugular venous obstruction can occur if the head is excessively flexed on the neck. At least two fingerbreadths of space should be allowed between the neck and mandible. Incorrect placement of the head holder and direct contact of its metal bars with the nose or skin can cause pressure necrosis[8,9,105,106] (Figure 21-11).

A horseshoe headrest is often used to support the head for shoulder procedures performed in the sitting position. Straps or adhesive tape secure the head to the headrest. Vigorous surgical manipulation of the arm and shoulder can move the patient's body toward the operative side of the table. If the head is firmly secured to the headrest, excessive traction or stretch can be placed on the neck and brachial plexus. If the restraining straps are loose, the head can become partially or completely dislodged from the headrest, introducing the potential for cervical spine injury. Accidental extubation can occur if the endotracheal tube is secured by a supporting device and the head is displaced. Profound hypotension and bradycardia from activation of the Bezold-Jarisch reflex may occur when shoulder surgery is performed in the sitting position under an interscalene block.[112,122]

Serious complications associated with the sitting position are among the reasons that the position is falling out of favor. VAE is the most feared complication, but pneumocephalus, quadriplegia, and peripheral nerve injuries are also possible. Pneumocephalus is a frequent occurrence after neurosurgical procedures performed using the sitting or supine positions and is typically a benign condition. Gravity is the most important factor in the development of pneumocephalus. Opening of the dura, drainage of cerebrospinal fluid, and surgical decompression allow relaxation of the brain and entrance of air, which rises to the top of the cranial vault. Contributing factors are those that decrease brain volume, such as the use of diuretics, hypocarbia, the presence of intraventricular shunts, and gross hydrocephalus.[123,124] Tension pneumocephalus, on the other hand, rarely occurs, but its advent requires immediate intervention to prevent rapid deterioration of the patient. The onset of tension pneumocephalus manifests as restlessness, deterioration of consciousness, convulsions, or other changes in neurologic status. Definitive diagnosis is made by the presence of air on computed tomographic scan. Prompt evacuation of the air collection through twist drill holes is indicated.[125,126]

The Prone Position

The prone position provides optimal exposure for a variety of procedures performed on the spine, certain orthopedic procedures, and some rectal procedures. The prone position has also been advocated for intracranial procedures, owing to the decreased risk of venous air embolism compared with the sitting position. Many modifications of the prone position exist (Figure 21-12). Anesthetists must become familiar with the various methods of securing the patient in the prone position and recognize the potential hazards of each variation or device.

In the prone position, the torso is typically supported on a frame or with rolls that extend from the shoulders to the iliac crests. Alternatively, supports can be placed crosswise at the pelvis and shoulders. The lower legs are supported with pillows, and the upper extremities may be tucked at the sides or supported on armboards with the arms flexed at the shoulders and elbows. Care must be taken to pad pressure points at elbows, knees, and ankles. Breasts and genitalia must be positioned to limit pressure on them.[68,70]

When a prone approach is planned, the patient is anesthetized on the gurney and then log-rolled onto the bed, frame, or rolls with good body alignment maintained. Thoughtful planning of monitor placement allows turning without removal of monitors during this critical period and avoids delays. Typically the patient is disconnected from the breathing circuit to avoid accidental extubation. The anesthetist should control the airway, head, and neck, as well as coordinate the turn.

Head, neck, shoulder, and arm mobility must be assessed preoperatively; arm placement can be limited by ankylosis of shoulder or elbow joints. Depending on the surgeon's preference, the arms

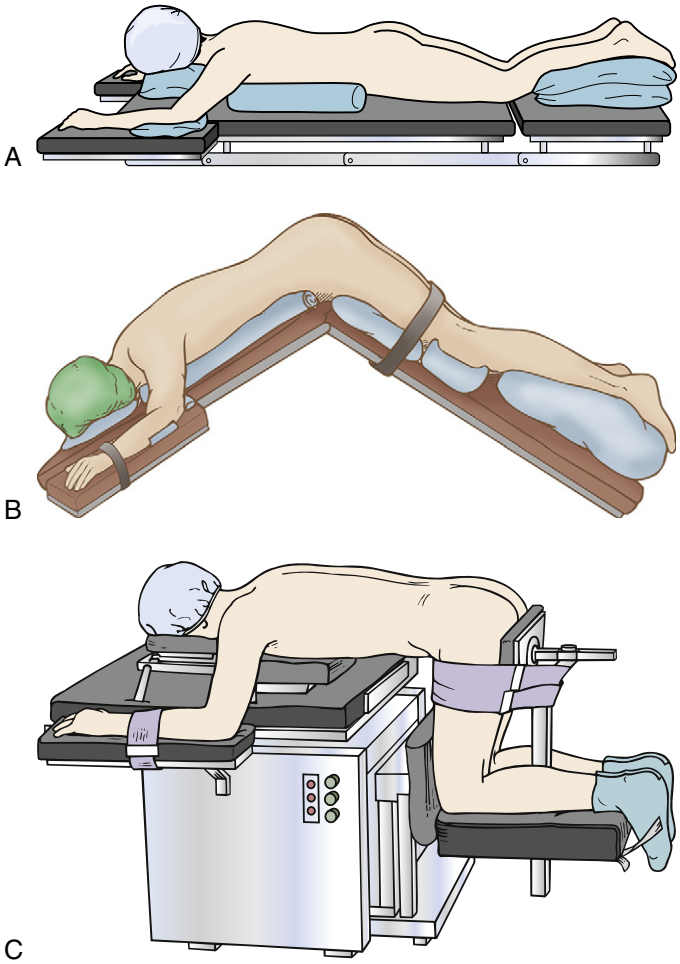

FIGURE **21-12** Variations of the prone position. **A,** Classic prone position with the torso supported on chest rolls. **B,** Jackknife position. **C,** Knee-chest position. (**A,** from Phillips N. *Berry & Kohn's Operating Room Technique*. 12th ed. St Louis: Mosby; 2013:506; **B** and **C** from Rothrock JC. *Alexander's Care of the Patient in Surgery*. 14th ed. St Louis: Mosby; 2011:171.)

may be tucked parallel to the sides with a draw sheet or supported on armboards. If tucked, the arms should be secured in a natural position with the palms facing the thighs. Plastic or metal arm "sleds," with sufficient padding, can be used to protect the arms and vascular access sites from compression by the bodies of the surgical team. If the arms are not tucked at the sides, they should be carefully rotated into position. The preferred arm placement is flexed, slightly abducted, and with the forearms and hands lower than the shoulders and adequately supported. The arms should rest at a comfortable height on the armboards and should not support the weight of the shoulders. Padding should be placed under the shoulders to prevent sagging of the shoulders and stretching of the brachial plexus.[33,68,70]

Particular care must be taken to maintain alignment of the head and neck in the prone position. The head should be supported in a neutral position with a head-holding device. Hyperextension or lateral rotation of the neck should be avoided, because either may compromise spinal cord blood flow, especially in elderly individuals with narrowing of the spinal canal due to osteoarthritis. Also, stretch injuries of the brachial plexus may occur with lateral head rotation.[38,68,80]

A primary goal of positioning the prone patient is to avoid pressure on the abdomen, which can impede venous return, increase venous pressures, and interfere with ventilation by inhibiting movement of the diaphragm.[33,82] Valves are not present in the intervertebral veins that drain the vertebral and spinal cord venous plexuses into the lumbar veins. External abdominal pressure is transmitted to the vena cava and communicated to the lumbar epidural veins.[33,38] Positioning devices that allow the abdomen to hang freely are associated with greater decreases in inferior vena cava pressures than those that compress the abdomen and therefore prevent engorgement of spinal venous plexuses. Engorged epidural veins are fragile and easily traumatized, and the ensuing blood loss will decrease surgical exposure and contribute to hypotension. Studies suggest that in the prone position, the degree to which pulmonary mechanics are altered depends on the positioning device used, not on body habitus.[33,82] The Jackson table resulted in the smallest change in pulmonary compliance and peak airway pressures when compared with the Wilson frame and chest rolls. The investigators hypothesized that the Jackson table allows the abdomen to hang freely, permitting better diaphragmatic excursion and lower intraabdominal and intrathoracic pressures.[82]

Meticulous attention must be paid to protection of the eyes, because corneal abrasions and POVL are complications of the prone position.[85] Several devices including three-point skull fixation, the horseshoe headrest, and foam cushions allow the head to be placed in a neutral position while the eyes are kept free of pressure. However, the head may slip or rotate on the horseshoe headrest, allowing pressure to be applied over the globe and placing the patient at risk of central retinal artery thrombosis. Although three-point skull fixation is often recommended for securing the head and protecting the eyes in the prone position, POVL has occurred despite the use of this device.[85]

CLOSED-CLAIMS STUDIES

Surgical positions are associated with numerous potential complications that can be detrimental to a patient's short- and long-term outcomes. Although the potential for various complications is generally well known, the precise incidence and cause of position-related injuries are often difficult to determine. Because the frequency of these events is low, contributing causes are frequently multifactorial, and uniform reporting of mechanisms does not exist. Position-related injuries are thought to be underreported in the scientific literature.[51,37] Fear of litigation or damage to one's professional reputation may prevent anesthesia providers from reporting such events. However, case reports, closed-claims studies, and retrospective analyses of databases can provide insight into position-related injuries and shed light on precipitating causes and outcomes.

Both the American Association of Nurse Anesthetists Foundation (AANA-F) and the American Society of Anesthesiologists (ASA) have conducted studies of closed malpractice claims from professional liability insurance companies. These studies provide a rich source of data about position-related complications. The ASA Closed Claims Project (ASA-CCP) was initiated in 1985. Since then, this ongoing project has collected data on 9214 anesthesia-related claims filed with more than 35 liability insurance carriers.[127,128] Because the ASA-CCP involves primarily anesthesiologists, the AANA-F conducted a similar study to examine outcomes of care provided by CRNAs. The AANA-F database covers 223 cases that occurred between 1989 and 1997 and is derived from records of the primary insurer of CRNAs at that time.[129,130] Dental claims are excluded from both the AANA-F and ASA-CCP studies.

In 2011, the ASA-CCP contained 5230 claims. An analysis of these claims revealed that death (26%), nerve injuries (22%), and permanent brain damage (9%) were the major causes of liability.[51]

Nerve damage included injuries to both the peripheral nervous system and spinal cord but not to the brain. Nerves most commonly affected were the ulnar (28%), brachial plexus (20%), lumbosacral nerve root (16%), and spinal cord (13%). Injuries to all other nerves accounted for only 8% of the nerve damage claims. Although claims for nerve injury have remained constant over time, claims for ulnar nerve injury have decreased while those from spinal cord injury have increased.[37,51]

Specific causative factors could not be identified in the majority of claims in the ASA-CCP. When the association of anesthetic technique with nerve injury was examined, regional anesthesia was more frequently associated with nerve-injury claims—particularly of the spinal cord and lumbosacral nerve root—than general anesthesia. However, 85% of ulnar nerve injuries were associated with general anesthesia. The quality of anesthesia care was judged as appropriate in 66% of all nerve injury claims, as compared with 42% of non–nerve-damage cases. However, care was deemed appropriate in only 46% of spinal cord damage claims. Other factors associated with nerve damage included positioning and positioning devices, intraoperative trauma, and paresthesias during regional block performance.[37]

The AANA-F closed-claims study compared 151 claims (68%) in which a CRNA was judged to have contributed to the adverse outcome (CRNA-related) with 72 claims (32%) in which the CRNA was judged not to have contributed to the adverse event (non–CRNA related).[130] Death (32%), nerve injury (12%), brain injury (12%), and eye injury (10%) were the primary outcomes of CRNA-related claims. No significant difference in the type of outcome was found between CRNA-related claims and non–CRNA-related claims. Reviewers evaluated the appropriateness of care and found care inappropriate in 52% of CRNA-related cases, appropriate for 30%, and impossible to assess in the remaining cases.

A subsequent analysis was conducted of 44 cases of nerve injury in the AANA-F database.[131] The distribution of nerve injuries was as follows: brachial plexus (15 [34%]), ulnar nerve (7 [16%]), radial nerve (5 [11%]), peroneal nerve (4 [9%]), spinal cord (4 [9%]), and lumbosacral nerves (3 [7%]). A variety of other nerves accounted for the remaining injuries. In the majority of claims filed, documentation of the patient's position and the use of protective padding was inadequate, preventing investigators from identifying possible causative factors. However, a higher percentage of nerve injuries were associated with inadequate positioning, preexisting patient conditions, general anesthesia, extremes of body habitus, and procedures lasting longer than 2 hours.

The AANA-F and ASA-CCP studies highlight the importance of following standards of care and properly documenting perioperative activities. Standards for nurse anesthesia practice identify thorough, complete, and accurate documentation as an expectation of nurse anesthesia practice.[132] In the event of a malpractice claim, thorough documentation assists reviewers in determining the quality of care provided.

Quality of care was judged as inappropriate in 34% of nerve injury claims from the ASA-CCP and 52% of all cases in the AANA-F study.[37,130] In both studies, monetary awards were higher in those cases resulting in more severe outcomes and when anesthesia care was determined to be less than appropriate. Although some suggest that position-related nerve injuries are largely preventable,[33] the ASA analysis of nerve injury claims revealed that payouts were frequently made even when anesthesia care was judged appropriate.[37] This suggests that current knowledge of methods for preventing nerve injury is inadequate and that further research into mechanisms of nerve injury is needed.

Several limitations are inherent in closed-claims studies. First, the purpose of data collected by professional liability insurance companies is to investigate malpractice claims, not to improve patient safety. Not all anesthesia-related injuries result in a liability claim. Therefore data from closed-claims studies are not a random or even representative sample, because only those cases in which a claim was filed and subsequently closed are included. Second, the incidence of various outcomes cannot be described because the total number of cases performed by insured providers is unknown.[130] For these two reasons, closed-claims data are not suitable for calculation of risk. However, analysis of closed-claims data can identify issues confronting practitioners and suggest methods for improving practice or making changes in systems.[130,133]

Other factors limit the conclusions that can be drawn from closed-claims data. Many cases that might be included in the database are eliminated because of inadequate documentation. In addition, closed-claim studies and quality assurance data categorize claims by type of injury rather than cause. Inadequate documentation and inability to determine the role played by various factors can limit the ability of reviewers to determine the cause of injury.[51] Finally, reviewers' knowledge of patient outcomes may bias their opinions on the quality of care provided.[129]

SUMMARY

Surgical positioning disturbs normal cardiovascular and respiratory physiology. These positional changes can be augmented by anesthetic techniques, patient pathophysiology, and body habitus. The implications of physiologic changes associated with each position should be considered when the procedure is planned, when positioning is initiated, and when the patient is returned to the supine posture. Anesthetists must recognize and anticipate both the publicized complications and the potential for damage inherent in each surgical position. Prevention is the best method for decreasing both the incidence of position-related injuries and the associated physical, psychological, and economic costs to the patient.

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Airway Management

◆ *Jeremy S. Heiner and Mark H. Gabot*

CHAPTER 22

Effective airway management is a cornerstone of safe anesthesia practice, and it is an essential skill that every nurse anesthetist should possess. Nurse anesthetists are responsible for managing the airway in the operating room as well as other healthcare settings. The maintenance of ventilation and oxygenation are primary goals during airway management for both difficult and routine airways. The best preparation for the management of a difficult airway is through knowledgeable, effective, and regular management of normal airways. Therefore, nurse anesthetists should be familiar with appropriate decision-making strategies and methods for providing adequate ventilation during airway management. These strategies and methods pertain not only to routine (non-difficult) airways but also to anticipated difficult airways, unanticipated difficult intubations or ventilations, failed airways, patients at risk for aspiration of gastric contents, and patients who present with airway obstructions.

An understanding of airway anatomy and appropriate airway assessment techniques will allow the nurse anesthetist to develop a comprehensive airway management plan. Prior to any airway manipulation, the prudent nurse anesthetist should complete a thorough airway examination using multiple airway assessments. The results of these assessments will guide the airway management plan, which may involve placing an airway while the patient is awake or after the induction of anesthesia using a variety of airway adjuncts. Familiarization with the operation of the different airway adjuncts is important so that the nurse anesthetist may become comfortable with their use in a variety of airway management situations and to facilitate safe practices for the establishment of a protected airway.

Removal of an airway management device should be incorporated as part of the overall airway management plan. Nurse anesthetists should consider patient, surgical, and anesthetic risk factors before removing any airway adjunct. When considering an awake or anesthetized extubation technique, the removal of an airway is ultimately determined by the degree of the patient's ability to meet extubation criteria and maintain adequate spontaneous ventilation and oxygenation. Finally, the risk factors and complications of airway management should be understood in order to develop the most appropriate and safe airway management plan for the patient.

ANATOMY AND PHYSIOLOGY OF THE AIRWAY

The airway is divided into upper and lower sections. Anatomic structures above the level of the cricoid cartilage constitute the upper airway and include the nose, mouth, pharynx, hypopharynx, and larynx. Anatomic structures below the level of the cricoid cartilage constitute the lower airway and include trachea, bronchi, bronchioles, terminal bronchioles, respiratory bronchioles, and alveoli. This section reviews primary structures, innervation, blood supply, and normal and abnormal function of the upper airway structures.

Developmental Anatomy

Upper Respiratory Tract

Unlike the structures of the lower respiratory tract, the upper respiratory tract arises from bony structures of the head. Endochondral bone is preformed in cartilage. The bones form initially from the optic, olfactory, and otic capsules. These merge with the midline cartilaginous structures to form the embryologic vestiges of the ethmoid, sphenoid, the petrous portion of the temporal bone, and the base of the occipital bone. Direct ossification of membranous tissue known as the *mesenchyme* occurs during early embryologic development to form membranous bone. The membranous bones include the temporal, parietal, frontal, and portions of the occipital bones and the pharyngeal arches. The pharyngeal arches are complex structures also known as the *branchial arches* that extend anterior to posterior. Development of these structures begins at day 22 (week 4 after fertilization).[1]

Embryologically, there are six arches that develop from five structures. Arches one through four and six go on to develop the airway structures, and the fifth arch disappears with fetal development. The arches all contain a covering of tissue that will eventually become the nerves, muscles, and cartilage of the airway. These will become the tissues of the oropharynx, middle ear, the hyoid bone, and the laryngeal cartilages. Arch one becomes the jaws; arch two becomes the facial structures and the ears; arch three becomes the hyoid bone and structures of the upper pharynx; arches four and six become the structures of the larynx and the lower pharynx; and arch five disappears. The tongue is formed from the mesoderm of multiple arches. The anterior two thirds of the tongue is developed from the first arch. The mesoderm of the third and fourth arches comprises the posterior third of the tongue. Spaces found between the arches are known externally as *clefts* and internally as *pouches*. The cleft between the first two arches becomes the external auditory meatus. The internal pouch between the first and second arches forms the majority of the tympanic cavity and the eustachian tubes. The other clefts disappear as the fetus develops. The pouches contribute to the development of the glandular structures of the head and neck. The palatine tonsils arise from pouch two; the inferior parathyroid glands and the thymus come from pouch three; the superior parathyroid glands arise from pouch four, and the ultimobranchial structures arise from the inferior portion of pouch four.[1]

Nose. The nose and mouth are the external openings to the respiratory tree. The large surface area of the nasal mucosa warms and humidifies inspired air but also provides almost two thirds of the resistance to breathing. The nose is the primary passage by which air enters the lungs. Because of the surface area over the turbinates and the sinuses, the nasal passages are well suited for the task of humidification of air and primary filtration. As air passes through the nose, it meets the turbinates, which cause directional changes in the airflow. Branches of three arteries (e.g., the maxillary [sphenopalatine], ophthalmic, and facial [septal]) provide a rich supply of blood to the

nasal mucosa. The innervation of the nose is from the nasopalatine and ethmoidal branches of the facial nerve. These nerves also supply the nasopharynx, nasal septum, and palate. Sensory-nerve supply to the nasal mucosa is from the ophthalmic and maxillary divisions of the trigeminal nerve. Parasympathetic innervation arises from the seventh cranial nerve and pterygopalatine ganglion. Sympathetic innervation is derived from the superior cervical ganglion. Sympathetic stimulation results in vasoconstriction and shrinkage of the nasal tissue. Depression of the sympathetic nervous system, as occurs with general anesthesia, may cause engorgement of the nasal tissues, increasing the likelihood of bleeding with manipulation from nasal airways or endotracheal tubes.

Mouth. The oral cavity is separated from the nasal passages by the hard and soft palates. The hard palate is stationary and remains in the same position. The soft palate covers the posterior third to half of the oral cavity. The soft palate rises during eating to prevent food and liquids from passing from the mouth into the nose and thereby decreases the chance of aspiration. With age, obesity, and other conditions, this structure may stretch and become more movable. When an individual is asleep or paralyzed, as with general anesthesia, this structure can fall back against the nasal passages, blocking air movement and causing symptoms of sleep apnea. The tongue is a large muscular organ that fills most of the oral cavity and is involved in the tasting and ingestion of food. It relaxes when the individual is either asleep or paralyzed, which increases the potential for airway obstruction. The uvula protects the passageway from the oral cavity into the oropharynx. This pendulous piece of tissue extends from the posterior edge of the middle of the soft palate into the oral cavity. If swollen, enlarged, or injured, it can be a cause of airway obstruction. The tonsils are walnut-shaped structures that sit on both sides of the posterior opening of the oral cavity. They are partially buried in the soft tissue at the base of the tongue and are protected by the anterior and posterior tonsillar pillars.

Pharynx. The pharynx is divided into three compartments: the nasopharynx, oropharynx, and hypopharynx (laryngopharynx). The pharynx extends from the base of the skull to the level of the cricoid cartilage. The nasopharynx lies anterior to C1 and is bound superiorly by the base of the skull and inferiorly by the soft palate. The openings to the auditory (eustachian) tubes and the adenoids are found in the nasopharynx. Sensory innervation of the mucosa is derived from the maxillary division of the trigeminal nerve. The oropharynx lies at the C2 to C3 level and is bound superiorly by the soft palate and inferiorly by the epiglottis. It opens into the mouth anteriorly through the anterior and posterior tonsillar pillars. The hypopharynx lies posterior to the larynx and is bound by the superior border of the epiglottis and the inferior border of the cricoid cartilage at the C5 to C6 level. The upper esophageal sphincter lies at the lower edge of the hypopharynx and arises from the cricopharyngeus muscle. This muscle acts as a barrier to regurgitation in the conscious patient.

Numerous nerves supply motor and sensory fibers to the airway. The glossopharyngeal, vagus, and spinal accessory nerves share nuclei in the medulla and innervate all the muscles of the pharynx, larynx, and soft palate. Afferent (sensory) stimuli elicited when the posterior wall of the pharynx is touched are carried by the glossopharyngeal nerve to the medulla, where they synapse with nuclei of the vagus nerve and the cranial portion of the spinal accessory nerve. The efferent response returns primarily through the vagus nerve, resulting in the gag reflex as the muscles of the pharynx elevate and constrict.

Two branches of the vagus nerve innervate the hypopharynx: the superior laryngeal nerve and the recurrent laryngeal nerve (RLN) (Figure 22-1). The superior laryngeal nerve divides into the internal and external branches. The internal branch of the superior laryngeal nerve provides sensory input to the hypopharynx above the vocal folds (cords). The external branch provides motor function to the cricothyroid muscle of the larynx.

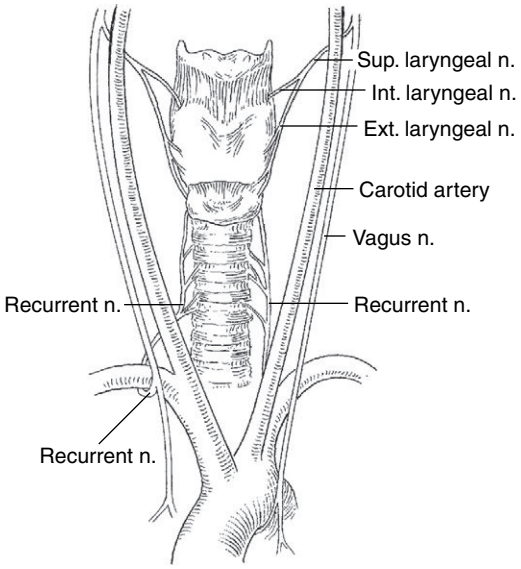


FIGURE **22-1** Anatomy of the right and left, superior and recurrent laryngeal nerves. *n,* Nerve.

The RLN provides sensory innervation to the subglottic area and the trachea. The recurrent laryngeal nerve is so named because it recurs (loops around) other structures. The right recurrent laryngeal nerve recurs around the brachiocephalic (innominate) artery, and the left recurrent laryngeal nerve loops around the aorta. Traction on either of these structures during thoracic surgery can cause injury to the RLN, causing hoarseness or stridor. The motor component of the RLN provides motor function to all the muscles of the larynx except the cricothyroid muscle.

The superior laryngeal nerve and the RLN may be damaged by surgery, neoplasms, and neck trauma. Dissecting aortic arch aneurysms and mitral stenosis place traction on the RLN, causing hoarseness. Unilateral injury to the RLN usually results in hoarseness but does not compromise respiratory status. The vocal cords compensate by shifting the midline toward the uninjured side. In the acute phase of bilateral injury to the RLN, unopposed tension and adduction of the vocal cords result in stridor, which may deteriorate into severe respiratory distress and possibly death. Patients with chronic injury develop compensatory mechanisms that allow for normal respiration and gruff or husky speech. Injury to the superior laryngeal nerve does not usually cause respiratory distress.

Larynx. The larynx begins with the epiglottis and extends to the cricoid cartilage. The larynx is composed of (1) three single cartilages (e.g., thyroid, cricoid, and epiglottis), (2) three paired cartilages (e.g., arytenoid, corniculate, and cuneiform), and (3) intrinsic and extrinsic muscles (Figures 22-2 and 22-3). These structures function in an intricate manner to provide (1) protection to the lower airway from aspiration, (2) patency between the hypopharynx and trachea, (3) protective gag and cough reflexes, and (4) phonation. In the adult, the larynx begins between the third and fourth cervical vertebrae and ends at the level of the sixth cervical vertebra (e.g., cricothyroid muscle). The anterior and lateral larynx is formed by the thyroid cartilage. Anteriorly the thyroid cartilage fuses and forms the thyroid notch. Posteriorly the thyroid cartilage rises toward the hyoid bone at the base of the

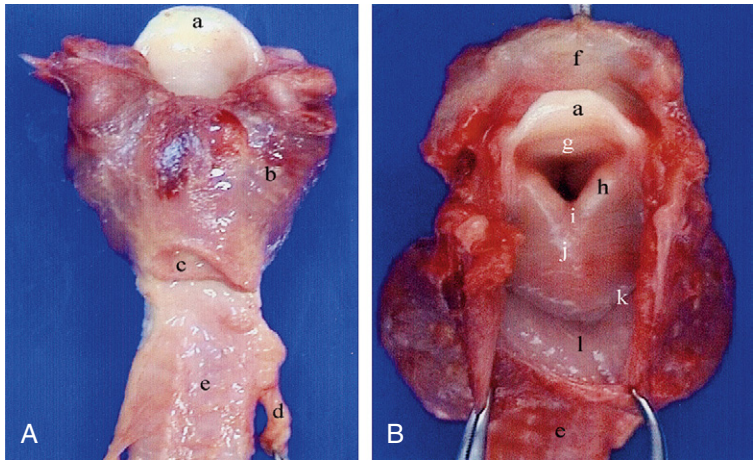


FIGURE **22-2** **A,** Posterior view of the pharyngolaryngotracheal region showing the close relationship between the pharynx, larynx, esophagus, and trachea. The inferior pharyngeal constrictor muscle (b) protects the posterior pharyngeal wall. The esophagus (c) is in close contact with the posterior tracheal wall (e). The laryngeal recurrent nerves (d) ascend in the tracheoesophageal groove. **B,** Superior and internal view of the pharynx and larynx showing the laryngeal cartilages covered by the mucosa (h, i, and j) in the anterior pharyngeal wall, the posterior pharyngeal wall (l), and the pyriform recess (k). (a) Epiglottis. (From Tarrazona V, Deslauriers J. Glottis and subglottis: a thoracic surgeon's perspective. *Thorac Surg Clin.* 2007;17:561-570.)

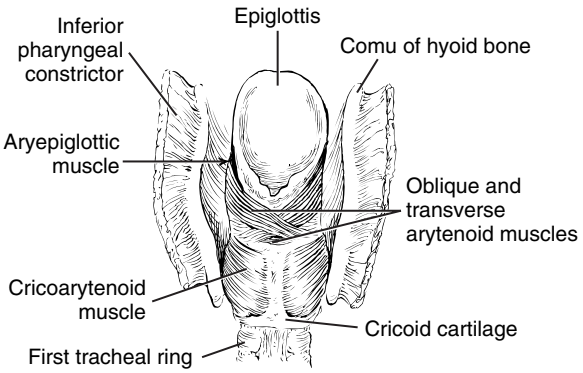


FIGURE **22-3** Posterior view of the larynx showing the laryngeal muscles.

tongue as the posterior cornu. The thyroid cartilage is connected to the hyoid bone by the thyrohyoid fascia and muscles of the larynx.

The posterior portion of the cricoid cartilage forms the posterior border of the larynx. Internal to the larynx are the epiglottis and three paired cartilages. The epiglottis exists as a single leaf-like cartilage. The epiglottis rests above the glottic opening where it closes the glottic aperture during swallowing. The superior vallecula is formed by the space between the epiglottis and the base of the tongue. The inferior vallecula is formed by the space between the inferior edge of the epiglottis and the true vocal cords.

The intrinsic muscles of the larynx control the tension of the vocal cords as well as the opening and closing of the glottis (Table 22-1). In contrast, the extrinsic muscles of the larynx connect the larynx, hyoid bone, and neighboring anatomic structures (Box 22-1). The primary function of the extrinsic muscles is to adjust the position of the trachea during phonation, breathing, and swallowing.

Blood supply to the larynx originates from the external carotid, which branches into the superior thyroid artery. The superior thyroid artery eventually gives rise to the superior laryngeal artery, which supplies blood to the supraglottic region of the larynx. The inferior laryngeal artery, a terminal branch of the inferior thyroid artery, supplies the infraglottic region of the larynx.

TABLE 22-1 Intrinsic Muscles of the Larynx

Role	Muscles Involved	Innervation	Main Function
Respiration	Posterior cricoarytenoids	Recurrent laryngeal nerve	Abduction of vocal cords
Phonation	Lateral cricoarytenoids	Recurrent laryngeal nerve	Adduction of vocal cords
	Lateral thyroarytenoids	Recurrent laryngeal nerve	Shortening and adduction of vocal cords
	Medial cricoarytenoids	Recurrent laryngeal nerve	Shortening of vocal cords
	Cricothyroids	External laryngeal nerve	Shortening and increasing tension of vocal cords
Sphincteric function	Interarytenoid		Closing of posterior commissure of the glottis
	Arytenoepiglottics		Closing of laryngeal vestibule

From Tarrazona V, Deslauriers J. Glottis and subglottis: a thoracic surgeon's perspective. *Thorac Surg Clin.* 2007;17(4):561-570.

Lower Respiratory Tract

As the fetus develops, the respiratory system evolves into complex developmental interactions between the endodermal-derived epithelium and the mesoderm. Both contribute to lung development. The lungs and airways develop through a process of five stages. These include the embryonic, pseudoglandular, canalicular, terminal sac phases, and maturation.[2]

During the embryonic phase, the endodermal respiratory diverticulum (laryngotracheal groove) develops. This occurs during week 4 through week 7. The laryngotracheal groove develops from the ventral surface of the foregut. During this period,

BOX **22-1**

Extrinsic Muscles of the Larynx

Muscles That Elevate the Larynx (Elevators)
- Stylohyoid
- Digastric
- Mylohyoid
- Geniohyoid
- Stylopharyngeus
- Thyrohyoid

Muscles That Depress the Larynx (Depressors)
- Omohyoid
- Sternohyoid
- Sternothyroid

From Tarrazona V, Deslauriers J. Glottis and subglottis: a thoracic surgeon's perspective. *Thorac Surg Clin*. 2007;17(4):561-570.

fibroblast growth factor (FGF-10) causes stimulation and proliferation of cells that will eventually express fibroblast homologous factor (FHF). As the laryngotracheal groove grows and develops, it becomes the primitive lung bud. By day 28, it has grown caudally to the splanchnic mesoderm. It divides into the right and left bronchial buds. This then progresses through the development and expression of the epithelial lining of the lower respiratory system. Cartilage, muscle, and connective tissue arise from the same tissues that form the smooth muscle of the blood vessels. The bronchopulmonary segments appear by day 42 of fetal development.

During the pseudoglandular stage, there is rapid growth and proliferation of the peripheral airways. This occurs during week 6 through week 16. Repeated branching of the distal ends of the epithelial tubes results in 16 or more generations of the bronchial tubes and the development of the terminal bronchioles. The airways are filled with liquid at this time. The cellular structure is more characterized by tall columnar epithelium.

The next phase of development is known as the *canalicular stage*. This occurs most often during week 16 and week 26. At this time, the airways widen and lengthen. The proliferation of this space will eventually become the large volume of air space in the expanded lung after birth. Terminal and respiratory bronchioles and terminal saccules develop. Cuboidal cells of the terminal sacs differentiate into alveolar type II cells. Secretion of surfactant begins at this time. Type II alveolar cells that are adjacent to a vessel flatten and differentiate into type I cells. As the type II and type I cells develop, vascularization appears. The vascularization is associated with the development of the respiratory bronchioles and the alveoli necessary for air exchange after birth. Along with other growth factors, vascular endothelial growth factor (VEGF) participates in the formation of blood vessels that will surround the alveoli. At the end of this phase, air exchange is possible although inefficient.

The terminal sac phase occurs during week 24 through week 36. Branching of the respiratory bud continues, and further development of the terminal buds is expressed as primitive alveoli. Capillaries begin to develop and proliferate around the terminal buds and proliferate at the same time as the primitive alveoli develop. Cells further differentiate throughout this period, and by week 26, a primitive blood-gas barrier has developed.

By the week 36, mature alveoli are seen. This requires FGF and platelet-derived growth factor (PDGF). Development of alveoli will continue for approximately 3 years after birth. A change in the relative relationship of parenchyma to total lung volume

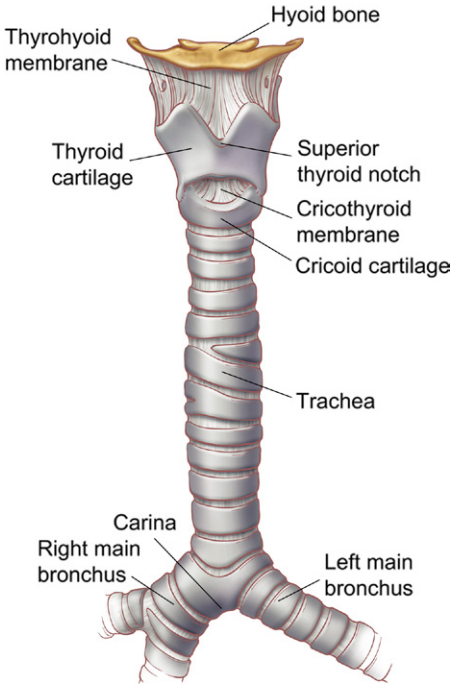


FIGURE **22-4** Principal features of the larynx and trachea. Anterior view. Tracheobronchial angles vary widely. The angle of the right mainstem bronchus is approximately 25 to 30 degrees, whereas the angle of the left mainstem bronchus is 45 degrees. (From Minnich DJ, Mathisen DJ. Anatomy of the trachea, carina, and bronchi. *Thorac Surg Clin*. 2007;17:571-585.)

contributes to lung growth until the second year of life. From the third year of life until adulthood, lung growth continues.[2]

Trachea. The trachea originates at the inferior border of the cricoid cartilage and extends to the carina (Figure 22-4). It is approximately 10 to 20 cm long in adults. The cricoid cartilage is the only cartilage of the trachea that is a complete ring. The remainder of the trachea is composed of 16 to 20 C-shaped cartilaginous rings. The posterior side of the trachea lacks cartilage, thereby accommodating the esophagus during the act of swallowing. The cartilaginous rings and plates continue until the bronchi reach 0.6 to 0.8 mm in size. At this point the cartilage disappears, and the bronchi are termed *bronchioles*. The function of the bronchi is to provide humidification and warming of inspired air as it passes to the alveoli.

The angle of bifurcation of the right mainstem bronchus is approximately 25 to 30 degrees. The bifurcation to the right upper lobe is approximately 2.5 cm from the carina. The angle of the left mainstem bronchus is 45 degrees. The left mainstem bronchus is approximately 5 cm long before it bifurcates into the left superior and inferior lobe bronchi.

The tracheobronchial trees receive sympathetic innervation from the first through fifth thoracic ganglia. Parasympathetic innervation is derived from branches of the vagus nerve. The carina is richly innervated, making it sensitive to sensory stimulation.

Diaphragm

The diaphragm arises from four structures: (1) septum transversum, (2) dorsal esophageal mesentery, (3) the pleuroperitoneal folds, and (4) the body-wall mesoderm. The diaphragm develops in the cephalic region and descends into the position between the abdominal and pleural cavity contents as the embryo develops. The nerve supply for the diaphragm arises from the cords of the third,

fourth, and fifth cervical nerves and travels with the descending diaphragmatic structure as the phrenic nerve. Owing to this process of descent, the phrenic nerves lie within the pericardium as the fetus matures and after birth. Because of the development of the diaphragm in the cephalic position and the merging of four structures, drugs that impair fetal development can result in many potential congenital deformities, including diaphragmatic hernia.[2]

AIRWAY EVALUATION

Evaluation of the airway is central to any airway management plan. A proper airway evaluation should be conducted in a thorough and systematic fashion on every patient to determine potential problems. A substantial amount of research has been conducted over the past 20 years and has identified individual airway assessment examinations as poor and unreliable predictors of difficulty. No single examination has emerged that has a consistently high sensitivity and specificity with minimal false-positive or false-negative reports.[3-6] Instead, many researchers have advocated for a more comprehensive airway management plan that involves the use of multiple airway tests.[6,7] Furthermore, an appropriate airway management plan considers the availability of equipment and personnel needed in the event that difficult airway management is encountered. Additional airway anatomy and physiology can be found in Chapters 26 and 38.

Multiple rating systems have been developed that assist in the assessment and recognition of a difficult airway.[8-11] However, no one rating system has proven to be superior over another. Instead, current recommendations concerning evaluation of the airway are to employ several assessments (Table 22-2). In order to recognize possible difficult airway conditions and to make "sensible airway management decisions," these assessments should be tailored to the patient, operative procedure, and situation (e.g., outside of the operating room [OR]).[6,12,13] It is generally agreed upon that an airway physical evaluation can improve the detection of a difficult airway. Then, after a thorough assessment, the anesthetist can formulate a comprehensive airway management plan that addresses the pertinent identified conditions.

Because of the lack of a system that reliably and consistently predicts airway difficulty with 100% certainty, some authors encourage a more focused approach on "ventilatability" rather than "intubatability."[14] Instead of focusing on conditions that affect the ability to intubate only, Murphy and Walls[15] advocated for a more all-encompassing assessment of the airway and described "four dimensions of difficulty" with airway management. The following four areas of airway management represent a modification of their "dimensions" and focus the airway assessment on conditions that could lead to difficulty with:

1. Bag mask ventilation
2. Direct laryngoscopy with direct tracheal intubation
3. Supraglottic airway ventilation
4. Invasive airway placement (e.g., needle cricothyrotomy, surgical cricothyrotomy)

A series of acronyms was developed to facilitate a thorough and systematic assessment of airway features (Box 22-2) that may lead to difficulty with hand mask, supraglottic device, endotracheal tube, and invasive airway ventilation and placement.[15]

Because a history of a difficult airway is a strong indication for current airway difficulties, an evaluation of the patient's anesthetic history should be included in the airway assessment.[16] A careful review of prior anesthetic records and information obtained directly from the patient or family members can reveal past difficulties and offer insight concerning specific techniques used to previously manage the patient's airway. Clues that may indicate a history of difficult airway management may include chipped or broken teeth, bruised lips, previous sore throat after general surgery, past postoperative dysphonia, a memory of tracheal intubation, an unexpected admission to an intensive care unit, or a pharyngeal, esophageal, or tracheal perforation.[16,17] Weight gain or loss can influence an airway and may not necessarily portray the same airway conditions as in the past. Furthermore, pathologies or conditions such as a tumor or hematoma, which may have previously caused difficulty, but have since been treated or removed, may not influence the current airway to the same degree they once did.

Multiple airway assessments exist that help the anesthetist predict difficulty with bag mask ventilation, direct laryngoscopy and tracheal intubation, supraglottic airway ventilation, and invasive airway placement (see Box 22-2). The following sections consider airway evaluations specific to each of the four areas of airway management.

TABLE 22-2 Components of the Preoperative Airway Physical Examination*

Airway Examination Component	Non-Reassuring Findings
Length of upper incisors	Relatively long
Relation of maxillary and mandibular incisors during normal jaw closure	Prominent "overbite" (maxillary incisors anterior to mandibular incisors)
Relation of maxillary and mandibular incisors during voluntary protrusion (ULBT)	Inability to protrude mandibular incisors anterior to maxillary incisors
Interincisor distance	Less than 3 cm
Visibility of uvula	Not visible when tongue is protruded with patient in sitting position (e.g., Mallampati class III or greater)
Shape of palate	Highly arched or very narrow
Compliance of mandibular space	Stiff, indurated, occupied by mass, or nonresilient
Thyromental distance	Less than three ordinary finger-breadths
Length of neck	Short
Thickness of neck	Thick
Range of motion of head and neck	Patient cannot touch tip of chin to chest or patient cannot extend neck

From Berkow LC. Strategies for airway management. *Best Pract Res Clin Anaesthesiol.* 2004;18(4):531-548.
*This table displays some findings of the airway physical examination that may suggest the presence of a difficult intubation. The decision to examine some or all of the airway components shown in this table depends on the clinical context and judgment of the practitioner. The table is not intended as a mandatory or exhaustive list of the components of an airway examination. The order of presentation in this table follows the "line of sight" that occurs during conventional oral laryngoscopy.
ULBT, Upper lip bite test.

Bag Mask Ventilation Assessment

Every anesthetist needs to possess adequate bag mask ventilation (BMV) skills. An adequate seal between the facemask and patient's face is imperative. Proper BMV can be achieved by placing the left thumb and index finger around the body of the facemask at both the mask bridge and chin curve, while compressing the left side of the mask onto the face with the palm of the left hand (Figure 22-5).

The middle and ring fingers can then be placed on the bony part of the mandible to help compress the mask to the patient's face and to raise the chin. The fifth finger can be placed at the angle of the mandible to provide an anterior jaw-thrusting maneuver. Mask retaining straps can be placed behind the patient's head and then be connected to the collar of the mask to apply pressure at various angles and promote a better mask seal.

If bag mask ventilation is believed to be inadequate, then a series of steps can be performed (Box 22-3) to facilitate ventilation. First, the patient's head and neck can be repositioned into a sniffing position. Second, if the tongue or airway soft tissue is thought to be the cause of obstruction, then the placement of an oropharyngeal airway (OPA) may help bypass the obstruction. However, the placement of an OPA can be considered prior to any attempt at BMV. Third, if BMV continues to remain inadequate, then the anesthetist should perform two-handed mask ventilation by placing both thumbs on either side of the facemask bridge with both index fingers on either side of the mask chin curve on the body of the mask. The middle fingers can then be placed on either side of the mandible at the chin, the ring fingers on the bony part of the mandible, and the fifth fingers on each angle of the mandible to provide a jaw-thrust while maintaining a secure mask seal. A second anesthetist or assistant can then compress the anesthesia bag for ventilation (Figure 22-6). If ventilation continues to remain inadequate, then a supraglottic airway device may be placed while the decision to awaken the patient is considered. In the event that all of these maneuvers fail, then invasive airway ventilation should be considered.

BOX **22-2**

Four Areas of Airway Management with Factors Associated with Difficulty

Bag Mask Ventilation

Mask seal impeded by beards, altered anatomy, or nasogastric tubes
Obstruction of the upper or lower airway
Obesity with redundant upper airway soft tissue and greater chest and abdominal mass compressing the lungs
Age greater than 55 related to loss of upper airway tissue elasticity
No teeth, leading to improper facial structure for the bag mask
Stiff lungs (e.g., increases in airway resistance or decreases in pulmonary compliance)
Sleep apnea or snoring

Direct Laryngoscopy with Tracheal Intubation

Look externally (if it looks difficult it probably is)
Evaluate the 3-3-2 rule*
Mallampati score (classes III and IV indicating increased difficulty)
Obstruction of the upper airway
Obesity with increased neck circumference and redundant soft tissue
Neck mobility that is impaired by disease of immobilization

Supraglottic Device Placement and Ventilation

Restricted mouth opening
Obstruction of the upper airway
Distorted airway preventing seal
Stiff lungs (e.g., increases in airway resistance or decreases in pulmonary compliance)

Invasive Airway Placement

Distortion of neck anatomy (e.g., hematoma, infection, abscess, tumor, scarring from radiation)
Obesity or a short neck limiting cricothyroid identification
Trauma in or around the cricothyroid area
Impediments causing limited access to the neck (e.g., halo device, fixed flexion abnormality)
Surgery causing limited access to anatomic landmarks

Adapted from Walls RM, Murphy MF. In: Walls R, Murphy M, eds. *Manual of Emergency Airway Management*. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2012:8-21.
*3-3-2 rule = 3 fingerbreadths between incisors; 3 fingerbreadths between tip of the chin (mentum) and chin-neck junction (hyoid bone); 2 fingerbreadths between chin-neck junction (hyoid bone) and thyroid notch.

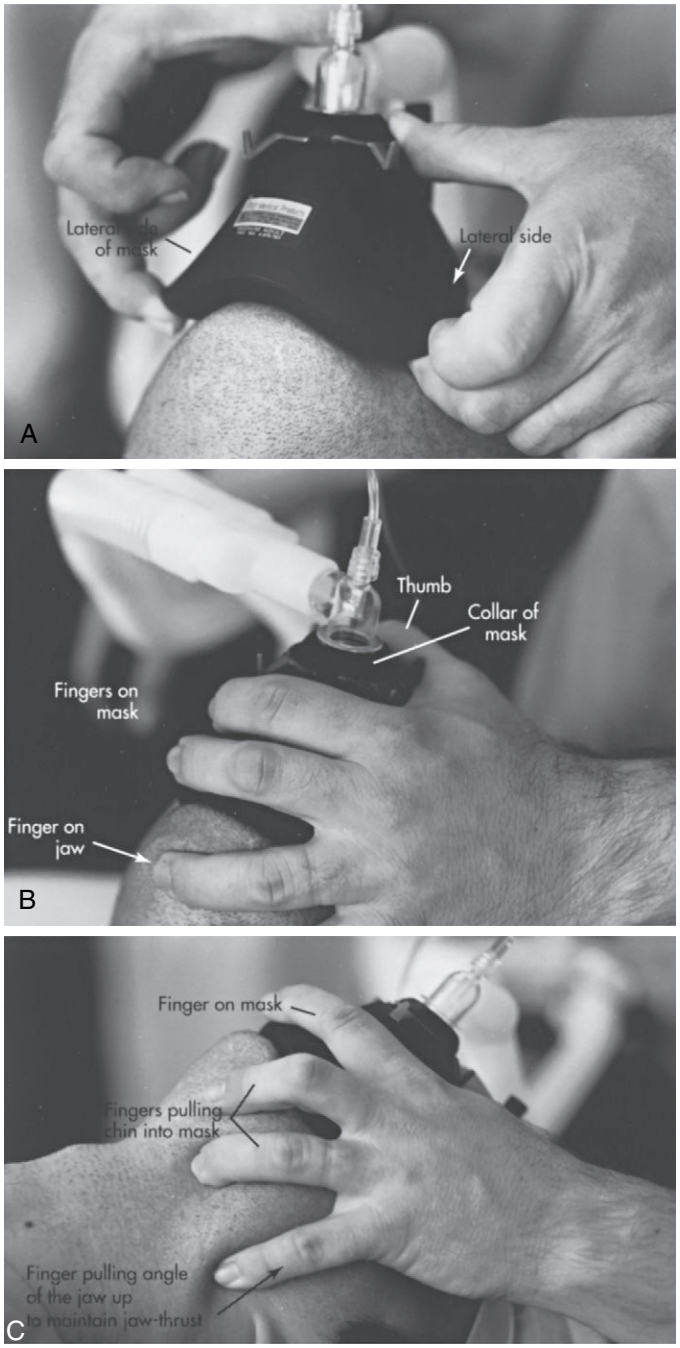


FIGURE **22-5** Proper hand placement for bag mask ventilation. **A,** Application of mask to face. **B,** Standard one-handed grip of mask to face. **C,** One-handed mask grip with jaw thrust. (From Hagberg CA. *Benumof's Airway Management*. 2nd ed. Philadelphia: Mosby; 2007.)

The incidence of difficult BMV has been described as being between 0.9% and 7.8%, and the incidence of impossible BMV as 0.15%.[18-22] Difficulty with BMV can result from problems in establishing an appropriate mask seal (such as with the presence of a beard). Inadequate ventilation during BMV is evidenced by (1) minimal or no chest movement; (2) inadequate or deficient exhaled carbon dioxide (e.g., lack of condensation and spirometic reading); (3) reduced or absent breath sounds; and (4) a decreasing oxygen saturation (e.g., less than 92%).[12,19] If difficulty is believed to be a possibility with BMV, positioning can be improved by elevating the shoulders, neck, and head, which is known as "ramping" the patient (Figure 22-7). Multiple factors have been identified as predictors for difficulty with BMV (see Box 22-2); these include mask seal impediments, upper airway obstructions, obesity, elderly patients, Mallampati scores of III or IV, a short thyromental distance, snoring, and poor lung compliance.[18,19,21,22]

Mask seal impediments such as facial hair, altered facial anatomy, lack of teeth causing the face to cave inward, or a nasogastric tube can cause air leakage out of the mask and prevent adequate positive pressure ventilation. Some of these factors can be modified, such as shaving the patient's beard, delaying removal of dentures, and removing the nasogastric tube. Although shaving a beard may be undesirable and removal of a gastric tube may cause a buildup of gastric secretions in the stomach, these interventions do allow for a better mask seal and more effective positive pressure ventilation upon induction of anesthesia.

BOX 22-3

Proper Sequence for Bag Mask Ventilation When Difficulty Is Encountered

1. Assure proper positioning of the patient.
2. Attempt ventilation with one hand (can consider use of mask strap on opposite side of mask to improve mask seal).
3. Reposition the head into a sniffing position.
4. Place oropharyngeal airway (may consider earlier placement).
5. Proceed with two-hand mask ventilation.
6. Consider placement of a supraglottic device, awaken patient, or proceed with invasive airway access if ventilation becomes impossible.

Obstruction may occur in the upper or lower airway and can severely limit the effectiveness of BMV. Upper airway obstructions should be considered an emergency and managed with extreme care because of the potential to become total airway obstructions. The hallmark signs of an upper airway obstruction in the unanesthetized patient include a hoarse or muffled voice, difficulty swallowing secretions, stridor, and dyspnea. Stridor and dyspnea are ominous signs of severe respiratory obstruction and indicate a 50% decrease in circumference from normal or a diameter reduced to 4.5 mm or less.[15] There are several potential causes of an upper airway obstruction (Boxes 22-4 and 22-5). The management of these conditions is discussed later in this chapter under "Management of the Difficult and Failed Airway." It is important to treat the airway with care because these conditions have the potential to severely impair ventilation and oxygenation, as well as cause difficulty with laryngoscopy and tracheal intubation.

Lower airway obstructions typically manifest with high peak airway pressures, low tidal volumes, and impaired ventilation. These conditions can be caused by pathologic, congenital, or acquired causes (see Boxes 22-4 and 22-5) and should be managed in a way that provides optimal ventilation and oxygenation for the patient.

Obstructive sleep apnea (OSA) and snoring were recognized as predictors of difficult mask ventilation.[18,19,21] Studies have revealed that patients with a history of snoring and sleep apnea are more likely to have difficulty with BMV, and more often these patients require two practitioners to effectively manage the airway.[18,19] An obstructive tongue, as well as posterior oropharyngeal soft tissue collapse, is thought to be the cause of difficulty and obstruction.[23] Patients with a history of OSA should be encouraged to bring their positive pressure device (e.g., CPAP [continuous positive airway pressure] or BiPAP [biphasic positive airway pressure] machine) from home to the hospital for use in the postanesthesia care unit (PACU).

Significant obesity (body mass index greater than 30 kg/m^2) has been identified as a potential risk factor for difficult BMV.[18,19,22] Difficulty with BMV may be the result of excessive weight from both chest and abdominal tissues causing compression on the lungs, especially in the supine position. Pregnant patients in the third trimester may also be difficult to ventilate because the gravid uterus can compress the lungs, creating elevated airway

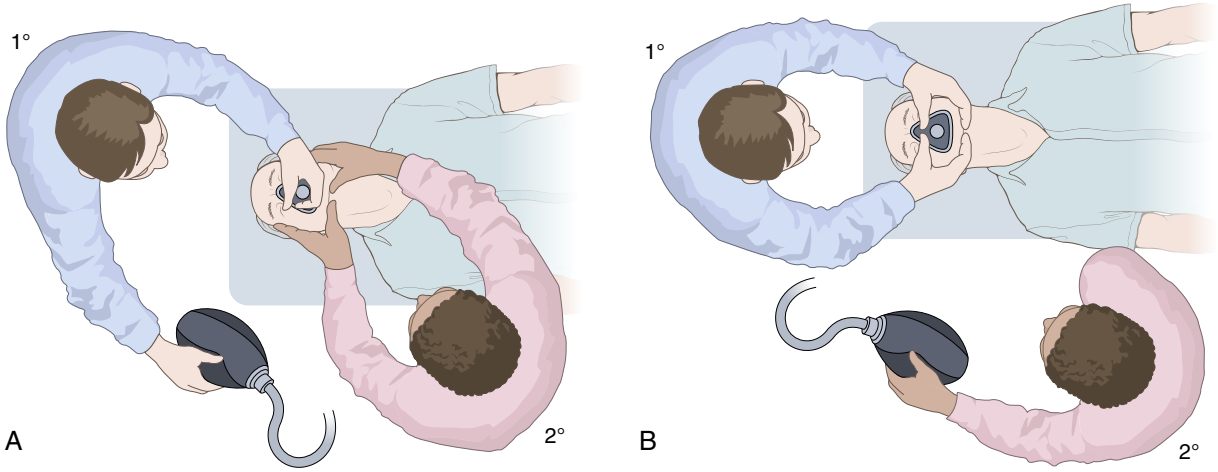


FIGURE 22-6 **A,** Two-person mask ventilation effort with second provider providing a jaw thrust. **B,** Two-person mask ventilation effort with primary provider maintaining a mask seal and performing a jaw thrust while second provider squeezes the anesthesia bag. (Redrawn in Miller RD, Pardo M. *Basics of Anesthesia*. 6th ed. Philadelphia: Saunders; 2011. Originally from Benumof JL. *Airway Management: Principles and Practice*. St. Louis: Mosby; 1996.)

resistance. Furthermore, obese patients tend to have decreased functional residual capacities (FRCs), which predisposes them to desaturate more quickly, even after appropriate preoxygenation periods. One study reported that the time to reach a preoxygenation end-tidal oxygen value of 85% or greater was similar in both obese and lean patients. However, the authors observed that apnea-induced desaturation occurred more quickly, and hypoxemia was more profound, in the obese population.[24] These results should be considered in the overall airway management plan because any time delay after the induction of anesthesia in the obese population may result in significant hypoxemia.

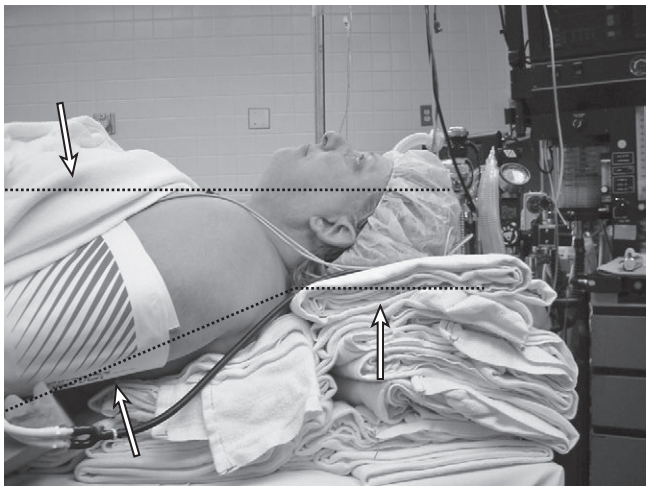


FIGURE **22-7** Example of a ramp created using blankets to improve positioning. Optimal positioning is observed when an imaginary horizontal line can be drawn from the sternal notch and extending just anterior to the ear on the face. (From Chestnut DH, et al. *Chestnut's Obstetric Anesthesia: Principles and Practice*. 4th ed. Philadelphia: Mosby; 2009.)

BOX **22-4**

Causes of Upper and Lower Airway Obstruction

Upper Airway Obstruction

Facial
Burns
Congenital abnormalities
Trauma

Oropharyngeal
Abscesses (e.g., peri-tonsillar)
Ludwig's angina
Sleep apnea
Tongue

Pharyngeal and Laryngeal
Angioedema
Foreign bodies
Epiglottitis
Hematomas
Hemorrhage
Laryngospasm
Laryngotracheobronchitis (croup)
Subglottis stenosis
Tumors or lesions

Lower Airway Obstruction

Trachea
Angioedema
Aspirated foreign bodies
Hematoma
Hemorrhage
Tumors or lesions

Bronchial and Alveolar
Acute respiratory distress syndrome (ARDS)
Aspiration pneumonia
Asthma
Bronchospasm
Chronic obstructive pulmonary disease (COPD)
Pulmonary edema

Extrapulmonary
Morbid obesity (BMI greater than 30 kg/m^2)
Pregnancy
Trauma

Redundant tissue of the upper airway may be another factor that leads to difficulty with BMV, because excessive soft tissue in the oropharyngeal and pharyngeal cavities can cause resistance to airflow during positive pressure ventilation.[15] Therefore ideal positioning (e.g., ramping the patient), adequate preoxygenation, a secondary airway management plan with alternative airway adjuncts readily available, and assistance from other anesthesia professionals should be considered prior to the induction of anesthesia in the obese patient.

Researchers have also identified obesity as a risk factor for difficult laryngoscopy and tracheal intubation, because excessive upper airway soft tissue may inhibit direct visualization of the glottis.[18,24] However, some researchers concluded that an increased body mass index (greater than 35 kg/m^2) had no effect on difficulty with laryngoscopy, leaving this to be a somewhat controversial subject.[25,26] Nevertheless, any prudent practitioner should consider multiple patient characteristics when evaluating difficulty.

Advanced age (greater than 55 years) is associated with difficult BMV.[18,19] Older patients may have decreased tone in the upper airway muscles and tissues as a result of inelastic or aged tissue. In addition, elderly patients commonly have loose teeth, missing teeth, or are edentulous; all of which can cause the airway soft tissue to sink inward. These factors contribute to a poor mask seal and the inability to perform adequate BMV. Anesthesia practitioners may consider leaving dentures in place (as long as they are easily removable) in the edentulous patient prior to instrumentation of the airway. This may be done to conserve the facial structure and facilitate a better mask seal.

Decreases in lung compliance can contribute to ineffective BMV because of the inability to effectively move ventilated gases into the alveoli. Conditions such as bronchospasm, pulmonary edema, acute respiratory distress syndrome, or pneumonia (see Box 22-4) can cause peak airway pressures to rise and compliance to decrease, resulting in ineffective BMV and poor oxygenation of the patient. If severe enough, these conditions may necessitate an abortion of the surgical procedure, and they require tracheal intubation and/or intensive care monitoring. Therefore it is important for the anesthetist to recognize potential upper and lower airway problems and realize the time limitations that exist in the event that BMV becomes inadequate.

Direct Laryngoscopy and Tracheal Intubation Assessment

Direct laryngoscopy (DL) and direct tracheal intubation (DTI) are two different procedures. Direct laryngoscopy is the process of airway instrumentation with a laryngoscope in order to acquire a

BOX **22-5**

Congenital and Acquired Disease States Associated with Difficult Airway Management

Congenital
- Pierre Robin syndrome
- Treacher Collins syndrome
- Goldenhar's syndrome
- Mucopolysaccharidosis
- Achondroplasia
- Micrognathia
- Down syndrome
- Infections involving the airway (Ludwig's angina)
- Rheumatoid arthritis
- Obstructive sleep apnea
- Ankylosing spondylitis
- Tumors involving the airway
- Trauma (airway, cervical spine)

Acquired
- Morbid obesity
- Acromegaly

From Berkow LC. Strategies for airway management. *Best Pract Res Clin Anaesthesiol.* 2004;18(4):531-548.

direct line of sight with the laryngeal opening. In contrast, DTI is the process of placing an endotracheal tube into the trachea proximal to the carina. Usually, when anesthesia professionals perform a DL, it is with the intent of completing DTI, and as a result these two procedures are generally performed together in sequence. Airway assessments specific to both DL and DTI are therefore discussed together in this section.

A primary goal during airway evaluation is to determine factors that predispose a patient to difficulty with DL and DTI. The distinction between these two procedures has not always been clear in the literature; however, the incidence of difficult tracheal intubation has been described to be between 1.5% and 8.5%, and the incidence of failed tracheal intubation has been estimated to be between 0.3% and 0.5%.[6,27-29] As described earlier, although individual airway assessments have demonstrated a decreased ability to reliably and consistently predict difficulty, a prudent practitioner should error on the side of patient safety by using a combination of assessment techniques when determining an airway is potentially difficult.

Shiga et al.[6] conducted a meta-analysis focused on determining the predictors of difficult intubation. They reported that when used alone, current airway evaluation methods had poor predictive values, and they concluded that the combination of Mallampati classification and thyromental distance (TMD) most accurately predicted difficult intubation.

Merah et al.[27] attempted to predict difficult visualization of the larynx in the West African population using a combination of airway predictive indices. They reported that the combination of modified Mallampati test, thyromental distance, and inter-incisor gap was the best predictor of difficult laryngoscopy. Some or all of these predictors have also been identified in Caucasian, Asian, and obstetric populations.[30-33] Prudent airway management aims at predicting the possibility of difficulty to formulate primary, secondary, and even tertiary airway management plans. If an airway turns out to be less difficult than previously anticipated, then the decision to error on the side of patient safety is obviously the better choice.

As stated earlier, there is no single airway assessment that reliably predicts difficulty with DL and DTI all of the time, and there are a myriad of airway evaluation techniques. A significant concern when performing the different airway assessments is the variation in measurements.[6] Inter-practitioner variability in the performance of airway evaluation techniques alters the validity of findings between studies. Therefore it is important that anesthesia practitioners remain consistent and perform the different airway assessments the way they were intended every time. The most commonly cited airway assessments used in combination to evaluate the airway include: (1) the modified Mallampati classification; (2) thyromental distance; (3) inter-incisor gap distance; (4) atlanto-occipital joint mobility and cervical range of motion; (5) mandibular protrusion test; (6) evaluation for obstruction of the upper airway; and (7) obesity (specifically neck circumference).

Mallampati Classification

The Mallampati classification is a commonly used technique of assessing mouth opening, size of the tongue, size of the oral pharynx, and assessment of posterior oropharyngeal structures. First developed by Rao Mallampati, this classification originally described three classes. Later Samsoon and Young[35] added a fourth class, which is now often referred to as the modified Mallampati test (MMT) (Figure 22-8 and Table 22-3). When performing the assessment, the patient is instructed to sit upright, extend the neck, open the mouth as much as possible, protrude the tongue, and avoid phonation. The MMT uses a classification system to evaluate tongue size relative to the oropharyngeal space, and is categorized as follows:

- *Class I:* Full visualization of the entire oropharynx including soft palate, uvula, fauces (archway between oral and pharyngeal cavities), and tonsillar pillars
- *Class II:* Visualization of the soft palate, fauces, and uvula
- *Class III:* Visualization of the soft palate and base of the uvula

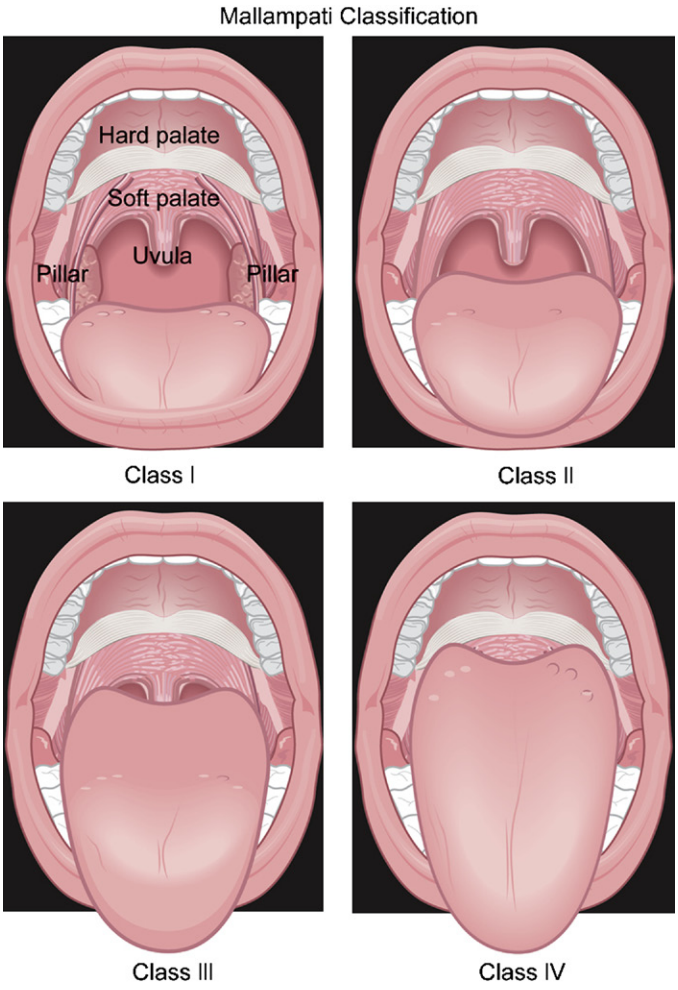


FIGURE 22-8 Modified Mallampati classification. Performed with the patient sitting up and maximally protruding his/her tongue; visibility of the soft palate, fauces, tonsillar pillars, and uvula were noted. Class I described full visualization of all structures. Class II allowed visualization of the soft palate, faucial pillars, and a portion of the uvula. Class III allowed visualization of the soft palate and base of the uvula. With class IV, only the hard palate is visible. (From Cleveland Clinic Center for Medical Art & Photography © 2009-2012. Reprinted with permission. All rights reserved.)

TABLE 22-3 Mallampati Airway Classification

Classification	Description of Visualized Structures
1	Soft palate, faucial pillars, entire uvula
2	Soft palate, faucial pillars, and a portion of the uvula
3	Soft palate and base of the uvula
4	Hard palate visible only

From Berkow LC. Strategies for airway management. *Best Pract Res Clin Anaesthesiol.* 2004;18(4):531-548.

- *Class IV:* Visualization of the hard palate only

Ezri et al.[36] suggested adding a class "zero" to the MMT, which is the ability to see any part of the epiglottis on mouth opening and tongue protrusion, and found a 1.2% incidence. However, most researchers, and likely most clinical practitioners, use the Samsoon and Young I to IV modification of Mallampati's classification.[35]

Evaluations of the MMT have shown some correlations with difficulty when either class III or IV is measured.[34,36] However, by itself the MMT has been unreliable at consistently predicting the presence or absence of a difficult airway.[37,38] Furthermore, anesthesia practitioner variability in the administration of the MMT, years of experience, and subjectivity of assessment can result in the assessment of different classifications between similar patients. However, when used in combination with other airway assessments, the MMT can help increase the predictive ability of both laryngoscopic and intubation difficulties. For example, the combination of increased Mallampati classification levels of III or IV and an increased neck circumference (greater than 43 cm measured at the thyroid cartilage) were predictors of intubation problems.[13,25] Other researchers identified the combination of increased Mallampati classifications, decreased thyromental distances, and limited inter-incisor openings as strong predictors of both laryngoscopic and intubation troubles.[6,27,32]

Cormack and Lehane Grading System

An objective scoring system that is frequently used by researchers to describe laryngoscopic difficulty with intubation is the Cormack and Lehane grading system. The goal of laryngoscopy is to attain the best possible view of the vocal cords and glottic opening. While performing DL, and prior to DTI, different views of the pharyngeal structures and the glottic opening may be observed. These views can be graded using the Cormack and Lehane grading scale (Figure 22-9). This scale offers an objective assessment of the glottic opening, or lack thereof, during laryngoscopy using direct line of site and is rated as follows[39]:

- *Grade I:* Most or full view of the glottic opening
- *Grade II:* Only the posterior portion of the glottic opening can be visualized; anterior commissure not seen
- *Grade III:* Only the epiglottis can be visualized; no portion of the glottic opening can be seen
- *Grade IV:* Epiglottis cannot be seen; only view is of the soft palate

Cormack and Lehane grades I and II are generally associated with easier intubations, whereas grades III and IV correspond with higher degrees of intubation difficulty.[39]

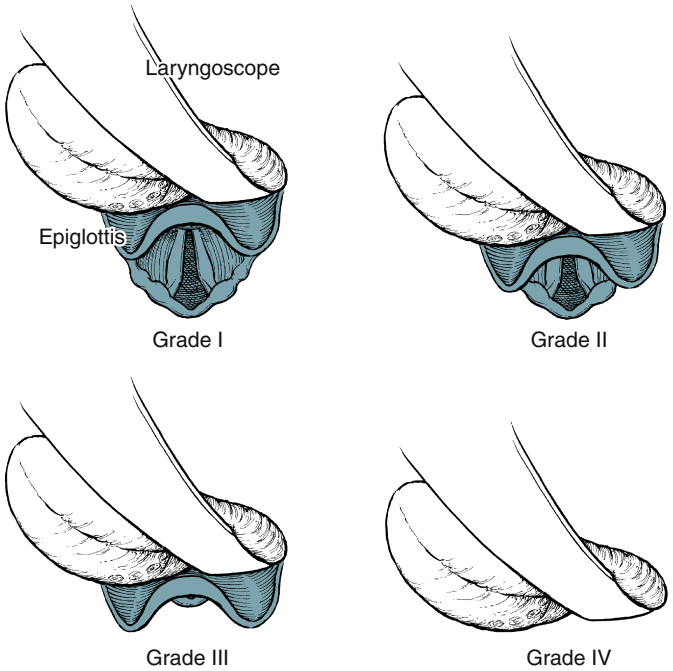


FIGURE **22-9** Cormack and Lehane grading system. Grade I is visualization of the entire glottic opening. Grade II is visualization of only the posterior portion of the glottic opening. Grade III is visualization of the epiglottis only. Grade IV is visualization of the soft palate only. (From Cormack RS, Lehane J. Difficult tracheal intubation in obstetrics. *Anaesthesia*. 1984;39(11):1105-1111.)

Thyromental Distance

The thyromental distance (TMD) is a measurement of the thyromental space. This space is an available pliable compartment, directly anterior to the larynx, where the tongue can be displaced during direct laryngoscopy to improve direct line of site with the glottic opening. The tongue is a noncompressible structure, but is malleable and therefore can be moved to other locations within the oropharyngeal and pharyngeal compartments. The thyromental space is bordered laterally by the neck, superiorly by the mentum, and inferiorly by the hyoid bone, which is semifixed.

The TMD is measured from the thyroid notch to the lower border of the mentum (at the chin) when the patient's head is extended and mouth is closed (Figure 22-10, *B*). A TMD less than 6 cm, or "3" ordinary fingerbreadths, is associated with a higher incidence of difficult intubation. Research has indicated that the thyromental space should accommodate most any tongue size, but that a small space would only facilitate a relatively small tongue.[31,40] Furthermore, if the thyromental space has been rendered noncompliant from radiation or pathologic factors (e.g., tumors), then the tongue may not be able to properly fit, causing it to protrude into the pharyngeal space. A malplaced tongue that does not fit into the thyromental space can obstruct the direct line of site with the glottic opening during laryngoscopy.

A condition that does not allow the tongue to fit into the thyromental space is known as mandibular hypoplasia. Patients with mandibular hypoplasia (e.g., TMD less than three fingerbreadths)

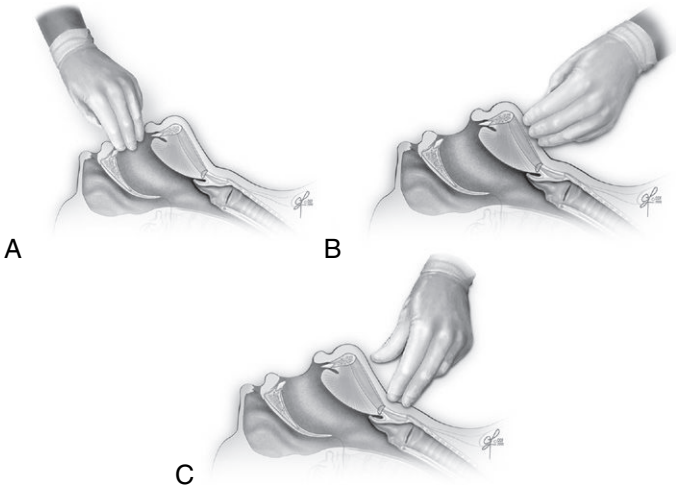


FIGURE **22-10** **A,** Oral access: mouth opening (three fingerbreadths) between upper and lower teeth. **B,** Mentum and hyoid bone, otherwise known as the thyromental distance (three fingerbreadths). **C,** Thyroid notch and hyoid bone (two fingerbreadths). (From Cleveland Clinic Center for Medical Art & Photography © 2009-2012. Reprinted with permission. All rights reserved.)

may present with both a difficult laryngoscopic view and a difficult intubation. This is because the tongue cannot be positioned into the small submandibular space. Furthermore, the larynx may be tucked underneath the tongue or be positioned relatively anterior to the base of the tongue in the pharyngeal space, causing difficulty with laryngoscopic views. This condition is commonly called an "anterior larynx," and unless the tongue can be pulled anterior away from the pharyngeal space, little can be done to improve the direct line of site view.

The assessment of a long TMD (greater than 9 cm) may also indicate a potentially difficult airway. The indication for difficulty is due to a large hypopharyngeal tongue, caudal larynx, and longer mandibulohyoid distance (MHD). The MHD measures the vertical distance from the angle of the mandible to the hyoid bone and is usually assessed by radiograph. A long TMD and MHD may position the glottic opening caudally in the neck and beyond the visual horizon. If the larynx is more caudally situated in the pharyngeal compartment, then the tongue is also likely to be positioned lower because the tongue muscle is hinged to the hyoid bone.[41,42] This can lead to both a greater distance to the glottic opening with a laryngoscope and an obstructed view caused by a greater amount of tongue mass in the hypopharyngeal space. In addition, a history of sleep apnea and snoring can provide further evidence of a possible hypopharyngeal tongue, which has been shown to cause difficulty with both mask ventilation and intubation.[42,43] Again, like other airway assessment tests, researchers have found limited predictability when the TMD test was used by itself, and therefore recommend that it be used as part of a multivariable airway assessment.[9,25,29]

The 3-3-2 rule has been described by some authors as a nonscientifically based test to ensure that upper airway geometry is adequately assessed.[44] The 3-3-2 rule is an assessment that evaluates various airway proportions using finger breadths as a measurement (see Figure 22-10). It is a combination of different geometric dimensions that relate mouth opening and the size of the mandibular space to the position of the larynx in the neck.[11,15] The first "3" estimates oral access (inter-incisor gap distance), which should accommodate at least three fingerbreadths. The second "3" assesses the mandibular length (TMD) from the tip of the mentum to the mandible-neck junction and gauges the ability of the tongue to displace within the submandibular space during laryngoscopy. The "2" is a modification of the MHD, which is a nonradiographic measurement from the mandible-neck junction to the tip of the thyroid notch, and assesses the position of the larynx (glottic opening) in relation to the base of the tongue. More than two fingerbreadths indicates that the larynx may be positioned too far down the neck and could be difficult to visualize. Less than two fingerbreadths indicates that the larynx may be tucked under the base of the tongue, which would be indicative of an anterior larynx. This combination of airway assessments allows the anesthetist to perform multiple airway measurements in a rapid and sequential manner.

It may be worth mentioning the sternomental distance (SMD), although it has been described as a poor predictor (even when used as part of a multivariable assessment) of airway management difficulty. The SMD is measured from the sternal notch to the lower border of the mentum at the chin with the head extended and the mouth closed. Normal SMD is greater than 12 cm. Distances of less than 12.5 cm have been described as a preoperative predictor for difficult DTI.[31,45]

Inter-Incisor Gap

As discussed above, the inter-incisor gap is important to assess when performing a DL because mouth opening can affect the ability to create a direct line of sight with the laryngeal opening.[16] If mouth opening is narrow, it may be problematic to introduce the laryngoscope blade's 2-cm flange along with the endotracheal tube (ETT) into the mouth while maintaining good visualization of the vocal cords. An adequate inter-incisor opening is at least 2 to 3 average fingerbreadths, or a minimum of 4 cm.[46] An increase in maxillary incisor length can reduce the inter-incisor gap and create a sharper angle between the oral and glottic openings. Furthermore, prominent incisors or "buck teeth" increase the risk of dental damage from the metal laryngoscope blade. Finally, loose or awkward teeth can either impede the placement of a laryngoscope blade and ETT or create an obstruction in the event a tooth is dislodged and falls into the laryngeal opening or trachea.

Atlanto-Occipital Joint Mobility

The full range of neck flexion and extension varies from 90 to 165 degrees and decreases approximately 20% between ages 16 and 75 years. The atlanto-occipital joint provides the highest degree of mobility in the neck with a normal head extension of up to 35 degrees. Proper atlanto-occipital joint mobility is required for an adequate sniffing position. The sniffing position is important because it helps to improve laryngoscopic views by promoting displacement of the tongue by better aligning the oral, pharyngeal, and laryngeal axes (Figure 22-11). Evaluation of atlanto-occipital joint extension is conducted with the patient seated upright in a neutral face forward position; the patient is then asked to lift the head back with chin up as far as possible. When extension is reduced to 23 degrees, visualization may become difficult.[47] If the patient demonstrates substantial or complete immobility of the atlanto-occipital joint, then significant laryngoscopic compromise should be anticipated. Furthermore, cervical spine diseases such as cervical pathology (e.g., degenerative disease, rheumatic disease, neurologic pathology, trauma, or previous surgical intervention) or spinal abnormalities such as with Down syndrome may lead to difficult laryngoscopy and difficult airway management in general.

Mandibular Protrusion Test

The mandibular protrusion test, also known as the upper lip bite test (ULBT), is an evaluation technique that demonstrates the patient's ability to extend the mandibular incisors anterior past the maxillary incisors. The purpose of this airway test is to assess the mobility of the patient's temporomandibular joint function and forward subluxation of the jaw and to note the patient's maxillary incisor length (e.g., presence of buck teeth). The presence of these indicators can lead to problematic oral airway placement, noneffective relief of soft tissue obstruction from poor mandibular movement, difficulty introducing the laryngoscope blade into the mouth, and an obstructive view of the glottic opening caused by maldisplacement of the tongue. Difficulty with laryngoscopy arises when the patient is unable to protrude the mandibular incisors anterior past the maxillary incisors (Figure 22-12). The test has three classifications[47]:

- *Class I:* Patient can protrude the lower incisors anterior past the upper incisors and can bite the upper lip above the vermilion border (line where the lip meets the facial skin)
- *Class II:* Patient can move the lower incisors in line with the upper incisors and bite the upper lip below the vermilion border, but cannot protrude them beyond
- *Class III:* Lower incisors cannot be moved in line with the upper incisors and cannot bite the upper lip

Assessment of an ULBT class III indicates a potential difficult laryngoscopic view, whereas class I indicates a good view using conventional laryngoscopy.[48]

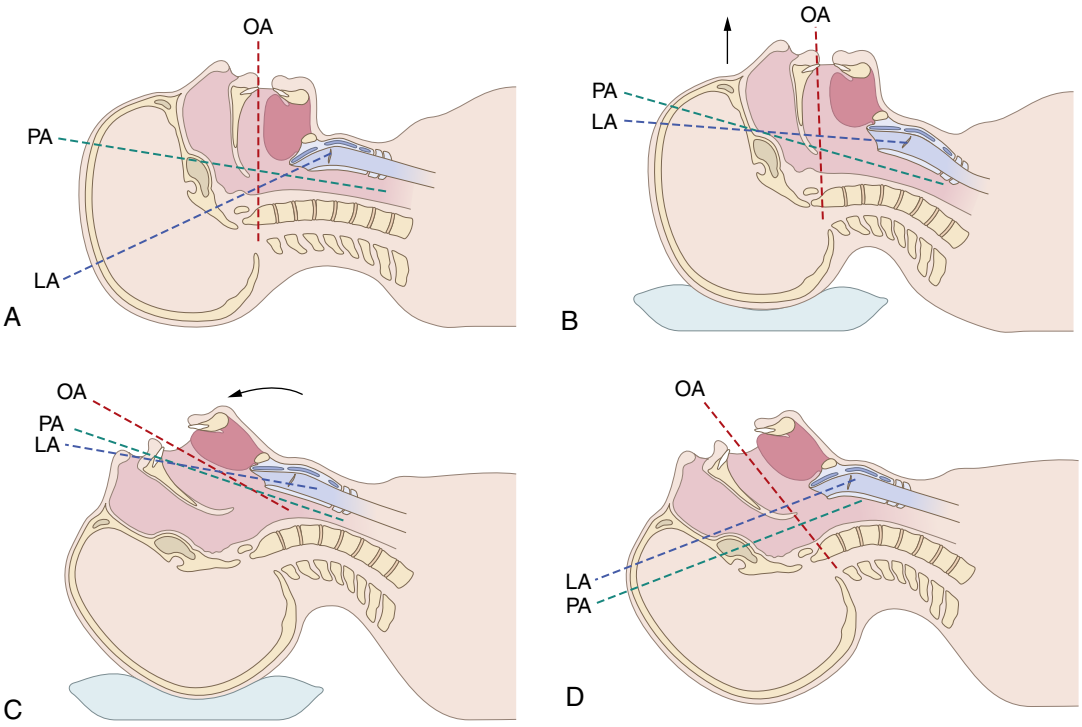


FIGURE **22-11** Oral axis (OA), pharyngeal axis (PA), and laryngeal axis (LA) for intubation. **A,** Nonaligned position. **B,** Head resting on a pad causes flexion of the neck and aligns the PA and LA. **C,** Head resting on pad causes flexion of the neck, with neck extension into sniffing position aligns the OA, PA, and LA. **D,** Extension of the neck without head elevation aligns PA and LA, but not the OA. (From Miller RD, Pardo MC. *Basics of Anesthesia*. 6th ed. Philadelphia: Saunders; 2011.)

The ULBT was found to be a valuable assessment tool for the prediction of difficult ventilation when used in combination with other assessment techniques such as increased neck circumference and a history of snoring.[49] Furthermore, the ULBT has shown to be useful in the assessment of temporomandibular joint function and the prediction of difficult laryngoscopies when used in combination with the modified Mallampati classification.[5,50] However, the ULBT has shown to be an unreliable assessment technique when used in the edentulous population and has demonstrated poor predictability when used as a single screening test for the assessment of laryngoscopic difficulty.[51]

Supraglottic Airway Assessment

Supraglottic airway (SGA) ventilation may be the primary means of managing an airway, or it can be used for rescue ventilation in the event that facemask ventilation is difficult or fails. Similar predictors related to difficulty with mask ventilation, laryngoscopy, and intubation can also indicate difficulty in placing and then ventilating with a SGA device. These predictors include restrictive mouth opening, a distortion in upper airway anatomy, and both upper and lower airway obstruction (see Box 22-2).

The inter-incisor gap is an important assessment to consider when introducing any airway adjuncts into the mouth. As identified earlier, an assessment of less than three fingerbreadths or less than 4 cm indicates a restricted oral access that can make some SGA devices difficult to introduce into the mouth.[16] Furthermore, some researchers have indicated that reductions in atlanto-occipital joint movement from conditions such as ankylosing spondylitis and rheumatoid arthritis may cause difficulty with some SGA placements such as the laryngeal mask airway (LMA).[52,53]

Obstruction at the level of the larynx, trachea, or below can reduce or completely block ventilation from a SGA device (see Box 22-4). In addition, fixed upper airway lesions, such as oropharyngeal tumors or a disruption or distortion in the upper airway anatomy, may make SGA placement difficult and lead to ineffective ventilation from a compromised "seat and seal."[44,54]

Finally, conditions affecting the lower airways resulting in decreases in pulmonary compliance or increases in airway resistance can cause peak airway pressures to rise, which may also make SGA ventilation difficult. For example, bronchospasm or acute respiratory distress syndrome require higher ventilatory pressures for adequate gas exchange within the lungs. Because an SGA device is seated above the larynx, positive pressure ventilation with such a device may not be able to generate the necessary pressures needed to push gases deep within the lungs. Instead, ventilated gases will follow the path of least resistance, and when airway pressures reach 25 cm H_2O or higher, these ventilated gases could overcome esophageal sphincter pressures causing inflation of the stomach, increases in intragastric pressure, and a possible risk of vomiting and pulmonary aspiration.

Invasive Airway Assessment

An assessment of the neck is part of any comprehensive airway examination and should be conducted with the intent of identifying factors that may lead to difficulty with the placement of an invasive airway. The need for an invasive airway usually occurs on an emergency basis. An invasive airway consists of a needle cricothyrotomy, surgical cricothyrotomy, or a tracheotomy. Because surgeons are more likely to perform a tracheotomy, rather than anesthesia personnel, the primary focus here will be on assessments aimed at identifying factors that lead to difficulty with both the needle and surgical cricothyrotomy emergency procedures.

Even though there is no absolute contraindication for the placement of an emergency cricothyrotomy, there are conditions

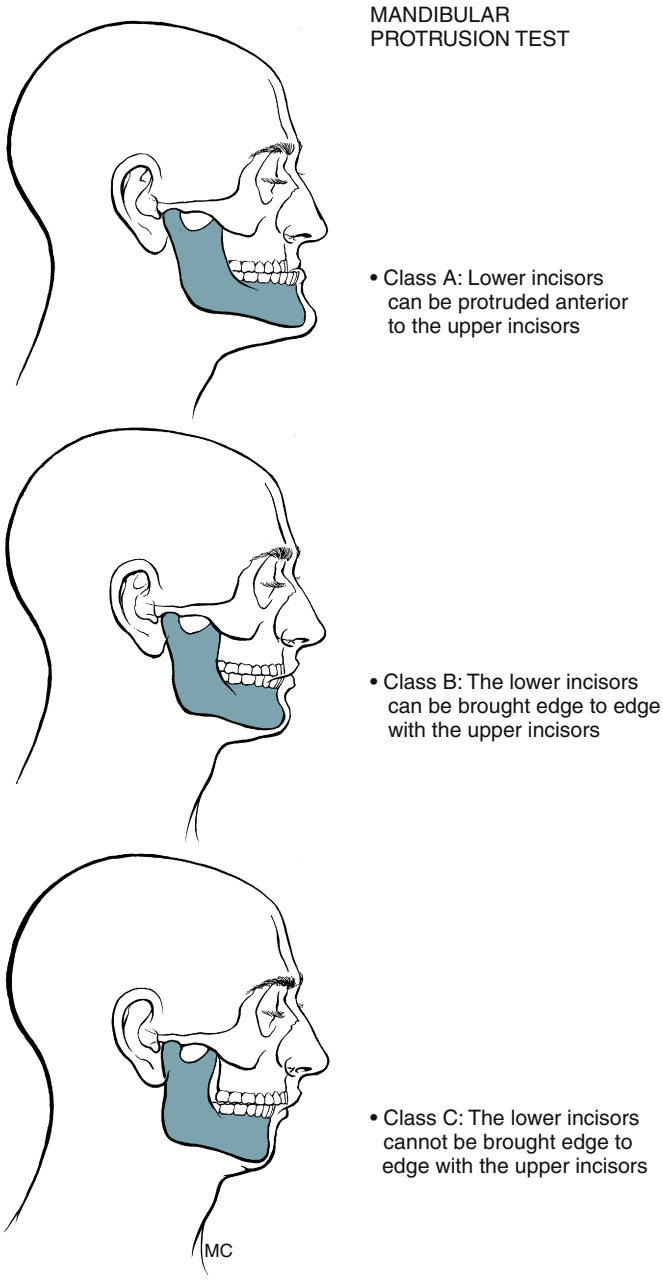


FIGURE **22-12** Mandibular protrusion test classes A, B, and C (also known as the upper lip bite test). (Redrawn from Munnur U, de Boisblanc B, Suresh MS. Airway problems in pregnancy. *Crit Care Med.* 2005;33:S259-68.)

that make performing this procedure difficult to impossible (see Box 22-2). Murphy and Walls[15] described using the pneumonic *SHORT*, as a means for remembering *surgery, hematoma, obesity, radiation,* and *tumors*, which are conditions associated with difficult cricothyrotomy placement. Any condition that causes a distortion of the airway such as trauma, surgery, infection, tumors, or physical impediments in or around the cricothyroid area may cause difficulty with invasive airway access. A hematoma from surgery (e.g., carotid endarterectomy), an infection of the soft tissue around the airway (e.g., Ludwig's angina), an oral or pharyngeal abscess, a tumor in or around the neck, or radiation causing scarring of the neck tissue can distort the neck anatomy and make a cricothyrotomy neck incision challenging. However, none of these factors should be considered a contraindication when emergency airway access is required. In addition, recent or past neck trauma or surgery can alter neck anatomy and cause scarring or acute bleeding, again making invasive airway access difficult. Finally, neck impediments such as a halo device or a rigid cervical collar may impede emergency access or make the procedure technically difficult and should be removed whenever possible.

Patient physical conditions that may also cause difficulty with the placement of a cricothyrotomy include a short neck, obesity, scarring, or fixed flexion abnormality. Both a short neck and excessive soft tissue around the neck can make finding the cricothyroid membrane and surrounding anatomic landmarks challenging. When performing the preoperative airway assessment on patients who exhibit any of these characteristics, practitioners should consider marking the cricothyroid membrane, prior to airway manipulation, in order to save time locating the membrane in the event of an emergency. Scarring from radiation or previous trauma around the cricothyroid area can distort neck anatomy and cause difficulty gaining access to the trachea. Furthermore, any fixed flexion deformity of the cervical vertebra can also lead to difficulty gaining access to the appropriate anatomic landmarks. Therefore the appropriate equipment should be readily available, such as an emergency cricothyrotomy kit, in order to save time when and if emergency airway access is indicated.

Radiologic Imaging

Imaging technologies, such as magnetic resonance imaging (MRI) and computed tomography (CT) can identify pathologies and alterations in airway anatomy and increase the predictive value of anticipated difficulty. These technologies can help anesthetists formulate appropriate airway management plans. An advantage of the CT scan includes the ability to accurately depict pathology involving bones and soft tissues and provides clinicians with the ability to view images in the sagittal, coronal, axial, and three-dimensional views. Furthermore, CT scans have become the "gold standard" for ruling out fractures of the cervical spine.[55]

Whereas CT scans can image both bone and soft tissue, an MRI offers detailed information on soft tissues only. An MRI can help assess the impact the pathologic processes have on soft tissue, such as the altered patency of an airway caused by a tumor in the neck. However, currently both the CT and MRI tests are not used on a routine basis because of the economic costs and time-delaying factors associated with their use, especially if there is no indication to perform them.

When assessing the airway and preparing for manipulation, the anesthetist should perform a multivariable assessment. This assessment is based on patient, surgical, and situational requirements and is crucial for the identification of factors that are associated with difficult bag mask ventilation, direct laryngoscopy and tracheal intubation, as well as difficult SGA ventilation and invasive airway placement.

TRACHEAL INTUBATION

Tracheal intubation remains a cornerstone of traditional airway management. Therefore the anesthetist must be an expert in tracheal intubation and possess the necessary skill and expertise with various equipment and techniques. Tracheal intubation may be performed by traditional methods (e.g., direct laryngoscopy, fiberoptic intubation) or by more novel techniques (e.g., intubating laryngeal mask airway, video-assisted laryngoscopy, retrograde intubation). The technique chosen for tracheal intubation is dependent on the patient's history, physical examination including airway assessment, and previous anesthetic history (e.g., difficult intubation). Indications for tracheal intubation can be found in Table 22-4.

TABLE 22-4 Indications for Tracheal Intubation

Condition	Indication
Anesthesia and surgical	High risk of aspiration of blood (e.g., head and neck trauma, bleeding into respiratory tract) or gastric contents (e.g., severe gastroesophageal reflux disease, inadequate gastric emptying, gastrointestinal obstruction) Anticipated, predicted difficult airway Intraoperative patient positioning that may impede access to the airway (e.g., prone, lateral decubitus) Ineffective oxygenation or ventilation with supralaryngeal airway (e.g., mask ventilation, laryngeal mask airway)
Surgical	Airway access shared with surgeon (e.g., otolaryngologic and head-neck surgery) Surgery requiring paralysis by neuromuscular blocking medications (e.g., intraabdominal surgery) Surgical procedures affecting ventilation and perfusion (e.g., cardiothoracic surgery) Prolonged surgical time
Medical	Inadequate airway protection or suppressed airway reflexes (e.g., Glasgow coma scale less than 10) Ineffective oxygenation or ventilation with supralaryngeal airway (e.g., noninvasive positive pressure respiratory assist device, mask ventilation, laryngeal mask airway) Critical illness (e.g., inadequate respiratory function, acute respiratory distress syndrome, sepsis) Controlled management of arterial carbon dioxide content (e.g,. prevention of hypercapnea for increased intracranial pressure)

Modified from Henderson J. Airway management in the adult. In: Miller RD, et al, eds. *Miller's Anesthesia*. 7th ed. Philadelphia: Churchill Livingstone; 2009:1573-1610.

The procedure for tracheal intubation is preceded by careful attention to optimal head and neck positioning for laryngoscopy. Flexion of the neck and extension of the atlanto-occipital joint, or "sniffing position," allows for proper alignment of the oral, pharyngeal, and tracheal axis (see Figure 22-11). This can be accomplished using pillows, towels, blankets, or by using the OR table's positioning functions (Figure 22-13). Manipulation of the head and neck must be used with caution in patients with decreased cervical range of motion caused by degenerative disease, rheumatic disease, neurologic pathology, trauma, or previous surgical intervention (Figure 22-14).

Adequate pre-oxygenation is essential prior to the induction of anesthesia because it helps to delay arterial desaturation during subsequent apneic situations. Effective pre-oxygenation increases the oxygen content and eliminates much of the nitrogen (approximately 79% of room air) from the functional residual capacity (FRC) and can theoretically provide oxygen to the blood for up to 12 minutes in a healthy individual. However, without pre-oxygenation the oxygen reserve in the FRC is limited, leading to a decrease in the time an anesthetist has to secure the airway. Adequate pre-oxygenation should include instructing the patient to breathe at normal tidal volumes for 3 to 5 minutes with a fresh gas flow of no less than 5 L using a tight mask fit. The respiratory bag should move with each inspiration/expiration, there should be a good end-tidal CO_2 waveform, and the fraction of expired oxygen should begin to increase. This is easily accomplished by applying the facemask as soon as the patient arrives in the operating room and before the application of other monitors. If time is limited, "fast-track" pre-oxygenation, in which the patient takes four vital capacity breaths in 30 seconds, can be used before induction of anesthesia. This technique can be useful in the emergent situation.[11]

Pre-oxygenation and the induction of general anesthesia (e.g., intravenous or inhalation technique) will assist the anesthetist in minimizing complications of tracheal intubation such as hypoxia and hemodynamic aberrancy. In addition, the administration of muscle relaxants (e.g., depolarizing or nondepolarizing) may provide optimal relaxation of the intrinsic and extrinsic muscles of the larynx to promote both laryngoscopy and passage of the endotracheal tube through the rima glottis.

The technique for direct laryngoscopy is dependent on the type of laryngoscope blade used for the procedure, but the premise of control/displacement of the tongue from right-to-left and elevation of the epiglottis remains the same for both techniques. The use of the curved (e.g., Macintosh) laryngoscope requires the anesthetist to (1) place the tip of the laryngoscope in the vallecula, (2) tension the hyoepiglottic ligament by applying a gentle lifting force, which promotes (3) indirect elevation of the epiglottis. In contrast, the use of the straight (e.g., Miller) laryngoscope requires the anesthetist to (1) place the tip of the laryngoscope posterior to the epiglottis and (2) apply gentle force to directly lift the epiglottis. Levering action should never be applied to the patient's dentition. Such action risks dental damage and diminishes the quality of the laryngoscopic view.

If an adequate laryngoscopic view cannot be achieved after direct laryngoscopy, then strategies and algorithms for the difficult or failed airway should be followed. Maintenance of adequate oxygenation and ventilation is the utmost priority of tracheal intubation and can be facilitated by the use of various adjunctive airway equipment and techniques.

MANAGEMENT OF THE DIFFICULT AND FAILED AIRWAY

Management of the difficult airway is a multilayered process that begins with the airway assessment, considers decision-making strategies suggested by the various difficult airway algorithms, continues with a primary airway management plan, and culminates with an understanding of what to do when initial airway management plans fail. As part of a thorough airway management plan, the anesthetist should consider patient characteristics and conditions that predispose them to difficulty with facemask ventilation, supralaryngeal device use, laryngoscopy, tracheal intubation, and cricothyrotomy. As discussed in previous sections, multiple patient characteristics and conditions are associated with difficult airway management. However, attempts at prediction are much less important than demonstrating the appropriate actions to undertake when difficulty is encountered. No test is likely to be perfect; therefore it remains essential that every anesthetist must be trained and equipped to deal with both identified difficult airways and the less common unexpected failed airway.

The unexpected failed airway, also termed the *unanticipated difficult airway*, consists of an airway that has previously been evaluated with no external identifiers indicating difficulty. In other words, the anesthetist does not "expect" or does not "anticipate" difficulty with facemask ventilation, laryngoscopy, intubation, or other airway management techniques. However, after the patient is anesthetized difficulty with ventilation, intubation, or both occurs. Thankfully, the unexpected failed airway is rare. Researchers have attempted to identify indications to help airway management experts recognize these situations early. A common cause of an unanticipated difficult intubation has been shown to be

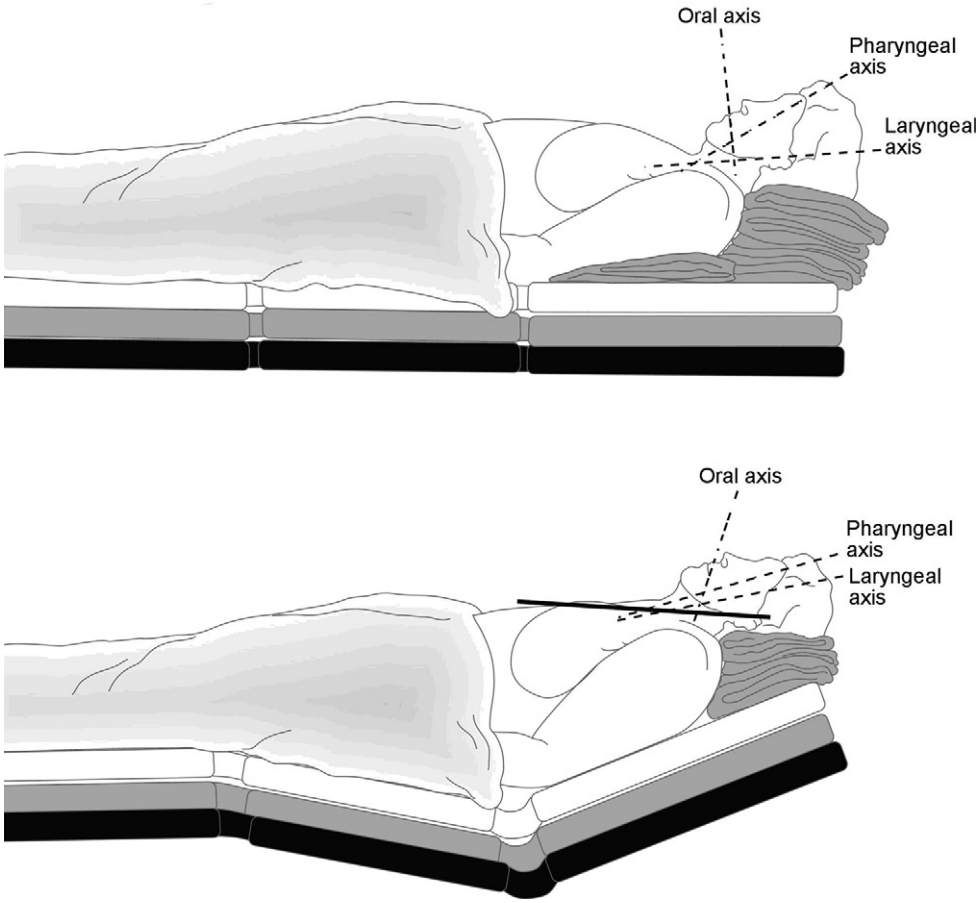


FIGURE **22-13** Improving oral, pharyngeal, and laryngeal axis alignment by raising the head of the operating room (OR) table. **A,** supine position. **B,** Head-up position. (From Thompsen J, et al. Anesthesia case management for bariatric surgery. *AANA J.* 2011;79(2):147-160.)

enlarged lymphoid tissue at the base of the tongue (i.e., lingual tonsil hypertrophy), which cannot be evaluated externally.[56,57] Instead, this condition is discovered during laryngoscopy by a failure to visualize the glottic opening and a description of a grade III or IV airway.

Definition of a Difficult and Failed Airway

The definition of a difficult airway varies within the existing literature, making it challenging to identify the true incidence. However, in broad terms a difficult airway has been described as a clinical situation in which a trained anesthetist experiences difficulty with facemask ventilation, laryngoscopy, intubation, or all of these.[12] A significant amount of subjectivity is possible between observers when performing the different airway assessments leading to various interpretations of predicted airway difficulty. Ultimately, it is not enough to simply identify a difficult airway, but instead to possess the knowledge and skills that guide intervention after difficulty has been identified or when unanticipated difficulty is encountered. Knowing what to do when an airway proves difficult will ensure that proper ventilation is provided in a timely manner.

There are four ways to maintain airway patency and effect ventilation, and thus oxygenation of the tissues. The methods of providing ventilation are as follows:

1. Mask ventilation with an appropriate mask seal with or without a jaw thrust maneuver
2. Placement of a supraglottic airway device such as an LMA
3. Placement of a tube below the vocal cords, such as endotracheal intubation
4. Placement of an invasive airway such as a cricothyrotomy tube

Problems or indications of complexity with one or more of these four methods of providing ventilation would suggest a difficult airway.

When managing an airway, the anesthetist must recognize signs that indicate difficulty with various airway management techniques. Indications of difficult facemask ventilation include (1) gas flow leaks out of the facemask and increasing use of the oxygen flush valve; (2) poor chest rise; (3) absent or inadequate breath sounds; (4) gastric air entry; (5) poor carbon dioxide return and an altered capnographic waveform; (6) a decreasing oxygen saturation of less than 92% as measured by pulse oximetry using a 100% inspired oxygen concentration; and (7) necessity to use an oral or nasal airway and perform a two-handed mask ventilation technique.[19,58] Difficult laryngoscopy and tracheal intubation have been consistently identified in the literature as the inability to visualize any portion of the vocal cords (e.g., Cormack and Lehane grade III or IV) after multiple attempts using a standard laryngoscope. In addition, difficulty with laryngoscopy and intubation has been described as requiring multiple operators in the presence or absence of tracheal pathology. Furthermore, evidence of a failed intubation was identified as a failure to place an endotracheal tube after multiple laryngoscopic attempts.[12] Difficulty with a supraglottic device may also be apparent when placement

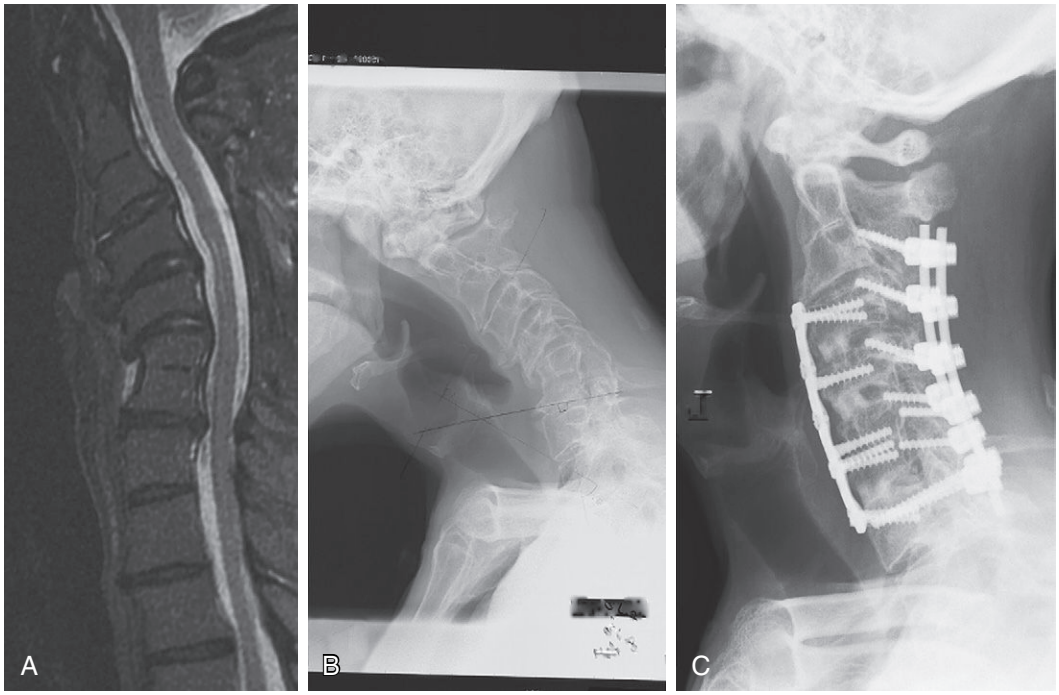


FIGURE **22-14** Sagittal magnetic resonance image (MRI) **(A)** and lateral radiograph **(B)** of a 60-year-old man with a prior laminectomy and Klippel-Feil malformation at C2-C3 shows progressive fixed kyphotic deformity. **C,** Lateral postoperative radiograph after a three-staged procedure, including posterior release, C3-T1 posterior spinal fusion, and C3-T1 correction to anterior cervical discectomy and fusion, shows marked reduction of fixed deformity. (From Chi JH, et al. Complex deformities of the cervical spine. *Neurosurg Clin N Am*. 2007;18(2):295-304.)

requires multiple attempts or requires more than one airway practitioner. Furthermore, objective indications of difficulty with supraglottic ventilation are similar to those described for facemask ventilation earlier, as well as a leak pressure less than 10 to 15 cm H_2O and a poor expired tidal volume.[17] Finally, difficulties with invasive airway device placement, such as a cricothyrotomy, are apparent with bleeding at the site of insertion, an inability to identify the correct anatomic structures, or with difficulty accessing the cricothyroid membrane and puncturing through into the trachea.

Incidence of a Difficult and Failed Airway

Adverse events related to difficulty with airway management continue to occur within the OR, and researchers agree there is continued "room for improvement."[59] In 2008 the Royal College of Anaesthetists in the United Kingdom and the Difficult Airway Society gathered information on administration of 2.9 million general anesthetics in an attempt to identify the incidence of major complications related to airway management. The major complications identified were death, brain damage, emergency surgical airway placement, and unanticipated intensive care unit admission. They found that a major complication occurred at a ratio of 1:22,000 general anesthetics with a mortality rate of 1:180,000.[59] Other researchers have focused strictly on the occurrence of a difficult airway, such as a laryngoscopic view grade II or III, and have reported a 1% to 18% incidence. The incidence of failed tracheal intubation is relatively uncommon and has been reported as 0.05% to 0.35%, with the high end of this range relating to obstetric patients and other surgical patients with known difficulties.[58] As previously mentioned, the incidence of difficult facemask ventilation has been described between 0.9% and 7.8%, with the variation in results occurring as a result of different study parameters. Finally, researchers have reported a supraglottic device complication rate of 0.19%, mostly caused by an inadequate seal and failed placement.[60]

The incidence of difficult intubation and ventilation is much higher in patients with neck or mediastinal pathology, previous surgery, or radiation. For example, Ayuso et al.[61] evaluated 181 patients with pharyngolaryngeal disease and found that 50 (28%) were difficult to intubate, and 4 (2.8%) were impossible to intubate. Ovassapian et al.[62] performed a retrospective analysis on patients with deep neck infections, such as Ludwig's angina, and found a 3.8% incidence of failure to intubate necessitating a tracheostomy. The true incidence of situations in which practitioners cannot intubate and subsequently cannot ventilate (CICV) is difficult to assess because of the failure to consistently and accurately report these occurrences. However, some authors have reported an incidence of 1:2250 in nonparturients and as much as 1:300 in parturients.[14,63] Kheterpal et al.[22] reported four cases of impossible mask ventilation and intubation in 53,041 cases involving anesthetics.

When assessing the frequency of emergency cricothyrotomy placement, Cook et al.[59] reported and incidence of 1 in every 12,500 to 50,000 general anesthetic cases. Other researchers explained that the incidence of emergency cricothyrotomy placement is strongly influenced by the clinical situation and contributing patient factors.[64] For example, the incidence of emergency cricothyrotomy placement resulting from failed tracheal intubation in the emergency department (ED) has been reported as 0.3% to 0.8%, increased to 1.4% in trauma patients, and was reported as high as 11% in the prehospital setting.[65-67] Other research also concluded that difficult airways may be encountered more frequently outside of the OR. A recent audit from the United Kingdom reported that airway-related adverse events, which led to death or brain damage, were 30 to 60 times more likely to occur in the ED or intensive care unit (ICU).[68]

Difficult Airway Algorithms

When considering how to approach airway management, certain issues should be considered prior to the induction of anesthesia. Rosenblatt[16] identified five questions, termed "the airway approach algorithm," which can help the anesthetist initially develop an airway management plan:

1. Is airway management necessary?
2. Will direct laryngoscopy and tracheal intubation be straightforward?
3. Can supralaryngeal ventilation be used?
4. Has the risk for aspiration been minimized or is the stomach empty?
5. In the event of airway failure, will the patient tolerate an apneic period?

If the answer to each of these questions is "yes," then the airway is deemed manageable by conventional means and the anesthetist may proceed with the induction of anesthesia followed by muscle relaxation to provide optimal conditions for laryngoscopy and intubation. If however, the answer to any question is "no," then the anesthetist should either abandon airway management altogether and proceed with an alternative anesthetic option (e.g., monitored anesthesia care, regional anesthesia), or follow the guidelines set forth by various professional associations for the management of anticipated airway difficulty.

Difficult airway management is multifactorial and necessitates an awareness of the interactions between patient conditions, the clinical setting, and the anesthesia provider's experience and skill level. Each of these factors alone or in combination can contribute to poor outcomes during airway manipulation and must be considered when developing airway management strategies. Tools that help the anesthetist formulate plans for safe airway care in the face of both known and unanticipated difficulties are known as difficult airway algorithms. Multiple difficult airway algorithms exist, but perhaps the most notable is the American Society of Anesthesiologist's (ASA) difficult airway algorithm (Figure 22-15).

ASA Difficult Airway Algorithm

The difficult airway algorithm, established in 1991 by the ASA, gave anesthesia practitioners the first standardized approach for the management of the anticipated or unanticipated difficult airway. The practice guidelines were updated in 2003 to reflect current management strategies.[12] The algorithm provides guidelines for dealing with difficult facemask ventilation, difficult laryngoscopy, difficult tracheal intubation, and failed intubation. Assessment of the airway and use of the difficult airway algorithm provide the practitioner with four end-points: (1) intubation awake or asleep, (2) adequate or inadequate facemask ventilation or LMA ventilation, (3) approach to intubation by special means, and (4) surgical or nonsurgical emergency airway access. Each of these end-points entails using specific airway equipment and techniques to facilitate ventilation (Table 22-5). According to the algorithm, an organized plan should be initiated when a difficult airway is encountered. In essence, the philosophy of the ASA difficult airway algorithm has been explained by the following[69]:

1. Plan ahead, and be prepared for failed attempts at intubation.
2. If you are suspicious of airway trouble, intubate awake.
3. If you get into trouble and can still ventilate the patient, wake him or her up.
4. When making intubation choices, do what you do BEST.

Other Difficult Airway Algorithms

An important fact to keep in mind is that many of the guidelines suggested in difficult airway algorithms are based on the opinions of experts in the field of airway management, but lack empirical evidence. Reasons given have included the significant challenges with the design of randomized controlled trials, the infrequency of certain difficult airway events (e.g., failed airway or cricothyrotomy), and an inability to account for confounding variables such as individual practitioner experience.[70] However, the widespread distribution of the different guidelines has resulted in a reduction in airway-related critical accidents.[70,71] Overall, it is important to remember that difficult airway algorithms are simply guidelines that provide structure for decision making and are tools for use when managing difficult airways, but they do not preclude personal responsibility and sound clinical judgment.

There are similarities between the ASA difficult airway algorithm and other airway algorithms. For example, in the event of failed intubation, the ASA difficult airway algorithm reverts to facemask ventilation, and if that proves inadequate, moves to ventilation with an LMA. The Difficult Airway Society's (DAS) algorithm suggests using the LMA as means for ventilation and oxygenation immediately after a failed intubation, and then if the LMA fails, suggests reverting back to facemask ventilation. Both the ASA and DAS algorithms advocate for awakening the patient if initial attempts at intubation fail, but subsequent ventilation attempts succeed. Furthermore, both recommend the placement of either needle or surgical cricothyrotomy if intubation has failed and both facemask and LMA ventilation have proven to be inadequate; this is also termed the CICV situation.[12,72,73]

It is worth noting the important role of the LMA (and perhaps other SGA devices) within the difficult airway algorithms. The LMA is used for rescue ventilation at two points in the ASA difficult airway algorithm: first, in the anesthetized patient whose trachea cannot be intubated but can be ventilated with a facemask (anesthetized nonemergency limb); and second, in the anesthetized patient whose trachea cannot be intubated and whose lungs cannot be conventionally ventilated (anesthetized emergency limb). The DAS algorithm describes a similar strategy, and comparable uses can also be found in other national recommendations from Germany and Italy.[73-76] Brimacombe[77] identified five major considerations that highlight the role of the LMA in difficult airway management:

1. The anatomic and technical factors indicating difficulty with facemask ventilation, laryngoscopy, and tracheal intubation do not generally influence LMA insertion and function; thus the LMA has a high likelihood of success in instances where mask ventilation or tracheal intubation have failed or proven to be difficult.
2. The LMA can be used for both ventilation and as a conduit for intubation.
3. The LMA provides a method of ventilating the lungs, allowing additional time to perform tracheal intubation in an unhurried manner.
4. Usually, LMA insertion is atraumatic, allowing the opportunity to use optic devices that depend on clear unfettered airways for visualization.
5. The LMA is routinely used as an airway management tool, which increases the anesthetist's comfort and skill level.

The number of laryngoscopic attempts and total procedural duration for intubation are quantifiable objective measurements used by multiple airway management guidelines as indications of airway difficulty. Most airway management guidelines allow between 2 to 4 laryngoscopic attempts and between 5 to 10 minutes of total procedural time before they classify the airway as a failed laryngoscopic intubation.[63,70,78] Limiting the number of laryngoscopic attempts is done to prevent excessive airway instrumentation leading to airway trauma and increased difficulty. It has

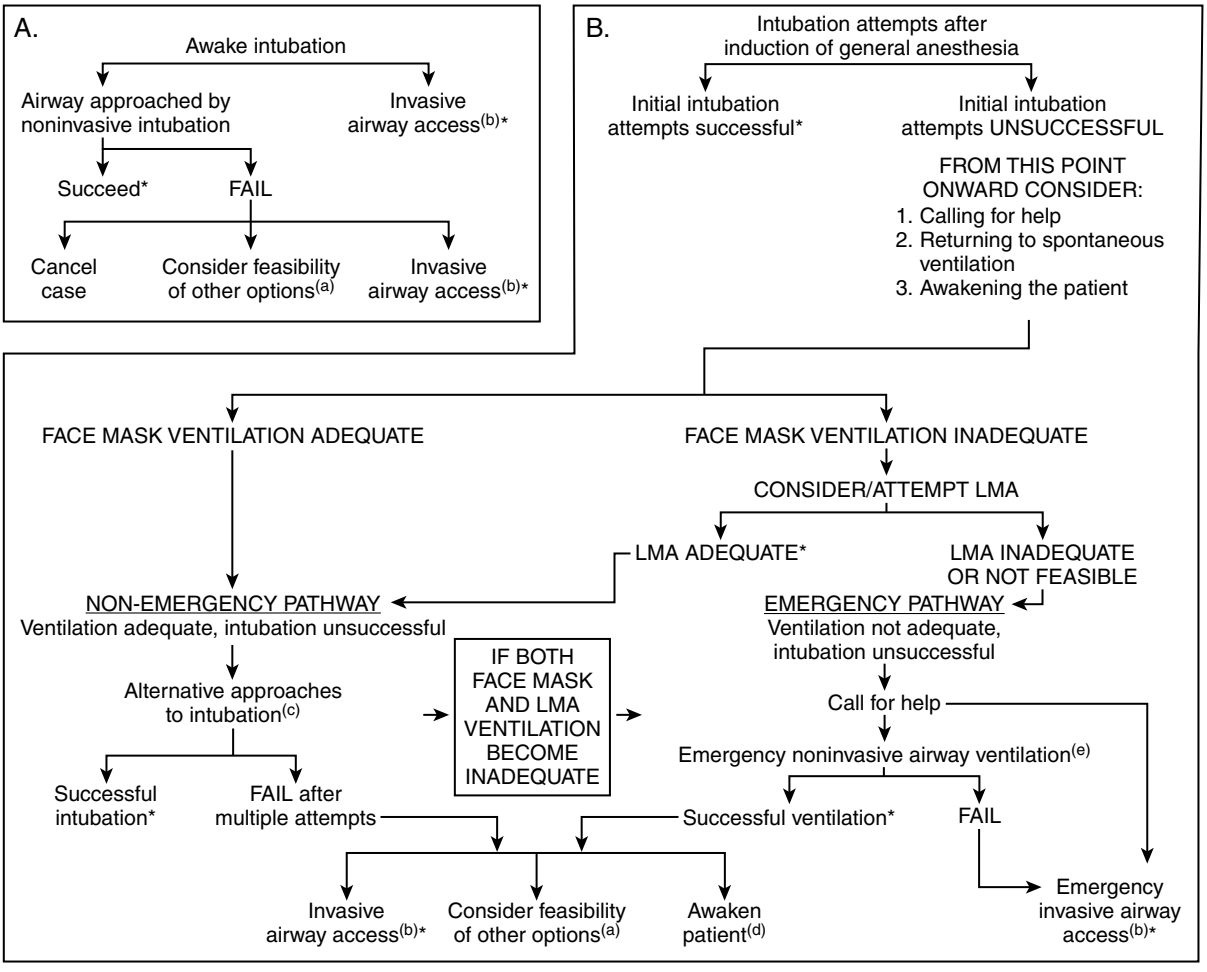
1. Assess the likelihood and clinical impact of basic management problems:
   - A. Difficult ventilation
   - B. Difficult intubation
   - C. Difficulty with patient cooperation or consent
   - D. Difficult tracheostomy

2. Actively pursue opportunities to deliver supplemental oxygen throughout the process of difficult airway management

3. Consider the relative merits and feasibility of basic management choices:

A.	Awake intubation	vs	Intubation attempts after induction of general anesthesia
B.	Noninvasive technique for initial approach to intubation	vs	Invasive technique for initial approach to intubation
C.	Preservation of spontaneous ventilation	vs	Ablation of spontaneous ventilation

4. Develop primary and alternative stategies:



*Confirm ventilation, tracheal intubation, or LMA placement with exhaled CO_2.

a. Other options include (but are not limited to) surgery utilizing face mask or LMA anesthesia, local anesthesia infiltration, or regional nerve blockade. Pursuit of these options usually implies that mask ventilation will not be problematic. Therefore, these options may be of limited value if this step in the algorithm has been reached via the Emergency Pathway.
b. Invasive airway access includes surgical or percutaneous tracheostomy or cricothyrotomy.
c. Alternative noninvasive approaches to difficult intubation include (but are not limited to) use of different laryngoscope blades, LMA as an intubation conduit (with or without fiberoptic guidance), fiberoptic intubation, intubating stylet or tube changer, light wand, retrograde intubation, and blind oral or nasal intubation.
d. Consider re-preparation of the patient for awake intubation or canceling surgery.
e. Options for emergency noninvasive airway ventilation include (but are not limited to) rigid bronchoscope, esophageal-tracheal Combitube ventilation, or transtracheal jet ventilation.

FIGURE **22-15** The American Society of Anesthesiologists (ASA) Difficult Airway Algorithm. (From ASA Task Force on Management of the Difficult Airway: practice guidelines for management of the difficult airway: an updated report. *Anesthesiology.* 2003;98(5):1269-1277.)

been described that when an unanticipated difficult intubation is encountered, the first attempt is usually the "awareness" look, and that the second attempt should be performed under the best possible conditions (e.g., proper head and neck extension, head and shoulders elevated, experienced practitioner). If subsequent attempts are performed, they should be done using alternative approaches (e.g., blade change, introducer usage, video laryngoscope), and possibly performed by a different anesthetist.[79]

Finally many of the airway algorithms advocate for the use of alternative airway techniques, including awake intubation, as long as ventilation is adequate and time permits. The choice of which alternative airway technique or difficult airway adjunct to use should be based on the anesthetist's clinical judgment, which again should consider patient conditions, the clinical setting, and the anesthesia provider's experience and skill level.

Difficult Airway Cart

A dedicated difficult airway cart or box should be made readily available at some location in the OR. This cart should be checked on a routine basis to ensure that all materials are available and all devices are working properly. There is no definitive list of equipment, and the contents of the difficult airway cart should be decided on by the anesthesia department personnel based on the likely caseload and department budget. The recommended basic elements of the difficult airway cart should contain devices for (1) standard laryngoscopy; (2) intubation by alternative means; (3) tube position control; and (4) equipment for anesthetizing the airway (Box 22-6).[70] Some difficult airway carts may also contain video laryngoscopy devices. In addition, the capacity to perform flexible fiberoptic bronchoscopy (FOB) should be immediately available.

TABLE 22-5 Airway Adjuncts and Alternative Airway Techniques

Supraglottic Airways	Video Laryngoscopes	Stylets	Fiberoptic Scopes	Cricothyrotomy
LMA Classic LMA Proseal or Supreme Intubating LMA "Fastrach" C-Trach Cobra PLA Streamlined liner of the pharynx airway (SLIPA) I-Gel Combitube King LT/LTS-D	GlideScope McGrath Laryngoscope Airtrach Shikani Optical Stylet Bonfils Pentax-AWS Bullard Laryngoscope	Eschmann stylet Lighted stylet (e.g., Trachlight) Tube exchangers	Fiberoptic bronchoscope Fiberoptic laryngoscope with various blade sizes Fiberoptic flex tip laryngoscope blades	Melker Fastrach Commercial retrograde wire intubation kit

LMA, Laryngeal mask airway; *LT*, laryngeal tube; *LTS-D*, disposable laryngeal tube with gastric access; *PLA*, peri-laryngeal airway.

BOX 22-6

Suggested Components of the Difficult Airway Cart

Standard Airway Equipment
- Oral and nasal airways of various sizes
- Tongue blades
- Flexible stylets
- Endotracheal tubes (cuffed and uncuffed) from size 2.5 to 8.0
- Miller laryngoscope blades sizes 0, 1, 2, 3, 4
- Macintosh laryngoscope blades sizes 2, 3, 4
- Laryngoscope handles—regular and stubby
- Extra laryngoscope batteries and bulbs
- Magill forceps
- Salem sump—16 and 18 French
- Suction catheters—10, 12, 14 French
- Oxygen mask
- Nasal cannula
- Oxygen with 15 L/min regulator
- Ambu bag

Alternative Airway Equipment
- Laryngeal mask airways—sizes 3, 4, 5
- Intubating laryngeal mask airway
- Combitube
- Lighted stylet (e.g., Trachlite)
- Eschmann stylet (e.g., gum elastic bougie)
- Tube exchanger—small, medium, large
- Ventilating stylet
- Needle cricothyrotomy set
- Retrograde intubation set
- Melker percutaneous dilational cricothyrotomy set
- Transtracheal jet ventilator

Tube Position Control
- Stethoscopes
- CO_2 detectors
- Esophageal detector device

Topical or Infiltration Anesthesia
- Syringes—3, 5, 10, and 20 mL (three or four of each size)
- Angiocatheters—14, 16, 18, 20 gauge (three each)
- Xylocaine jelly 2%
- Lidocaine—4% topical, 2% for injection
- Surgilube
- Nebulizer
- Atomizer
- 4×4 gauze pads

Video Laryngoscopes
- Airtraq
- C-MAC
- GlideScope
- McGrath

Fiberoptic Bronchoscopy Equipment
- Tongue clamp
- Light source
- Endoscopy mask
- Ovassapian intubating airway

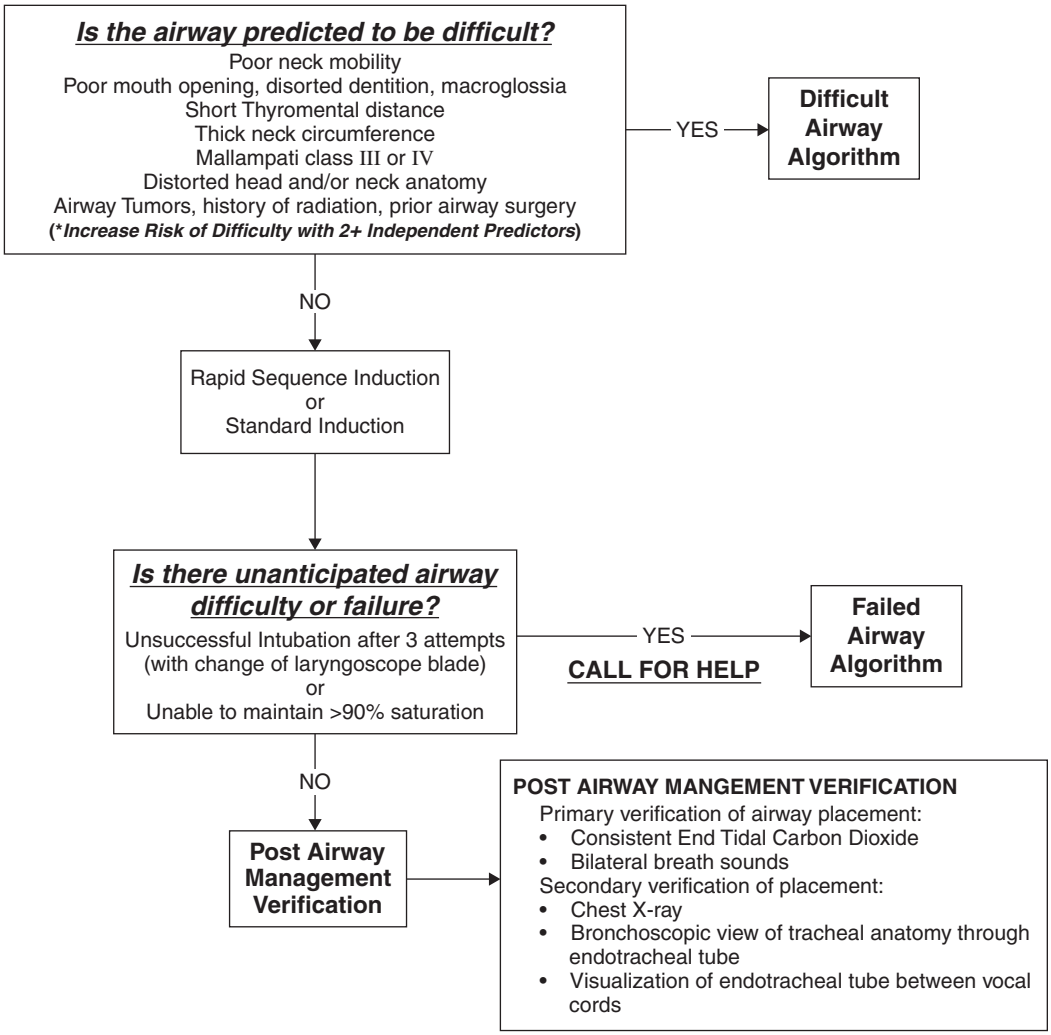


FIGURE **22-16** Standard airway strategy.

Smart Airway Strategies

In an attempt to compile and simplify existing airway management algorithms, and to provide information concerning current alternative techniques for difficult airway management (e.g., video laryngoscopes), the following smart airway strategies have been developed. These airway management strategies were prepared using information from the ASA difficult airway algorithm, the Difficult Airway Society's airway management guidelines, Canadian Airway Focus Group's algorithm for the proposed management of the unexpected difficult airway, the Rush Medical Center approach to emergency airway management, and current literature concerning airway management.[12,73,80-83]

The smart airway strategies are not intended as a minimum standard of practice, nor are they to be used as a substitute for good clinical judgment. Instead, they are guidelines that reflect current opinions by professional associations, airway experts, and research. The smart airway strategies are guided by questions, which help to direct clinical decision making according to either a "yes" or "no" answer. Included at different points within the strategies are considerations with respect to airway assessments, adjunctive airway use, and methods of airway management. The smart airway strategies should be regarded as a tool to help the anesthetist develop a basic airway management plan (Figure 22-16), to provide a structural framework for the management of an identified difficult airway (Figure 22-17), and to assist with decision making after initial attempts at airway management fail (Figure 22-18).

Standard Airway Strategy

The *standard airway strategy* (see Figure 22-16) will be the most commonly followed strategy. It begins by asking the question "Is the airway predicted to be difficult?" Multiple airway examinations are provided to assist with the overall airway examination. As mentioned earlier, the presence of two or more independent predictors increases the risk of difficulty with airway management. If the answer to the initial question is "yes" and airway management is anticipated to be difficult, then the anesthetist should proceed to the *anticipated difficult airway strategy*. If the answer is "no," then the anesthetist should proceed with either an anesthetic standard or rapid sequence induction. The question then becomes "Is there unanticipated airway difficulty or failure?" If the answer is "yes," as demonstrated by unsuccessful intubation after three laryngoscopic attempts (with a change in laryngoscope blades), or difficulty with ventilation as evidenced by the inability to maintain an oxygen saturation greater than 90%, then the anesthetist should call for help and proceed to the *failed or unanticipated difficult airway strategy*.

If no difficulty was encountered and the airway was successfully managed, then the anesthetist should proceed with *post airway management verification*, which consists of primary and

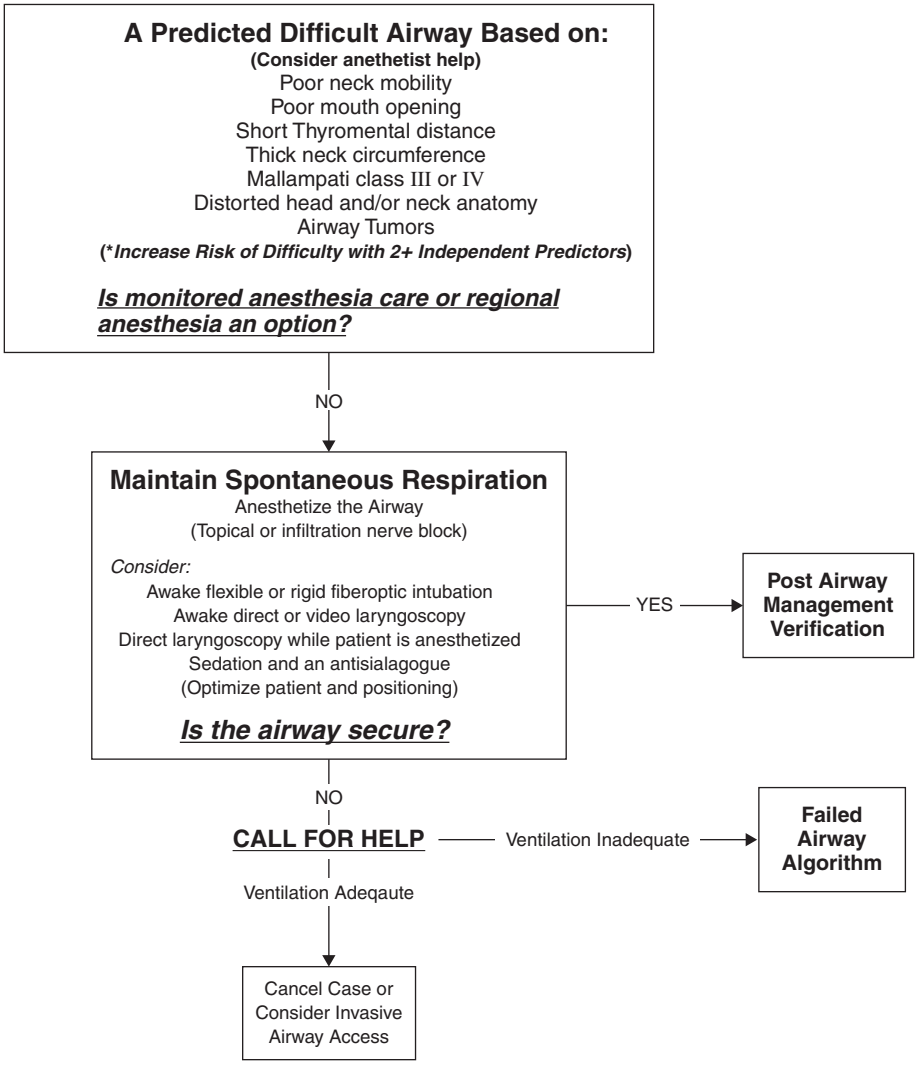


FIGURE **22-17** Difficult airway strategy.

secondary verifications. Primary verification of tube placement is apparent when consistent end tidal carbon dioxide tracing on the end tidal CO_2 monitor is observed and bilateral breath sounds are auscultated. Secondary verification of placement is evident by a chest radiograph confirming ETT placement, a bronchoscopic view through the airway of the tracheal anatomy including the carina, and visualization of the ETT between the vocal cords.

Anticipated Difficult Airway Strategy

The anticipated difficult airway strategy (see Figure 22-17) is used when the airway has been evaluated and predicted to be difficult. Again, multiple airway examinations are provided for review and the presence of two or more independent predictors increases the risk of difficulty with airway management. Anytime the airway is predicated to be difficult, additional anesthesia providers should be present. The strategy then asks "Is monitored anesthesia care or regional anesthesia an option?" If the answer is "no," the strategy then states to employ airway management methods that "maintain spontaneous respiration." Devices that assist with the placement of an ETT while the patient is awake and breathing spontaneously include a rigid or fiberoptic device, a standard laryngoscope, or video laryngoscope. The airway should be anesthetized using either topical or infiltration nerve blocks, and both sedation and an antisialagogue to dry out secretions in the airway should be considered. Techniques for anesthetizing the airway are discussed in subsequent sections. The anesthetist may consider securing the airway after anesthetizing the patient with intravenous or inhalational techniques while maintaining spontaneous ventilation. This method of airway management should be based on the clinical judgment of the practitioners present, the skill of the anesthetist, and patient characteristics (such as an uncooperative patient). Additional airway adjuncts and a cricothyrotomy kit should be readily available.

After attempting to place a definitive airway while the patient is awake or anesthetized, the question then becomes "Is the airway secure?" If the answer is "yes," then proceed to *post airway management verification*. If the answer is "no," then call for help and assess whether ventilation is adequate. If ventilation is inadequate, then proceed to the *failed or unanticipated difficult airway strategy*. If ventilation is adequate, and previous attempts for securing the airway have failed, then cancel the case and consider other anesthetic options. If the case must proceed, then consider placement of an invasive airway.

Failed or Unanticipated Difficult Airway Strategy

The failed or unanticipated difficult airway strategy (see Figure 22-18) is a critical time-sensitive strategy. If help has not already

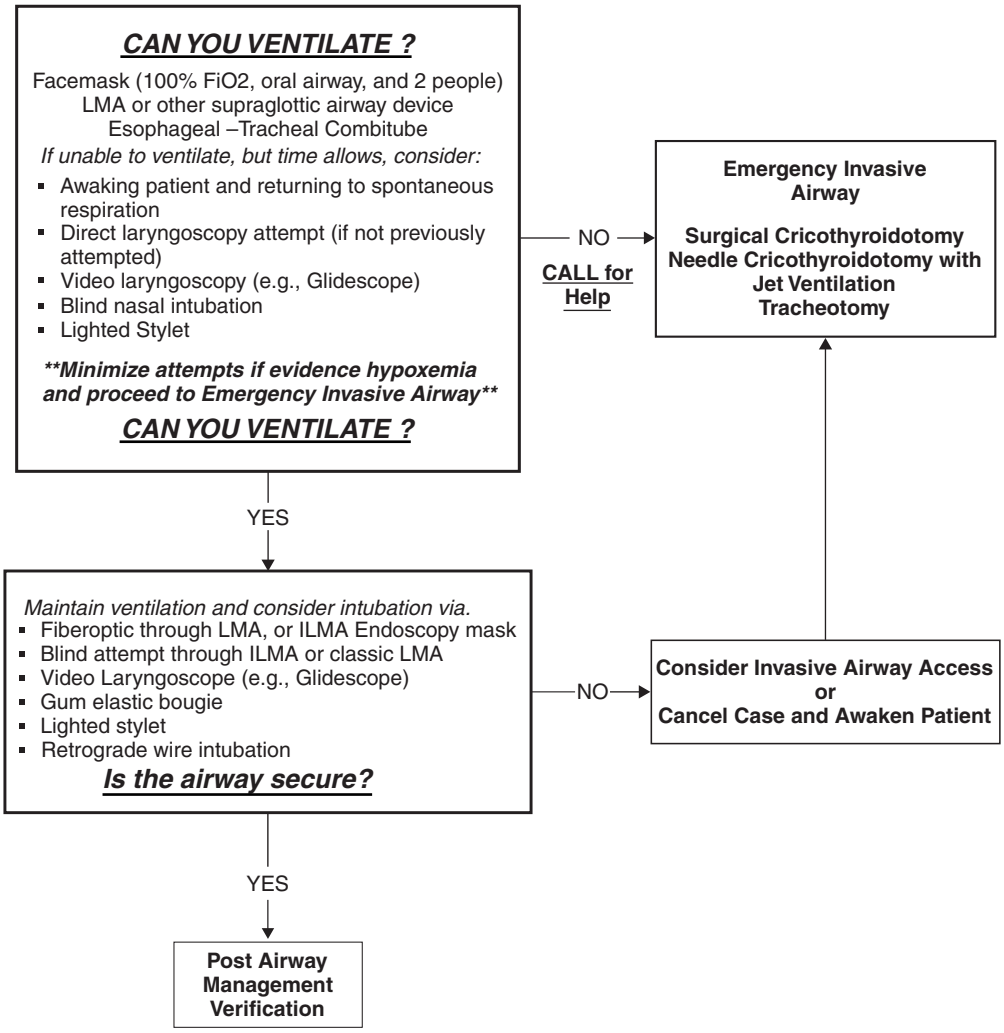


FIGURE **22-18** Failed or unanticipated difficult airway strategy.

arrived, then help should be called for again and confirmed en route. The most important question is "CAN YOU VENTILATE?" Ventilation is essential and must be the primary goal. It should be attempted with either a facemask, SGA device (e.g., LMA), or with an esophageal-tracheal Combitube. At this point in the airway strategy, the anesthetist may consider awakening the patient, attempting a direct or video laryngoscopy (if not already attempted), blind nasal intubation, or lighted stylet intubation. The choice of which technique to use should be based on the patient's condition, criticality of the situation, and skill of the anesthesia provider. However, these considerations should be minimized if there is evidence of hypoxemia, and invasive airway placement must be considered because persistent unsuccessful intubation attempts have been associated with complete airway obstruction, brain damage, and death.[71,84] Again, the question to ask is "CAN YOU VENTILATE?" If the answer is "no," and the anesthetist cannot intubate and subsequently cannot ventilate, then the anesthetist should move to "emergency invasive airway" access and ventilation. Invasive airway placement can be accomplished by a surgical cricothyrotomy, a needle cricothyrotomy with jet ventilation, or a tracheotomy.

If, however, the anesthetist is able to ventilate after other attempts at ventilation or intubation have failed, then additional airway options can be considered. While ventilating the patient, intubation of the trachea can be accomplished using (1) a fiberoptic bronchoscope placed through an LMA, an intubating laryngeal mask airway (ILMA), or an endoscopy mask; (2) a blind intubation attempt through an ILMA; (3) video laryngoscope (e.g., Glidescope); (4) gum elastic bougie; (5) lighted stylet; or (6) retrograde wire intubation. This list is not all-inclusive and other airway adjuncts can be considered; however, trauma to the airway should be avoided and ventilation must be preserved.

After additional attempts at airway management, the question then becomes "Is the airway secure?" If the answer is "no," then the anesthetist should awaken the patient. If awakening the patient is not an option, then the placement of an invasive airway needs to be considered. However, if the answer is "yes," and the airway is secure, then the anesthetist should proceed with *post airway management verification*. In addition, when surgery is finished and airway control is no longer needed, the anesthetist should follow strategies for protected extubation later in this chapter.

Frequent training in the clinical setting, at workshops, or during simulation scenarios can help increase familiarity with difficult airway management strategies and the use of different airway adjuncts, and may play a role in decreasing complications associated with difficult airway management.[85-87] Furthermore, anesthetists should personally prepare a predefined algorithm to use in the event of an unexpected difficult or failed airway. A predefined algorithm is a back-up plan used when ventilation, laryngoscopy, or intubation prove to be difficult. A back-up plan such as a gum elastic bougie followed by the IMLA if needed has shown to be effective in many

unexpected difficult airway situations.[88] Ultimately, the primary goal of difficult airway management is to avoid entering the territory of cannot intubate and cannot ventilate. An awareness and proficiency with the different airway management techniques and strategies, each of which has unique advantages and disadvantages depending on the clinical situation, will assist the nurse anesthetist in safe and effective difficult airway management.

Awake Intubation

When airway management is anticipated to be difficult, many airway guidelines suggest that the airway should be managed while the patient is awake and breathing spontaneously. Because the patient will maintain spontaneous ventilation and pharyngeal/laryngeal muscle tone during airway management, regional anesthesia for the airway (e.g., airway blocks) provides an increased margin of safety and therefore should have a place in every anesthetist's armamentarium.[28] It is imperative to note that the provision of regional anesthesia for the airway can be a time-consuming endeavor and may need to be abandoned if the patient is unwilling or unable to cooperate. Sedation medications are used as an adjunctive therapy to help calm the patient during an awake laryngoscopic intubation attempt. Agents that have been used include midazolam, propofol, etomidate, ketamine, fentanyl, remifentanil, and dexmedetomidine.[89] Agent selection depends on the clinical situation (e.g., an emergency that requires immediate airway access versus an anticipated difficult airway for a scheduled surgery), availability of the medication, and the provider's familiarity with the sedative agent. In addition, combinations of these medications are frequently used in clinical practice to reduce the total amount of any one drug given, especially since most cause respiratory depression in a dose-dependent fashion.

Caution should be exercised in patients with any degree of respiratory compromise or who are at risk for developing respiratory failure, because even small doses of sedative medications may induce apnea. Furthermore, sedative and opioid analgesic agents decrease both pharyngeal and laryngeal muscle tone, which can lead to a total obstruction of the airway. Finally, deep sedation, or sedation levels that approach general anesthesia, defeat the purpose of performing an awake intubation and increase the risk for loss of airway reflexes, upper airway obstruction, and airway failure.[89] Therefore it is important for the anesthetist to remain vigilant during the administration of sedative medications in the anticipated difficult airway and to provide judicious sedation to assist with comfort and decrease anxiety, but to avoid oversedation that may increase the risk of apnea.

Awake Intubation Techniques

An awake intubation is the placement of an endotracheal tube into the trachea in situations where the patient is not under the influence of general anesthesia. Awake is somewhat of a misnomer because it is very challenging to place an endotracheal tube without the use of local anesthesia, sedation, or both because of the strong reflexes that exist in the airway. However, the patient is awake in the sense that they are cooperative and ventilating spontaneously. Awake intubation is an essential component of difficult airway management and should be a primary option any time a difficult intubation is anticipated. There are two awake techniques that can be considered after the patient has been prepared and the airway has been anesthetized:

1. Perform a laryngoscopy with a standard laryngoscope or video laryngoscope to diagnostically determine whether the patient is difficult to intubate.
2. Perform a tracheal intubation using a flexible fiberoptic bronchoscope that has a preloaded ETT and can be passed into the trachea in a known difficult airway.

TABLE 22-6 Medication Considerations for Awake Intubation

	Medication	Indication
Intravenous Medications	Antisialagogue (glycopyrrolate or atropine)	Dry secretions in the airway
	Propofol Midazolam Ketamine Etomidate Dexmedetomidine Fentanyl Remifentanil	Provides sedation, anxiolysis, and assists with patient cooperation *Caution with respiratory depression and decreased muscle tone*
	Bicitra Metoclopramide Histamine 2 blocker (e.g., famotidine, ranitidine, cimetidine)	Aspiration prophylaxis
Topical or Infiltration Medications	Phenylephrine 1%	Vasoconstrictors for nasal intubation
	Lidocaine 2%, 4%	Topical local anesthesia
	Cetacaine	Topical local anesthesia
	Benzocaine 20%	Topical local anesthesia
	Cocaine 4%	Topical local anesthesia and vasoconstrictor
	Lidocaine 2%	Infiltration nerve block

It is generally better to secure the airway on the first visualization; however, there may be situations in which it is best to anesthetize and paralyze the patient for an optimum view of the laryngeal opening. However, these situations will need to be determined by the clinician.

When performing an awake intubation, the anesthetist may elect to place an oral or nasal ETT. The nasal route often has a direct line to the laryngeal opening; however, this route may carry an increased risk of hemorrhage or soft tissue damage. Examples of situations where an awake intubation would be necessary include patients with previous airway difficulty, unstable neck fractures, halo devices, small or limited oral openings, upper airway impingement by a mass, and patients in the critical care setting. An important consideration to remember is that topical anesthesia and instrumentation of an inflamed, compromised airway can produce rapid airway compromise, and the anesthetist must be prepared to quickly intervene, which may include performing an emergency invasive airway.[89] However, with proper patient preparation and a sufficiently anesthetized airway, an awake intubation can be accomplished quickly, safely, and with minimal discomfort to the patient.

Patient Preparation

For maximum patient cooperation, the awake procedure must be clearly explained and consent obtained. It is difficult if not impossible to proceed if the patient is uncooperative or unwilling to participate. Depending on the situation and the patient's condition, judicious use of anxiolytics and narcotics may be considered as previously discussed. Examples of medications that may be considered when anesthetizing the airway are contained in Table 22-6.

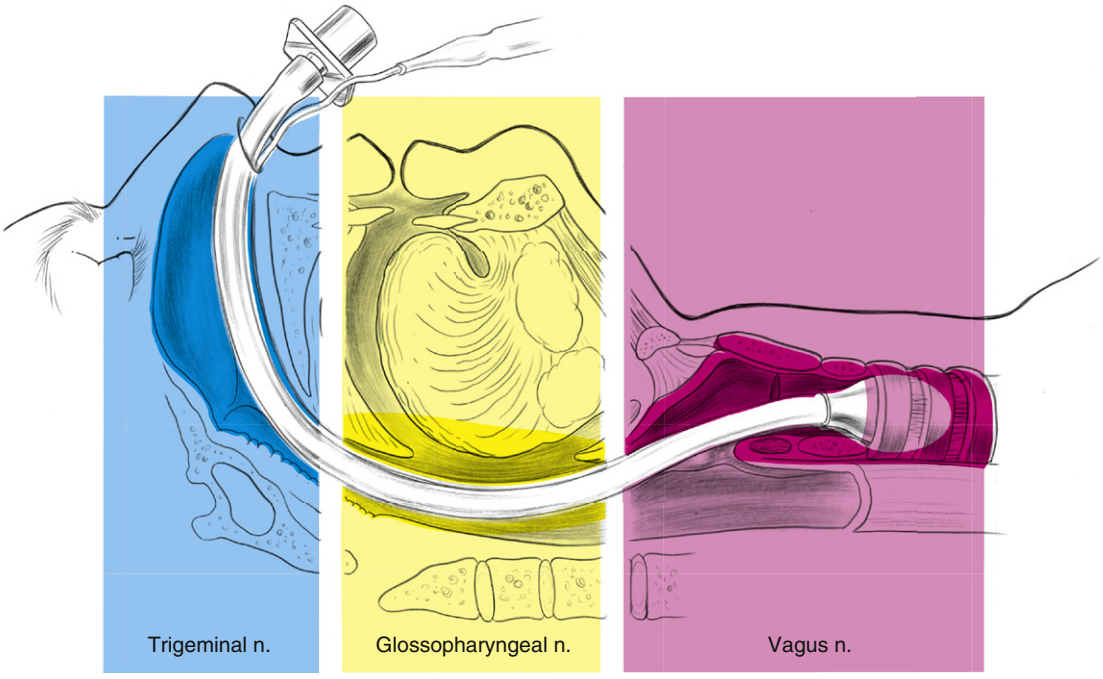


FIGURE **22-19** Cranial nerve innervation of the upper airway. (From Brown DL, et al. *Atlas of Regional Anesthesia*. 4th ed. Philadelphia: Saunders; 2010.)

Administration of an antisialagogue (such as glycopyrrolate) can help dry secretions and maximize the view of the laryngeal structures. Furthermore, an antisialagogue will decrease the secretion of saliva, allowing topical local anesthetics to penetrate the mucosa to a greater degree and enhancing the anesthesia in the oral cavity, tongue, oropharynx, and hypopharynx. However, 20 minutes is usually required to effectively decrease secretions.

The risk of aspiration must always be considered when the airway reflexes have been anesthetized. Therefore medications that decrease stomach acid production and promote gastric emptying should be considered. Vasoconstriction of the nasal passages reduces the risk of mucosal damage and hemorrhage. Solutions containing oxymetazoline 0.05% (afrin), or phenylephrine (Neo-Synephrine) can be sprayed into the nose 2 to 3 minutes prior to application of the local anesthetic.

The most widely used local anesthetic for anesthetizing the airway is lidocaine in various forms and concentrations. Cocaine 4%, benzocaine 20%, and tetracaine are also effective anesthetics. In addition to its local anesthesia–producing effects, cocaine causes vasoconstriction and can be considered for local anesthesia in the nasal cavity. Peak serum lidocaine levels are highest 30 minutes after instillation. Use of lidocaine within the recommended dosage keeps serum lidocaine levels below toxic levels.[90,91] The evidence regarding the maximum safe dose for the topical administration of local anesthetics is controversial. However, an estimate of the maximum safe dose of local anesthesia should be calculated prior to any administration (e.g., lidocaine 4-5 mg/kg). Finally, clinical judgment of the situation is required and the anesthetist should continually assess for signs and symptoms of toxicity.

AIRWAY BLOCKS

Anesthesia for the airway can be provided by either topical anesthesia, infiltration, or a combination of the two. The anesthetic requirements for the airway include sensory inhibition of the nasal, oral, pharyngeal, laryngeal, and tracheal mucosa. Specific branches of three cranial nerves need to be anesthetized to perform an awake oral or nasal intubation. The three cranial nerves include the trigeminal, glossopharyngeal, and vagus nerves (Figure 22-19). Both the ophthalmic and maxillary divisions of the trigeminal nerve provide sensory innervation to the nasal septum and lateral wall. In addition, the mandibular division of the trigeminal nerve forms the lingual nerve, which provides sensation to the anterior two thirds of the tongue. The glossopharyngeal nerve provides sensory innervation to the posterior third of the tongue, the soft palate, and the oropharynx. Finally, the vagus nerve provides sensory innervation to the hypopharynx, larynx, and trachea via the superior and recurrent laryngeal nerves. The internal laryngeal branch of the superior laryngeal nerve provides sensation above the vocal cords, and the recurrent laryngeal nerve provides sensation below the vocal cords (Figure 22-20).

Topical Anesthesia

Anesthesia to the nasal septum, nasal wall, and nasopharynx blocks the anterior ethmoidal, nasopalatine, and sphenopalatine nerves that originate from the ophthalmic and maxillary divisions of the trigeminal nerve. These areas can be anesthetized by insertion of 5 mL of viscous lidocaine down each naris. The solution then liquefies to a greater degree and may coat the back of the throat. The nasal and oral cavities, as well as the nasopharynx and oropharynx, may also be anesthetized by adding 4 mL of 4% lidocaine with 1 mL of 1% phenylephrine to either a handheld nebulizer or a nebulizer attached to a facemask.[89] As the patient breathes through the nose and mouth, small droplets of local anesthetic are deposited on the mucous membranes. This method is also effective for anesthetization of subglottic tissue. However, this procedure requires a minimum of 10 to 20 minutes and may necessitate additional topical anesthesia during the awake procedure.

An alternative approach to nebulization is providing topical anesthesia by atomization using a device such as the DeVilbiss atomizer (Figure 22-21), or mucosal atomization device. Atomization produces larger droplets than nebulization, resulting in an

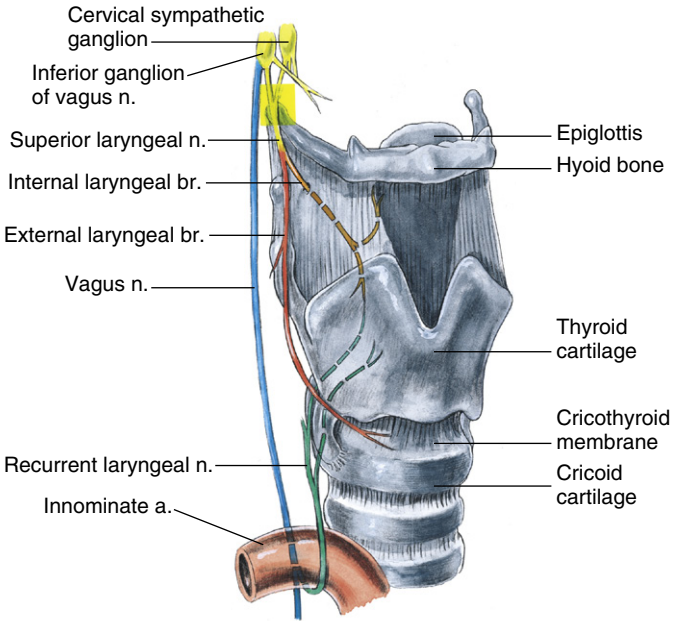


FIGURE **22-20** Laryngeal anatomy and nerve innervation. (From Brown DL, et al. *Atlas of Regional Anesthesia*. 4th ed. Philadelphia: Saunders; 2010.)

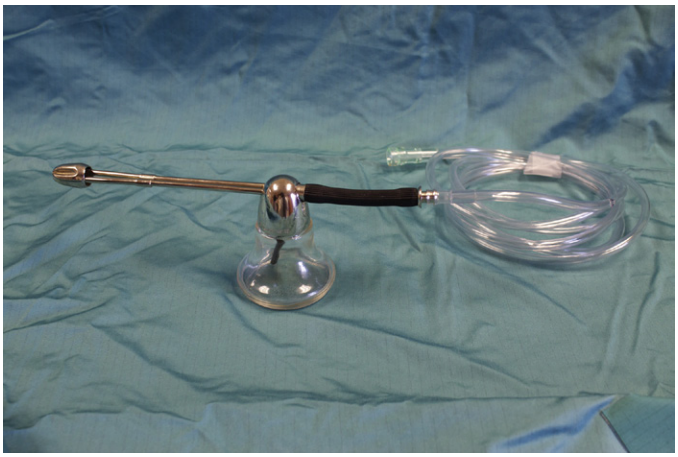


FIGURE **22-21** DeVilbiss atomizer.

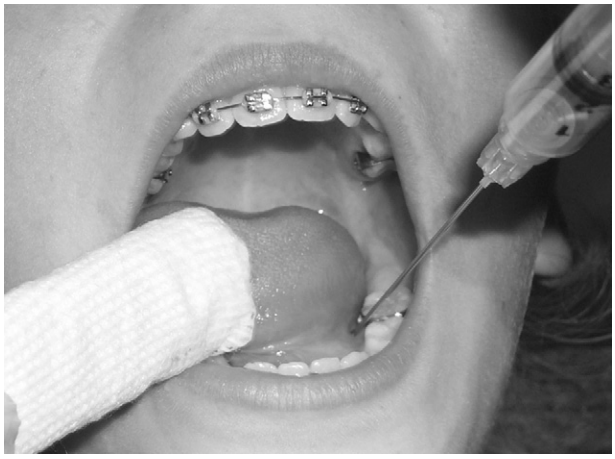


FIGURE **22-22** Glossopharyngeal nerve block.

increase of medication raining onto the upper airway mucosa and producing a denser block. The technique is to have the patient take 5 to 8 deep breaths on the atomizer through both the mouth and nose, which helps the fluid follow the same path as ventilated gases. Like nebulization, a similar dose of 4% lidocaine and 1% phenylephrine can be used for atomization.

Anesthetizing the mouth and oropharynx decreases the gag and coughing reflexes associated with awake intubations. Local anesthesia to this region blocks nerve transmission originating from the trigeminal (anterior two thirds of the tongue) and glossopharyngeal nerve. Topical sprays provide effective anesthesia to the anterior portion of the tongue and mouth. Benzocaine 20% (Hurricaine) spray is a topical anesthetic with a quick onset and short duration. A half-second spray delivers approximately 0.15 mL (30 mg), which is estimated to be approximately one third of the toxic dose (100 mg). Cetacaine spray contains benzocaine 14%, tetracaine 2%, butyl aminobenzoate 2%, benzalkonium chloride, and cetyl dimethyl ethyl ammonium bromide. The combination of these medications shortens the onset time and increases the duration of action.[92] Methemoglobinemia is associated with the use of benzocaine and has been reported after the use of these topical sprays. Therefore only conservative amounts of these sprays should be used. An alternative method for providing anesthesia to the mouth and tongue is to have the patient swish and gargle for 2 minutes with 2% or 4% lidocaine solution. The patient should then spit out the solution.

Topical anesthesia for the oropharynx and posterior tongue can be provided by using a "lidocaine lollipop," which can be made by coating the tip of a tongue blade with lidocaine ointment and then pulling the tongue forward while placing the lidocaine ointment on the back of the tongue. The tongue blade should be held in place for 1 to 2 minutes to allow the lidocaine ointment to liquefy and coat the oropharynx. Additionally, either nebulization or atomization using lidocaine can provide effective topical anesthesia provided adequate time is allowed.

Topical anesthetization of the vocal cords may be accomplished by instilling local anesthetic directly onto the cords. This can be accomplished in one of two ways. After the nasal cavity has been anesthetized, a nasal airway or ETT is passed and positioned in close approximation to the vocal cords. The patient is instructed to take a deep breath. On inspiration, 5 mL of 2% lidocaine is inserted down the lumen of the nasal airway. This causes the patient to cough, indicating that local anesthetic was deposited on the vocal cords. Another option is through the use of a fiberoptic bronchoscope or video laryngoscope. After visualization of the vocal cords is achieved, local anesthetic solution can be deposited directly onto the vocal cords through the injection port of the fiberoptic scope or by using a laryngeal tracheal anesthesia device.

Topical anesthetization of the upper airway can be achieved quickly and safely provided the anesthetist prepares the patient, calculates the appropriate toxic dose of local anesthetic to be used, and becomes familiar with these and other topical anesthesia techniques. Alternative upper airway anesthesia approaches, which can be used alone or in combination with topical anesthesia techniques, are infiltration nerve blocks.

Glossopharyngeal Block

The lingual branch of the glossopharyngeal nerve supplies sensory innervation to the posterior third of the tongue. To block the lingual branch, the practitioner first anesthetizes the tongue with topical anesthesia and then has the patient open his or her mouth and protrude the tongue forward. The anesthetist then displaces the tongue to the opposite side with a tongue blade, and what results is the formation of a gutter (Figures 22-22 and 22-23). Where the gutter meets the base of the palatoglossal arch, a 23- or

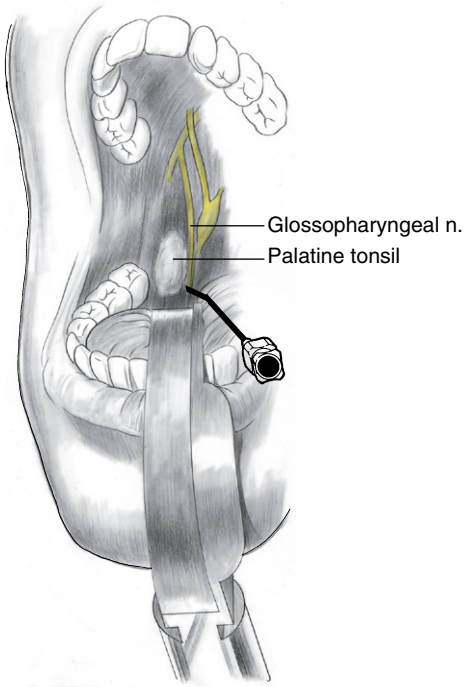


FIGURE **22-23** Glossopharyngeal nerve block anatomy and technique. (From Brown DL, et al. *Atlas of Regional Anesthesia*. 4th ed. Philadelphia: Saunders; 2010.)

25-gauge spinal needle is inserted approximately 0.25 to 0.5 cm and aspirated for air. If air is obtained on aspiration, the needle has been placed too deeply and should be withdrawn until no air is aspirated. If blood is obtained, the needle must be withdrawn and repositioned more medially. After correct positioning, 1 to 2 mL of 2% lidocaine is injected, and the block is then repeated on the opposite side.[89,92] The anesthetist should monitor for signs and symptoms of local anesthetic toxicity because a 5% incidence of intracarotid injection has been reported.[93]

Superior Laryngeal Nerve Block

The superior laryngeal nerve block provides a dense block of the supraglottic region. To perform the block, the practitioner locates the greater cornu of the hyoid bone, which lies beneath the angle of the mandible and can be palpated with the thumb and index finger on either side of the neck as a rounded structure (Figure 22-24). The anesthetist should then displace it toward the side that is being injected to help stabilize the bone and ease identification of structures and injection of the local anesthetic. The needle is inserted perpendicular to the skin to make contact with the inferior border of the greater cornu (Figure 22-25). The needle is then "walked off" the caudal edge of the hyoid bone where it then meets the thyrohyoid membrane. Resistance may be appreciated as the tip of the needle may be felt to "bounce" on the thyrohyoid membrane.[94] This site approximates the area where the superior laryngeal nerve pierces the thyrohyoid membrane. Aspiration should confirm there is no air or blood, and 1 mL of local anesthetic (e.g., 2% lidocaine) is deposited above this membrane. The needle is then advanced an additional 2 to 3 mm through the membrane and 2 mL of local anesthetic is deposited. The block is then repeated on the other side. Again, aspiration is performed before the injection of the local anesthetic. If air is aspirated, the needle has been placed too deep and is in the pharynx, and the tip of the needle should be withdrawn and repositioned.

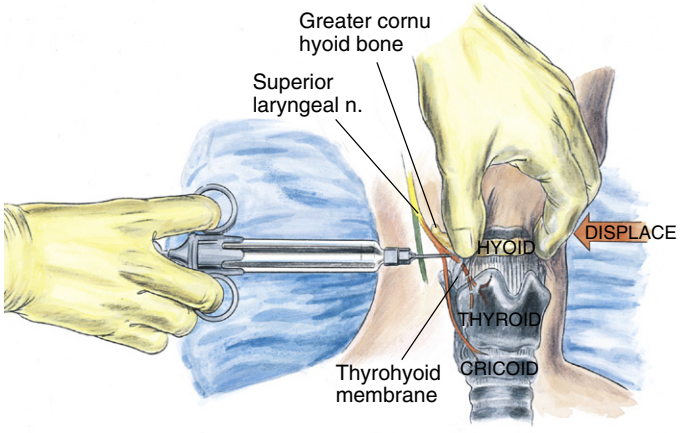


FIGURE **22-24** Superior laryngeal nerve block anatomy and technique. (From Brown DL, et al. *Atlas of Regional Anesthesia*. 4th ed. Philadelphia: Saunders; 2010.)

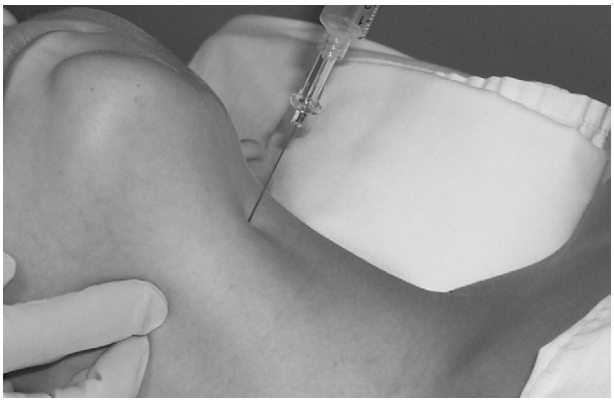


FIGURE **22-25** Superior laryngeal nerve block.

Transtracheal Block

The transtracheal block is accomplished by injecting local anesthetic through the cricothyroid membrane (Figure 22-26). To administer the block, the practitioner first palpates the cricothyroid membrane with the index and middle fingers (Figure 22-27) and the skin is localized. The anesthetist then attaches a 22-gauge needle or a 24-gauge angiocatheter to a syringe containing 3 to 5 mL of 2% lidocaine. The needle is placed midline and advanced in a caudad direction through the cricothyroid membrane while aspiration is continuously performed. When air bubbles are aspirated through the solution, the tip of the needle is in the tracheal lumen. If using an angiocatheter, the catheter is advanced into the tracheal lumen and the needle withdrawn, which may produce coughing.[94] The patient is then instructed to take a deep breath. On inspiration, the local anesthetic is injected into the tracheal lumen. This will cause the patient to cough, spraying the local anesthetic onto the vocal cords. Care must be taken to stabilize the needle so as not to tear the tracheal mucosa when the patient coughs. Use of the softer angiocatheter may decrease trauma.

CRICOID PRESSURE

British anesthetist Brian Arthur Sellick first described cricoid pressure in 1961 as the posterior displacement of the cricoid cartilage against the cervical vertebrae with the patient in a 20-degree head-up position to prevent regurgitation and possible aspiration of stomach contents during the induction of general anesthesia. As such, cricoid pressure (e.g., Sellick's maneuver) has remained a

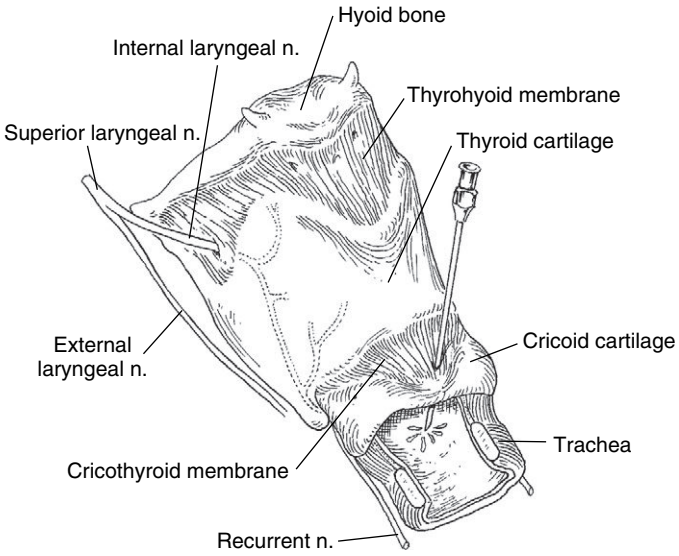


FIGURE **22-26** Transtracheal injection. *n*, Nerve.

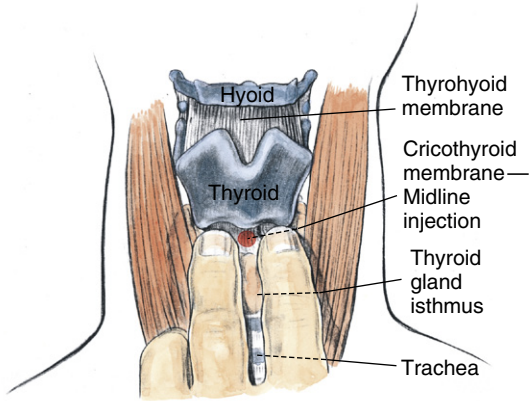


FIGURE **22-27** Transtracheal nerve block anatomy and placement. (From Brown DL, et al. *Atlas of Regional Anesthesia*. 4th ed. Philadelphia: Saunders; 2010.)

mainstay of anesthetic practice, particularly during rapid-sequence induction of general anesthesia in patients at high risk for gastric aspiration. Using a cricoid yolk, studies have shown that the optimal amount of force necessary to effectively occlude the esophagus without obstruction of the trachea is between 30 and 44 Newtons (N). It is recommended that 20 N (e.g., 2 kilogram-force) cricoid pressure be applied prior to loss of consciousness and that the pressure be increased to 40 N (e.g., 4 kilogram-force) after loss of consciousness (Figure 22-28).[95]

Recent evidence has questioned the perceived efficacy of cricoid pressure.[96] After an observational study using magnetic resonance imaging, Smith et al.[97] reported that in more than 50% of subjects, the esophagus can be found lateral to the cricoid ring. In addition, this proportion increases to 90% of subjects after the application of cricoid pressure, theoretically hampering esophageal occlusion during posterior displacement of the cartilaginous cricothyroid ring. A more recent report by Rice et al.[98] found that the anatomic location and movement of the esophagus during the application of cricoid pressure was irrelevant to the efficiency of the Sellick's maneuver in regard to clinical efficacy (e.g., prevention of gastric regurgitation into the pharynx). In a cohort of unsedated volunteers, magnetic resonance imaging showed that compression of the alimentary tract occurs with both midline and lateral displacement of the cricoid

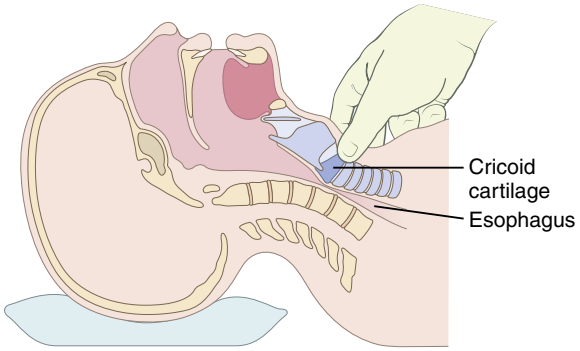


FIGURE **22-28** Application of cricoid pressure. (From Miller RD, Pardo MC. *Basics of Anesthesia*. 6th ed. Philadelphia: Saunders; 2011.)

cartilage relative to the underlying vertebral body. They concluded that the hypopharynx and cartilaginous cricoid ring is an anatomic unit that is essential to the efficacy of cricoid pressure.

The application of cricoid pressure is not a benign procedure. Cricoid pressure of 44 N applied to the awake individual has been associated with laryngeal discomfort and retching. Maintaining cricoid pressure during active vomiting may result in rupture of the esophagus.[99] The application of pressure during rapid-sequence induction has been shown to decrease upper and lower esophageal sphincter tone.[95] Furthermore, complications attributed to the inappropriate application of CP include (1) airway obstruction (e.g., partial or complete), (2) difficulty in placement of the laryngoscope blade, (3) impeding glottic visualization during laryngoscopy, and (4) difficulty with tracheal intubation.[96] Cricoid pressure may be difficult to apply properly; therefore it is imperative that anesthetists and other healthcare providers receive proper training in correctly applying cricoid pressure to minimize complications.[99] When used, cricoid pressure should be applied until correct placement of an endotracheal tube is confirmed through traditional methods.

ADJUNCT AIRWAY EQUIPMENT AND TECHNIQUES

Over the past two decades, multiple adjunctive airway devices have been developed for use in both routine and difficult airway management situations. Adjunctive airway devices include ETT guides, lighted stylets, rigid laryngoscopes, indirect rigid fiberoptic laryngoscopes, flexible fiberoptic bronchoscopes, and supraglottic ventilatory devices. Supraglottic airway ventilation devices include both airway masks (e.g., LMA) and tubes.

Devices and techniques used for difficult intubation and ventilation may include any one or a combination of airway adjuncts. Adjunctive airway equipment should be routinely used in nonemergent or simulated practice situations to increase the anesthetist's familiarity with the equipment and facilitate ease of use in emergent situations.[85-87] Ultimately, the choice of which airway adjunct to use during airway management will be based on the anesthetist's familiarity and skill with the device, as well as (1) the need for airway control; (2) the ease of laryngoscopy; (3) the ability to use supralaryngeal ventilation; (4) aspiration risk; and (5) the patient's tolerance for apnea.[16]

Supraglottic Ventilation Devices

Supraglottic airway ventilation devices consist of those airway adjuncts that provide ventilation above the glottic opening. Different terminology has been used to describe these devices depending on where they are placed. For example, devices that sit above or surround the glottis (e.g., LMA, facemask) are truly supraglottic.

FIGURE **22-29** Classic LMA. (Courtesy LMA North America, Inc.)

In contrast, those devices that pass behind the larynx and enter the upper esophagus (e.g., Combitube, King LT airway) are known as retroglottic or infraglottic devices. However, because ventilation with all of these devices is performed superior to the glottic opening, the term *supraglottic airway (SGA) ventilation* will be the preferred terminology. The choice of which SGA device to use is dependent on the clinical situation and preference of the provider. Indications for the use of these devices include (1) rescue ventilation for difficult mask ventilation and failed intubation; (2) an alternative to endotracheal intubation, in appropriately selected patients, for elective surgery in the OR; and (3) as a conduit to facilitate endotracheal intubation.[100]

Laryngeal Mask Airway

Since its introduction into clinical practice in 1981, the laryngeal mask airway (LMA) has been used extensively in airway management. Its development has been hailed as one of the most significant advances in airway management since the ETT.[101] The LMA can be used as the primary airway device during appropriate surgical procedures and is considered a valuable airway tool in managing the difficult airway. A great deal of literature exists that reports the successful use of the LMA as a primary airway device and as a conduit for intubation of the trachea.[101-103] Indeed, there are over 300 publications involving more than 3000 patients that have described successful usage of the LMA in patients with difficult to manage airways.[104]

The classic LMA (Figure 22-29) was used extensively in Europe, primarily in England, before its introduction in the United States. Several variations of the LMA exist, including the classic, ProSeal, Supreme, and Fastrach models. In daily clinical use, this airway can be used in place of bag mask ventilation during general anesthesia. An appropriately sized LMA is generally based on patient kilogram weight (Table 22-7). Laryngeal mask insertion is usually accomplished using the classic technique, which is fully deflating the cuff and placing a water-soluble lubricant on its posterior surface. The practitioner then inserts the LMA midline into the mouth with the posterior surface pressed against the palate of the mouth and then advances with the index finger along the palatopharyngeal curve. Reports have indicated between an 88% and 95% success rate on the first attempt with an experienced provider.[104,105] If initial attempts at LMA placement are difficult, then the LMA should be removed and attempted with the patient in a proper sniffing position. In addition, if the LMA encounters resistance when it reaches the oropharynx, it is many times due to the distal tip having folded back, and the airway simply needs to be retracted and advanced again. If continued resistance occurs, then the operator can place the right index finger between the superior portion of the LMA and the palate and "flip the tip" back into normal position while advancing the device with the opposite hand. When properly placed, final resistance denotes placement of the LMA's tip in the hypopharynx, and the black line on the tubing will be even with the upper lip. The cuff is then inflated, sealing the airway over the larynx. The esophageal opening at the base of the hypopharynx has no seal. If the cuff is overinflated, it can actually open the upper esophageal sphincter, or potentially cause posterior cricoarytenoid muscle fatigue.[106]

Alternative techniques and maneuvers can be used for LMA placement. The LMA also can be introduced into the mouth with the opening initially facing the palate. It is then advanced until the LMA reaches the oropharynx, when it is rotated 180 degrees counterclockwise and advanced into its final position. Another technique is to partially or fully inflate the LMA cuff with air before insertion. Finally, guided techniques using a gum elastic bougie or a laryngoscope to facilitate placement have been reported.[107]

TABLE 22-7 Appropriate LMA Sizing Based on Patient Weight

LMA Size	Patient Weight* (kg)
1	Less than 5
1.5	5-10
2	10-20
2.5	20-30
3	30-50
4	50-70
5	70-100

From Strauss RA, Noordhoek R. Management of the difficult airway. *Atlas Oral Maxillofac Surg Clin North Am.* 2010;18(1):11-28.
*The Classic, Proseal, Supreme, and Fastrach model sizes are based on similar patient weights.
LMA, Laryngeal mask airway.

FIGURE **22-30** ProSeal LMA. (Courtesy LMA North America, Inc.)

ProSeal and Supreme LMA

The ProSeal LMA (PLMA) was introduced in 2000, as an alternative supraglottic device to the classic LMA, and comes in the same sizes (Figure 22-30) as the classic LMA. Modifications compared to the classic LMA include: (1) a larger and deeper bowl with no

FIGURE **22-31** LMA Supreme. (Courtesy LMA North America, Inc.)

FIGURE **22-32** Fastrach LMA. (Courtesy LMA North America, Inc.)

grille; (2) the posterior extension of the mask cuff; (3) a gastric drainage tube running parallel to the airway tube and existing at the mask tip; (4) silicone bite block; and (5) anterior pocket for seating an introducer or finger during insertion.[108,109] The PLMA was designed with a second posterior cuff, that when inflated helps to separate the respiratory and gastrointestinal tracts, and a second tube developed for the insertion of a gastric tube into the esophagus without passing through the hypopharynx. The addition of this esophageal gastric drain tube allows the practitioner to identify misplacement, decompress the patient's stomach of air or solid contents, and may vent regurgitated stomach contents. Though not proven in clinical trials, cadaver studies indicate that the PLMA can protect the airway from regurgitated material.[16]

Compared to the classic LMA, insertion of the PLMA takes an additional few seconds, but the overall success is equivalent. In addition, the airway seal is improved by 50% allowing a positive ventilation pressure up to 30 cm H_2O (versus the 20 cm H_2O with the classic LMA). Indications for the use of the PLMA include situations in which the classic LMA may not provide sufficient ventilation or airway protection, and endotracheal intubation would rather be avoided. The PLMA has been used in laparoscopic (though this is controversial), obese, intensive care, trauma, and difficult airway cases.[109] A disposable version of the PLMA, named the LMA Supreme (Figure 22-31), has been developed and comes in rigid preformed sizes to facilitate ease of placement.

Fastrach LMA

The Fastrach LMA (Figure 22-32), also known as the intubating LMA (ILMA), was released in 1997 and was specifically designed for use in difficult airway situations.[103,110,111] The design of the Fastrach LMA provides the anesthetist with the opportunity to ventilate and then to attempt a blind endotracheal intubation through the laryngeal mask channel. It has been used successfully in the cannot intubate and cannot ventilate scenario, as well as in situations where difficult intubation is anticipated. The design of the Fastrach allows for reasonable control of the airway throughout the intubation process, first with the laryngeal mask, then with endotracheal intubation. The primary distinguishing features, as described by the Fastrach inventor, Dr. Archie Brain, include: (1) an anatomically curved rigid airway tube; (2) an integrated guiding handle; (3) an epiglottic elevating bar; and (4) a guiding ramp built into the floor of the mask aperture.[112]

The Fastrach LMA comes in sizes 3, 4, and 5, and involves a series of steps during placement and subsequent intubation (Box 22-7). As with all adjunctive airway equipment, the Fastrach LMA should be used in routine cases to ensure familiarity with the technique before its use is attempted in an emergent situation or with a difficult airway. However, most practitioners who are familiar with the insertion of the LMA adapt readily to insertion of the Fastrach. The Fastrach LMA has been successfully used in the OR for ventilation in 97% to 100% of anticipated and unanticipated difficult airway cases.[76] Successful use of the Fastrach was also demonstrated in prehospital emergency airway situations in which intubation was not possible by direct laryngoscopy. Placement of the ILMA was accomplished in 96% of the study population and successful intubation was performed blindly in 91%.[113]

Visualization of the vocal cords using the Fastrach LMA also can be accomplished with the aid of either a videoscope or fiberscope. The Fastrach LMA can be used as a conduit for intubation using a fiberoptic bronchoscope and preloaded ETT. The preformed ILMA silicone-coated tube provides a direct channel to the vocal cords. This technique provides visualization of the vocal cords and has been successfully documented in the literature.[110,114] An adaptation of the Fastrach is the C-Trach intubation device. This device adds a video screen that is magnetically mounted to the standard Fastrach. The C-Trach allows the anesthetist to visualize the ETT passing through the vocal cords, confirming proper placement of the tube.

LMA Considerations

Familiarity with the different LMA models, their ease and speed of insertion, and their high likelihood of success in difficult airway situations make them an extremely valuable airway rescue device. One of the concerns with the LMA is the possibility of aspiration during insertion or when the LMA is in place. Gastric inflation of the stomach, regurgitation, or aspiration of gastric contents can occur with LMA use. If ventilation is performed using positive pressure greater than 20 cm H_2O with the classic LMA and 30 cm H_2O with the PLMA, the stomach may become inflated. These devices can also be malpositioned or the cuff overinflated, resulting in failure to ventilate the patient. Malpositioning of the LMA in the airway and overinflation of the cuff may result in additional pressure to the sidewalls of the pharynx and pressure on the posterior wall of the larynx. If this occurs, it is possible that the epiglottis can be folded back against the glottic opening, sealing the airway. Pathology at or below the laryngeal level may render the LMA ineffective as a supraglottic device. Indeed, LMA failures have been reported in both obstructions within the hypopharynx and obstructions below the hypopharynx such as subglottic obstructions (e.g., tracheal thrombosis, tracheal stenosis, tumors), Hunter

BOX **22-7**

Fastrach and Blind Endotracheal Tube Placement

PreFastrach LMA and ETT Placement

1. Confirm integrity of LMA and ETT cuff (may use Fastrach reusable silicon-tipped ETT or standard prewarmed polyvinylchloride ETT) and then deflate cuffs.
2. Lubricate ETT with water-soluble lubricant at distal end and pass through to Fastrach lumen lubricate inside the channel.
3. Lubricate anterior and posterior surfaces of Fastrach cuff with water-soluble lubricant.

Fastrach LMA Placement

1. Hold device by the metal handle in dominant hand and open the airway.
2. Insert cuff into mouth with mask tip in contact with the palate (metal tube portion will be in contact with the chin).
3. Maintain firm pressure with the palate and posterior pharynx and rotate while advancing the Fastrach into place until resistance is felt or handle meets face (only metal end of silicone-coated tube will protrude from mouth).
4. Inflate the Fastrach cuff.
5. Confirm adequate ventilation (ventilation confirmation should indicate consistent $ETco_2$ waveform, positive change in color on CO_2-detecting devices, and equal bilateral breath sounds).
6. May manipulate device gently using handle until ventilation is optimized.

ETT Placement Through Fastrach LMA

1. Remove adaptor from ETT and set aside (may place on ventilator circuit for easy placement back onto ETT postintubation).
2. Place ETT through Fastrach LMA lumen until it reaches the 15-cm marking (at this position the ETT is about to push the epiglottic elevating bar up, moving the epiglottis out of the way).
3. Use the Fastrach handle to lift anteriorly and blindly insert ETT into trachea (should not encounter resistance) and inflate ETT cuff balloon.
4. Place ETT adaptor back on ETT and attempt ventilation (ventilation confirmation should indicate consistent $ETco_2$ waveform and equal bilateral breath sounds).
5. Consider leaving Fastrach LMA *in situ* (in emergency situations).

If Decision Is Made to Remove Fastrach LMA

1. Remove adaptor from ETT and set aside (may place on ventilator circuit for easy placement back onto ETT postintubation).
2. Deflate ETT balloon and Fastrach LMA balloon.
3. Place Fastrach stylet on the end of the ETT and provide counter traction caudally as the Fastrach LMA is removed.
4. When the ETT is visualized below the Fastrach cuff at the level of the mouth, hold ETT, remove stylet so that the ETT balloon cuff can pass through the Fastrach LMA lumen, and then remove the Fastrach LMA completely.
5. Replace ETT adaptor and reconfirm correct ETT placement in trachea (ventilation confirmation should indicate consistent $ETco_2$ waveform and equal bilateral breath sounds).

ETT, Endotracheal tube; *LMA,* laryngeal mask airway.

syndrome, obstetric patients, aspiration, or severe rheumatoid arthritis.[16] In obstetric anesthesia, the LMA is used when tracheal intubation has failed and ventilation with a facemask is difficult or impossible. In the cannot intubate and cannot ventilate scenario, the LMA should be attempted prior to a cricothyroidotomy.

Intubating Laryngeal Airways (Cookgas ILA) and Air-Q

Physician inventor Daniel Cook developed an oval-shaped supraglottic intubating airway that allows the anesthetist to maintain ventilation through the airway device or intubate with a standard ETT. The Cookgas ILA (Figure 22-33) comes with a removable stylet to stabilize the ETT while the laryngeal mask is removed. As with most devices, the ILA is able to be re-autoclaved only 40 times. A companion product, the Air-Q, is disposable. The stylet with the ILA cannot be autoclaved but can be sterilized with liquids up to 10 times. The ILA and Air-Q come in varying sizes, and both are usable on patients weighing from 20 to 100 kg.

Several other supraglottic laryngeal masks have been introduced for single airway use. Examples include the Ambu laryngeal mask airway, which combines an anatomic curve and a built-in bite block. The Cobra perilaryngeal airway (PLA) is a single lumen tube with a circumferential distal cuff just proximal to a distal adaptor that looks like a cobra head and is intended to expand hypopharyngeal tissue. Both the I-Gel and the streamlined liner of the pharynx airway (SLIPA) do not have inflatable cuffs, but do have the capacity to ventilate and contain reservoirs to capture regurgitated material.

Supraglottic Tubes

Several supraglottic tubes (also known as retroglottic or infraglottic tubes) have been developed over the past several years. Devices in this class include the Combitube, King Laryngeal Tube (LT) airway, Rusch Easy Tube, and LaryVent. These devices are placed blindly through the mouth and are positioned into the esophagus. These tubes have a distal balloon to occlude the esophagus, as well as a larger proximal balloon to occlude the posterior oropharynx. Between the two balloons is a ventilation port at approximately the level of the trachea. These devices can be used for both rescue and routine management, as well as for prehospital difficult airway situations.

FIGURE **22-33** Intubating laryngeal airway. (Courtesy Mercury Medical.)

Combitube. The Combitube (Figure 22-34) is a double-lumen airway device that is inserted blindly into the hypopharynx. The

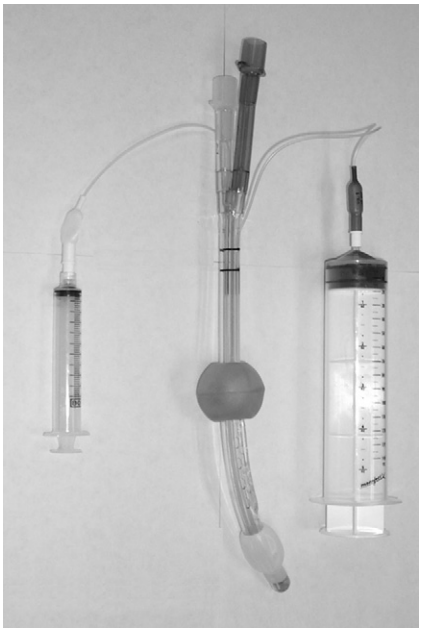


FIGURE **22-34** Combitube.

Combitube can be considered as a secondary rescue device in the event of intubation, gum elastic bougie, and LMA failure.[115] This device contains an esophageal lumen and a tracheal lumen. The esophageal lumen has a blocked distal port and perforations at the pharyngeal level, whereas the tracheal lumen has only an open distal end. Irrespective of where the tip is placed, the lungs may be ventilated.[116] The usual placement of the tip is into the esophagus. This blind insertion is easily accomplished, and the patient's head can be kept in the neutral position. To successfully insert the Combitube, cricoid pressure should be released while the mandible and tongue are lifted anterior. After insertion, the cuffs of both lumens are inflated and ventilation is first attempted with the esophageal lumen and assessed for verification. If there are no breath sounds and air is auscultated over the stomach, then it is probable that the tube was inserted into the trachea and the tracheal lumen is then used for ventilation. Bilateral breath sounds and the presence of end tidal CO_2 should be confirmed and indicate successful placement. The Combitube may offer some protection from aspiration due to the distal cuff occluding the esophagus. The Combitube is a supraglottic device, and pathology at or below the laryngeal level may make the Combitube ineffective. Reported complications include esophageal rupture.

King LT/LTS-D. King Systems introduced the King LT (also known as the laryngeal tube airway) in 2002, which is a minimally invasive airway device similar to the Combitube. This device is a single lumen (Figure 22-35) that has a ventilation outlet between the low-pressure oropharyngeal and esophageal cuffs. The device is inserted in a manner similar to the Combitube but has only one ventilation port. The King LT is a reusable supraglottic airway device created as an alternative to tracheal intubation or mask ventilation. This airway is designed for positive pressure ventilation, as well as for a spontaneously breathing patient, thereby allowing maximum versatility as an airway management tool.

The King LT has the capacity to achieve a ventilatory seal of 30 cm H_2O or higher. It is easy to insert, and a randomized comparison of the laryngeal tube has shown it to be as effective as the classic LMA during anesthesia with controlled ventilation.[102] Furthermore, there is evidence that King LT may be useful in situations where ventilation and intubation are difficult or have failed

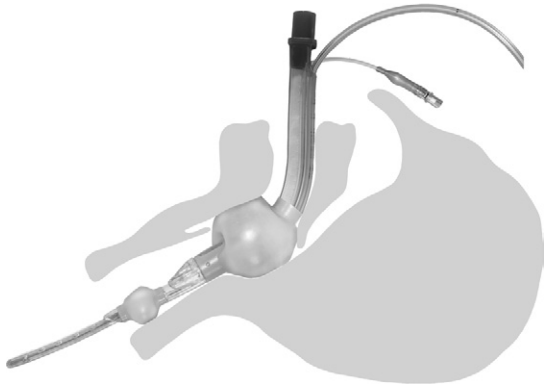


FIGURE **22-35** KING LTS-D. (Courtesy King Systems.)

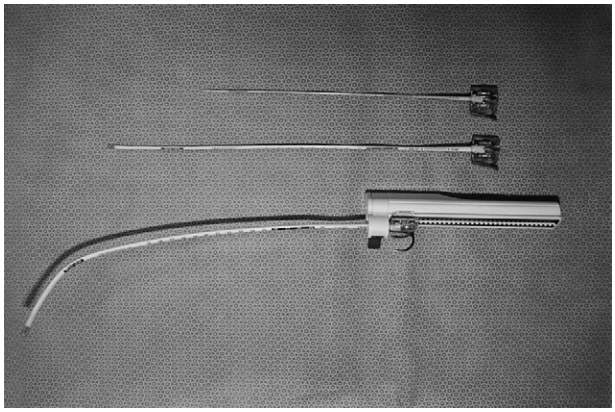


FIGURE **22-36** Trachlite lighted stylet.

altogether.[117] However, the research is limited and further inquiries into its usefulness have been suggested. The King LT is 100% latex free and can be autoclaved up to 50 cycles, or is available in a disposable model. The LT model has a single opening for ventilation. The King LTS-D is a disposable version that contains a second port which accommodates an 18-French nasogastric suction tube for insertion into the stomach.

Intubation Stylets

Trachlite Lighted Stylet

The Trachlite (Figure 22-36) lighted stylet is a recent adaptation of the light wand that uses transillumination of the neck to accomplish endotracheal intubation. Because the placement of the glottic opening is anterior to the esophagus, as the light source enters the trachea, a well-defined circumscribed glow is noticed below the thyroid prominence and can be readily seen on the anterior neck. Placement of the Trachlite in the esophagus results in a much more diffuse transillumination of the neck without this circumscribed glow. The Trachlite has a bright light source that does not require low ambient light for optimum performance. In addition, it has a retractable stylet that increases the success rate for intubation.

The success rate of the Trachlite is similar to that of conventional direct laryngoscopy. It is less affected by anterior placement of the larynx, is less stimulating than conventional laryngoscopy, and is associated with a lower incidence of sore throat. It can be used in both the anticipated and the unanticipated difficult airway when conventional laryngoscopy has failed.[118] The Trachlite also can be used in patients with a small oral opening and minimal neck manipulation.

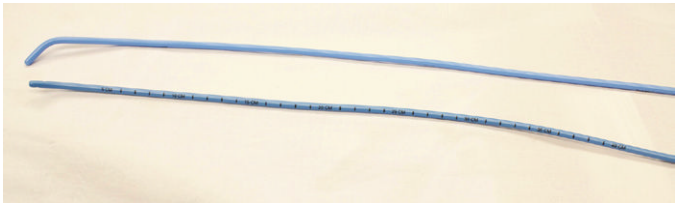


FIGURE **22-37** Eschmann stylet or Gum Elastic Bougie.

Because the Trachlite is inserted blindly using transillumination, risk of injury or failure is increased when the device is used in patients with any upper airway anomaly, such as foreign body, tumor, polyps, or soft-tissue injuries. If these anomalies exist, other airway adjuncts should be used. Furthermore, it may be more difficult to accurately place the Trachlite in patients with short, thick necks or redundant soft tissue. Finally, the Trachlite is not advertised as a rescue adjunct for the cannot intubate, cannot ventilate scenario, but instead has been suggested for situations in which intubation has failed, but time is available because ventilation is still possible.[15]

Eschmann Stylet (Gum Elastic Bougie)

The Eschmann stylet (Figure 22-37) is a flexible stylet with a bent distal tip that can be useful when the glottic opening is difficult to visualize (e.g., Cormack and Lehane grade II or III). Placement first involves visualization of the epiglottis or posterior arytenoid cartilages. The stylet is advanced behind the epiglottis and placed into the glottic opening. Feeling the stylet bounce along the tracheal rings as it is advanced into the trachea is a confirmation of placement, but is not always felt. The stylet should be advanced until the 25 cm marking is at the lip, where the stylet is then held in place. An ETT is inserted over the stylet and slid into place in the trachea. If resistance is felt, the ETT can be rotated 90 degrees and then advanced. An alternative technique is to advance the ETT over the Eschmann stylet until it is in the oropharynx, and then perform a direct laryngoscopy with a laryngoscope while an assistant holds the stylet in place. The ETT is then advanced through the glottic opening and into the trachea. Care should be taken not to advance the Eschmann stylet further into the trachea and risk a bronchial or distal tracheal puncture.

Airway Exchange Catheters

An airway exchange catheter (AEC) can be used during the changing of an ETT, or during the extubation of a difficult airway. These catheters allow gas exchange using either jet ventilation or oxygen insufflation from an adapter and bag mask (Figure 22-38). The AEC is introduced through the existing ETT with the distal tip placed proximal to the carina.[28] The ETT can then be removed and the new ETT placed over the AEC that acts as a stylet. If the new ETT encounters resistance during advancement, an attempt at rotating the ETT 90 degrees may facilitate passage. An alternative technique is to place the new ETT over the AEC and advance until the ETT is in the oropharynx and perform a similar technique as described above with the Eschmann stylet using a laryngoscope. The AEC also can be left in the trachea after the extubation of a difficult airway in the event that the patient requires reintubation. Care should be taken not to advance the AEC distally into either of the mainstem bronchi or to exert excessive force that could result in a tracheal or bronchus perforation.

Flexible Fiberoptic Scopes and Fiberoptic Stylets

Scopes can be either flexible or rigid and allow for the visual placement of ETTs. These devices can be used during routine airway management, but are more frequently employed when the airway exhibits indications of difficulty during the preoperative assessment or during management of an unanticipated difficult airway.

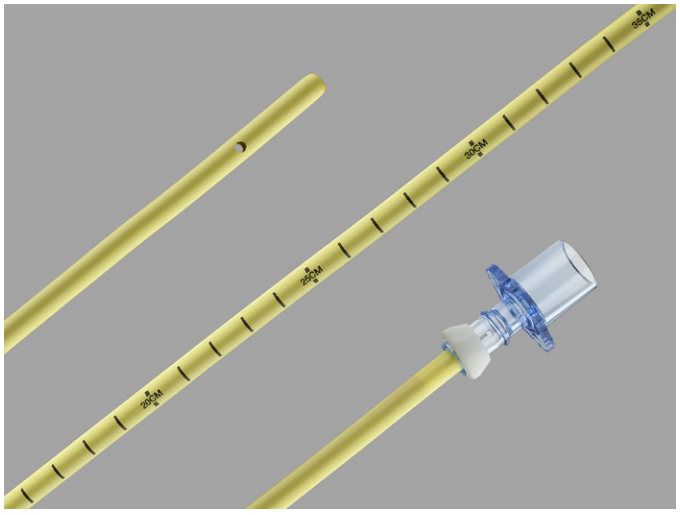


FIGURE **22-38** Cook airway exchange catheter. (From Cook Medical Incorporated, Bloomington, Indiana.)

Flexible Fiberoptic Laryngoscope (Bronchoscope)

The fiberoptic bronchoscope can be used to evaluate the airway, facilitate intubation of the patient with a difficult airway, check ETT placement, change an existing ETT, and perform postextubation evaluations.[119] The flexible fiberoptic laryngoscope consists of multiple strands of tiny glass fibers that transmit light. These fibers are bound together inside a rubberized coating that allows for flexibility. Within the scope are working channels that can carry oxygen, act as suction ports, or be used to instill local anesthetic. The handle contains an eyepiece for viewing and a lever for controlling the distal end of the scope through one plane (either up or down). The second plane is navigated by rotation of the scope by the operator's hand. Light is supplied by an external light source or by battery.

The limitations of fiberoptic laryngoscopy should be considered prior to performing this procedure, but ultimately the decision to proceed is based on the anesthetist's clinical judgment. Limitations with fiberoptic laryngoscopy include the following:

- The scope can become fogged, especially if it is cold. Soaking the scope in warm saline, the use of an antifog liquid, or placing the scope in the buccal mucosa below the patient's lip for 5 seconds before use may help prevent fogging.
- Viewing can be limited when multiple fiberoptic strands are broken or damaged. The scope should never be banged or dropped and should always be stored flat in a protective case or cart.
- Secretions or blood can obstruct the operator's view. This may be prevented with the instillation of oxygen at 10 to 15 L per minute through one of the side channels.
- The fiberoptic bronchoscope should be used with extreme caution in patients with epiglottitis, laryngotracheitis, or bacterial tracheitis, because manipulation of the fiberoptic bronchoscope through the glottis may cause enough stimulation to convert a partial obstruction into a total obstruction of the airway.
- Caution should be strictly exercised in patients with airway burns because of the restricted size and the hyperirritability of the airway.
- The use of the fiberoptic bronchoscope is very limited in airway trauma. The presence of blood and mucus in the

airway obscures the lens and makes visualization impossible. If significant soft-tissue trauma is present, edema of the tissues can prevent adequate visualization of the larynx and trachea.

- In situations in which both intubation and ventilation have failed and immediate airway access is required, it may be prudent to attempt a different airway technique because of time constraints or proceed directly to an invasive airway such as a cricothyrotomy.

Indications for fiberoptic intubation of the patient include the following:

- *An anticipated difficult airway.* These patients usually include a history of intubation difficulty and upper airway obstructions such as angioedema, tumors, abscesses, hematomas, Ludwig's angina, or lingual hyperplasia.
- *Cervical spine immobilization.* For example, patients with traumatic cervical injuries, an unstable cervical spine, or a cervical spine with a severely decreased range of motion may have cervical spine immobilization.
- *Anatomic abnormalities of the upper airway.* Patients with a restricted mouth opening or hypoplastic mandible or who are morbidly obese may fall into this category.
- *Failed intubation attempt, but ventilation possible with a mask or SGA device.* In these situations, the operator has time to set up and perform the fiberoptic technique using either an endoscopy mask or LMA as a conduit for the scope.

The fiberoptic bronchoscope can be used for oral or nasal intubation, with the patient either awake or asleep. An awake fiberoptic intubation is most commonly performed for an anticipated difficult airway. Preparation for an awake fiberoptic intubation includes educating the patient regarding what to expect, administration of an antisialagogue, anesthetizing the patient's airway, and providing adequate sedation.

The patient's airway should be anesthetized with either topical anesthesia, nerve blocks, or a combination of the two as previously described. Debate and controversy exist regarding the administration of drying agents and sedation. Radiation can cause fibrosis and loss of mucus-producing glands, so drying of the airway can be extensive with the use of an antisialagogue in this patient population. However, either atropine or glycopyrrolate may be administered 5 to 20 minutes before the procedure. Administration of light sedation may help reduce the patient's stress and provide for a more relaxed environment for the practitioner. A common practice is to use a combination sedation-analgesia technique such as the administration of fentanyl and midazolam. However, carefully titrated amounts using small bolus doses should be considered whenever control of the airway is in doubt. A short-acting titratable opioid such as remifentanil is an alternative choice that can be used during the stimulating portion of fiberoptic intubation.[120]

A Yankauer suction device must be accessible whenever the fiberoptic bronchoscope is used. Medications used in airway management should be readily available. These include local anesthetics, resuscitation drugs, induction agents, and muscle relaxants. If the equipment is to be used outside of the OR, the appropriate monitors should be placed in the difficult airway cart. This cart can become the central location for all emergency airway devices, including invasive airway equipment and LMAs.

Success with the fiberoptic scope is dependent on familiarity of the device and skill with its use. This may be accomplished by continued training with intubation manikins, high-fidelity patient simulators, or during routine airway management in the clinical setting.[121,122] With oral intubations, a fiberoptic guide

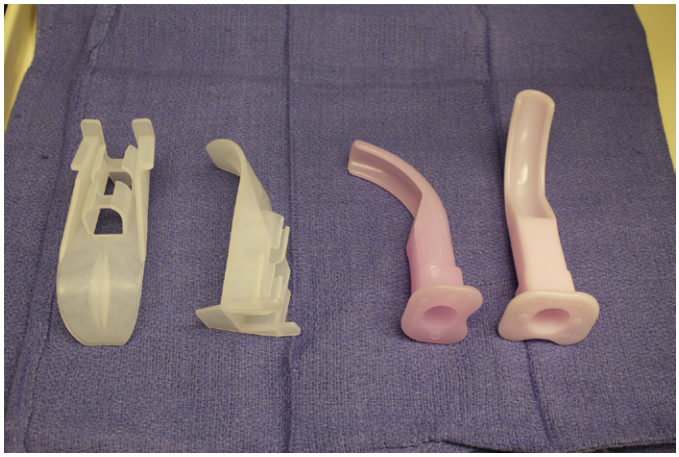


FIGURE **22-39** Williams airway (right) and Ovassapian airway (left).

FIGURE **22-40** Fiberoptic technique (frontal approach).

(such as the Williams, Berman, or Ovassapian airway) functions as a guide to facilitate placement of the scope into the pharyngeal area and also can help prevent damage to the fibers if the patient were to bite the scope (Figure 22-39). The operator can either perform the technique at the head of the bed with the patient in the supine position, or from the side using a frontal approach with the patient in a sitting position (Figure 22-40). The latter technique may help prevent tissues from falling against the airway impeding fiberoptic views, may help to decrease patient anxiety, and has been used in patients in whom upper airway masses have compressed the airway, causing difficulty breathing in the supine position.[123]

An ETT is first loaded onto the fiberoptic scope and is then inserted through either the mouth or the nose and advanced to the posterior pharynx. The anesthetist can manipulate the scope in two planes by adjusting the lever on the handle up or down and by rotating the scope laterally with the wrist. The operator should use the dominant hand to hold the handle with the arm bent and resting on the operator's shoulder or positioned to look through the eye piece on the handle, while the other hand holds the distal portion of the scope to keep it taut (see Figure 22-40). Care must be taken to keep the scope in the midline while the tip is advanced toward the epiglottis. The operator should be able to visualize the different airway structures as the scope is advanced through the oropharyngeal and pharyngeal space (if not using a fiberoptic guide). If at any point the view is lost and the operator is unsure of the scope's location in the airway, it

should be retracted until identifiable airway anatomy is visualized. Instillation of oxygen through the suction port not only aids in the oxygenation of the patient but also helps keep the optics clear. The tip of the scope is slipped through the glottic opening and advanced until the tracheal rings come into view. The ETT is slipped downward, with the scope used as a stylet, and then through the cords into the trachea. If resistance is felt, the ETT should be rotated 90 degrees, but should never be forced into the airway because this may cause airway trauma. After the ETT is advanced into the trachea, the operator can verify placement by visualization of the carina.

Suctioning is difficult through the suction port. A more advantageous use of this channel is to provide the patient with supplemental oxygen. A 2- to 4-L flow through this port can provide additional oxygen to the patient and keeps debris from collecting on or near the port and lens. The administration of local anesthesia through the port or an epidural catheter threaded down the port is another use of this channel.

All personnel who will be using the device should be trained in its care and cleaning. The bronchoscope should be handled with care because the fibers are very fragile and bending, curling, or any other type of kinking could break them. After use, the scope should be flushed with warm sterile water, and all of the channels cleaned thoroughly with the appropriate solutions and equipment. Manufacturers will indicate which detergent and sterilizing solution they recommend. Instructions regarding solution, dilution, soak times, and rinsing must be closely followed to ensure the integrity and longevity of the equipment.

Rigid and Semirigid Fiberoptic Stylets and Laryngoscopes

Though not a regular part of emergency airway management, rigid and semirigid fiberoptic stylets and laryngoscope devices have shown potential for use in difficult airways situations, when intubation has failed, as well as during routine airway management.[119,124,125] However, there is insufficient literature and few comparisons of performance with other airway adjuncts to support any specific recommendations. These devices provide the operator with an indirect view of the glottic opening through a transmitted image via a fiberoptic bundle that is enclosed in a preformed design. The use of both rigid and semirigid fiberoptic stylets allows the operator to see around the tongue and eliminate the need for neck mobility and significant mouth opening. Examples of semirigid fiberoptic stylets include the Shikani optical stylet (SOS) and the Levitan First Pass Success (LFPS) scope. Rigid stylets include the Bonfils Retromolar Intubation Fiberscope™, the airway rigid intubation fiberscope laryngoscope (RIFL), and the Bullard laryngoscope. Indications and limitations with the use of these devices are similar to those described for flexible fiberoptic laryngoscope. Furthermore, as with any airway adjunct, success generally correlates with the degree of skill and familiarity of the operator with the specific device.

Shikani Optical Stylet and Levitan FPS. The Shikani optical stylet (SOS) (Figure 22-41) is a malleable, semirigid, intubating fiberoptic stylet for use in adults and children. It features a battery-operated light source with a high-resolution eyepiece on the handle to which the stylet is attached. The SOS also has the ability to insufflate oxygen into the pharynx via the ETT that is placed over the stylet prior to intubation. The malleable distal end allows configuration for varying intubation angles; this can be particularly useful for patients with a rigid or unstable cervical spine. The SOS can be used alone or in conjunction with direct laryngoscopy or as a conventional light wand.[126] In comparison, the operation of the Levitan FPS scope is similar to the SOS, but is intended to be used with a standard laryngoscope.

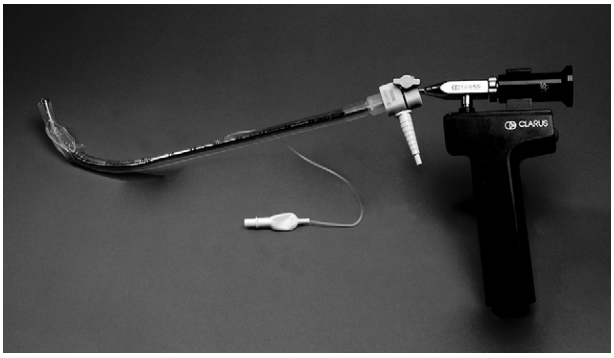


FIGURE **22-41** Shikani optical stylet. (From Marx JA, et al. *Rosen's Emergency Medicine*. 7th ed. St Louis: Mosby; 2010:20.)

Bonfils Retromolar Intubation Fiberscope, Bullard Laryngoscope, and RIFL. These devices have a rigid anatomic shape with fiberoptic bundles that provides an indirect view of the vocal cords. The rigid anatomic shape allows for visualization and intubation of the airway without aligning the oral, pharyngeal, and tracheal axes. These devices can be used on either an awake or an anesthetized patient. Because they do not require the sniffing position, they are ideal for patients with limited range of motion of the neck, such as those in cervical collars. Most have a channel for insufflation of oxygen while performing intubation, and a small combination battery pack that permits portability.

The Bonfils fiberoptic stylet has a rigid shaft that is 40 cm long, has an anterior bend of approximately 45 degrees, and is meant to be advanced in the airway using a retromolar instead of a midline approach. Advancement of the ETT occurs after the stylet has passed through the vocal cords. The RIFL is a hybrid rigid design and incorporates a rigid stylet that ends with a flexible tip that can be adjusted up to 135 degrees with the use of a trigger on the handle as the device is advanced down the airway. The distal tip is manipulated as the operator slowly advances the stylet until it passes through the vocal cords where the ETT is then slid off of the RIFL and placed into the trachea.

The Bullard scope is a rigid fiberoptic laryngoscope with an anatomically shaped blade that is meant to sit proximal to the vocal cords. It also has a detachable stylet to position the ETT along the right side of the blade, which allows the ETT to pass wherever the scope is looking.[127] When advancing the ETT, the arytenoids can obstruct passage through the glottic opening; however, this problem can usually be solved with either gentle cricoid pressure or lifting slightly with the blade. A complication with the use of rigid and semirigid fiberoptic stylets and laryngoscopes is the potential for airway trauma.

Video Laryngoscopy

Video laryngoscopy has been described as the most significant advancement in the way intubation is performed since the development of the laryngoscope in the 1940s.[128] Indeed, some authors believe anesthesia and emergency departments will reach the point where they will not want to be without a video laryngoscope.[129] These devices include a microvideo camera on the laryngoscope blade, which enables the transmission of video images to an external viewing screen. Glottic visualization is indirectly accomplished and tracheal intubation is performed while the operator views the external monitor. Video laryngoscopy is

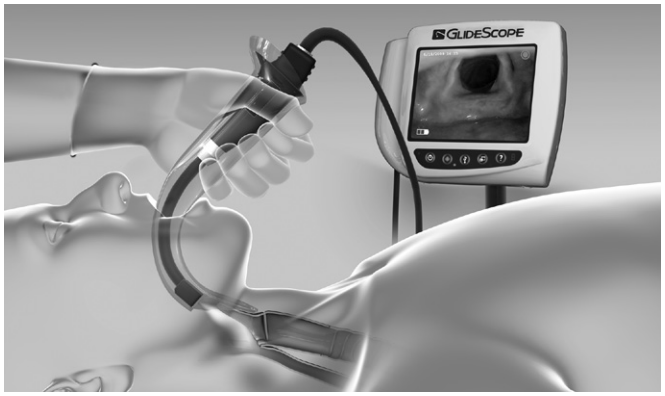


FIGURE **22-42** GlideScope AVL Single Use in airway. (Used with permission, © verathon. Inc.)

a popular choice for anticipated difficult airways and as a rescue strategy when unexpected difficulty occurs. Furthermore, some authors have advocated for its use as the primary laryngoscopic technique and have found that video-assisted laryngoscopy provides improved visualization of the larynx over standard laryngoscopy.[63,130] Video laryngoscopy can be learned quickly and has several distinct advantages over traditional laryngoscopy such as the following[131]:

- Magnification of the airway allows the operator to visualize airway structures in greater detail.
- Blade design and anterior angulation, along with placement of the video camera on the distal portion of the blade, permit the operator to visualize structures that would otherwise be difficult or impossible to see under direct laryngoscopy.
- The external monitor allows other practitioners to visualize airway anatomy and understand current airway conditions.
- The recording capabilities allow for education, documentation, and research.

Disadvantages of video laryngoscopy include cost, which can reach approximately $10,000 or more. In addition, as with other optic devices, blood and secretions can obscure the viewing of airway structures. No specific device is recommended over another; however, speed, simplicity, reliability, and efficiency are desirable characteristics to be considered.[132]

GlideScope Video Laryngoscope

The GlideScope (Figure 22-42) is a video laryngoscope that provides a laryngoscopic view equal to or better than that of direct laryngoscopy without manipulation of the head into a sniffing position.[133] The device is made of medical grade plastic that is modified to resemble a Macintosh blade. The blade has a 60-degree anterior bend and is 18 mm wide. A camera is located in the middle part of the blade and transmits a signal via a video cable to a separate external liquid crystal display (LCD) monitor.[132] In addition, the GlideScope features an antifog system that heats the lens around the video camera preventing fogging of the device during laryngoscopy. Multiple models have been developed such as the portable GlideScope Ranger intended for prehospital and military field use, and the GlideScope Cobalt, which incorporates a disposable one-time use blade over a lighted video baton.

When performing video-assisted laryngoscopy with this device, the blade should be inserted midline and as soon as the tip of the blade is past the teeth, the operator should begin viewing the LCD monitor to identify the different airway structures and navigate to the glottic aperture. The blade should ultimately be placed into the vallecula followed by a gentle tilt of the handle that allows for visualization of the vocal cords. The ETT should be formed into a shape that is similar to the GlideScope blade to facilitate placement. This can be done using a regular ETT stylet, the rigid stylet provided by GlideScope. An alternative method is to bend the ETT and regular stylet at a right angle just proximal to the cuff. The ETT is inserted into the right side of the mouth by direct visualization and is advanced to the oropharynx. The operator should then view the monitor and use a gentle forward rotation to align the tip of the ETT with the glottic opening. Once aligned, the ETT should be advanced through the vocal cords under video visualization.[131] At this point the stylet may be withdrawn to help facilitate advancement of the ETT. The GlideScope should be cleaned before each use following the manufacturer's recommendations.

FIGURE **22-43** McGrath scope (Courtesy LMA North America.)

Karl Storz C-MAC Video Laryngoscope

The C-MAC video laryngoscope uses a blade design similar to a standard Macintosh blade, but unlike the GlideScope uses a less sharp anterior curve. This facilitates ETT placement, but may be less effective in difficult "anterior" airways.[131] The device includes a distally placed microvideo camera that resists fogging and provides an enhanced field of view. In addition, the C-MAC incorporates a video recording system that can be used for education and documentation. The insertion and technique of the device is similar to direct laryngoscopy, except the operator places the ETT using video visualization. Because the angle of the blade is less acute than that of the GlideScope, the ETT can be formed into a shape consistent with regular direct laryngoscopy.

McGrath Video Laryngoscope

LMA America introduced a video scope in 2007 called the McGrath video laryngoscope (Figure 22-43). This device uses one AA battery and has a rotational 1.7-inch color LCD screen attached to the handle. A one-time use disposable laryngoscope blade fits over the light source and is adjustable to three different positions. The blade is a modification of the Macintosh blade, and like the GlideScope has a similar anterior angle. The McGrath does not have an antifog mechanism. The device is extremely portable because the camera and monitor are both built into the

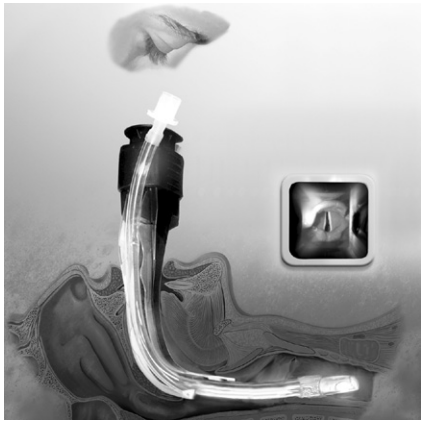


FIGURE **22-44** Airtraq visualization. (Courtesy Prodol Meditec.)

device. Technical use and placement of an ETT is similar to that described with the GlideScope.

Other Video Devices

The Pentax Airway Scope and the Res-Q-Scope II both incorporate a small video screen into the handle of the device. Both use disposable blades with a 90-degree distal bend and allow for preloading of an ETT prior to airway manipulation. Neither has antifog capabilities, though the plastic material on the Pentax is supposed to limit but not eliminate fogging. Both are less expensive alternatives than the previously mentioned video laryngoscopes; however, lens contamination by fogging and blood or secretions severely limit their viewing capabilities.

Airtraq Optical Laryngoscope

The Airtraq (Figure 22-44) is an optically enhanced laryngoscope that uses a series of mirrors, prisms, and lenses to magnify and enhance the laryngeal view and is much less expensive than video laryngoscopes. Like the video laryngoscopes, this device is designed to provide a view of the glottic opening without manipulating the neck into a sniffing position. The blade of the Airtraq has two channels. The first channel has a lighted, heated lens, and the second channel is for passage of an ETT up to a diameter of 8.5 mm. The Airtraq has a unique system that provides antifogging when the LED light is on for at least 30 seconds. There is an optional video camera that clips onto the viewfinder. In simulated difficult laryngoscopy scenarios, the Airtraq was successful in achieving tracheal intubation, required less time to intubate successfully than standard laryngoscopy, and was considered by the anesthetists as easy to use.[127]

Initial set up includes placing the ETT into the side channel until the tip is positioned at the end of the channel. The LED light is turned on for at least 30 seconds prior to placing the device into the mouth to initiate the antifogging system. The tip of the Airtraq is placed in the vallecula in a manner similar to that used with the Macintosh blade. Once in place, the scope is lifted vertically, allowing the epiglottis to flip up onto the blade and the cords to be visualized. Once the cords are visualized, the ETT is advanced through the device's channel and into the trachea. If the practitioner has difficulty visualizing the cords or advancing the ETT through the cords, the scope should be withdrawn slightly.

Subglottic Interventions and Emergency Invasive Airway Access

With the advent of the ILMA and other effective airway rescue devices, there has been less of a need for invasive airway access such as a cricothyrotomy. However, the anesthetist should be familiar with, and maintain regular training in, emergency invasive subglottic airway techniques. This is particularly true if the anesthetist were to encounter a situation in which a failed intubation and subsequent failed ventilation were to occur. In these situations the anesthesia provider must be familiar with and avoid any delay in performing an emergency invasive subglottic airway such as surgical cricothyrotomy or needle cricothyrotomy with transtracheal jet ventilation.

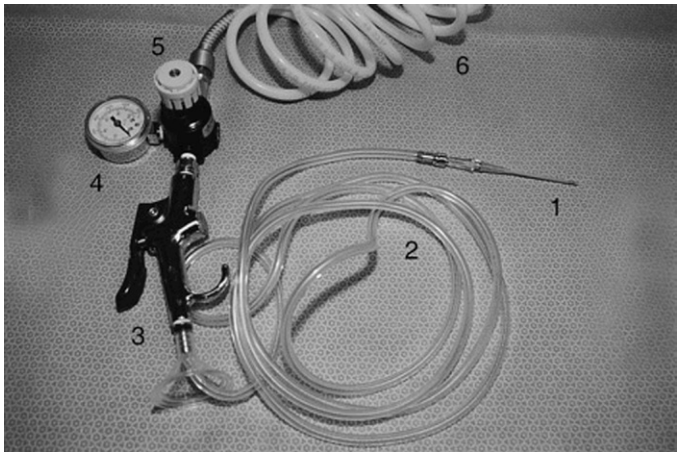


FIGURE **22-45** Transtracheal jet ventilation system assembly: (1) intravenous angio-cath, (2) small-bore tubing assembly with Luer-Lock fitting, (3) manual on/off valve, (4) pressure gauge (e.g., PSI), (5) adjustable pressure regulator, and (6) high-pressure hose assembly with Diameter Index Safety System (DISS) oxygen fitting (not shown).

Needle Cricothyrotomy with Transtracheal Jet Ventilation

Percutaneous transtracheal jet ventilation (PTJV) is attempted after the placement of a needle cricothyrotomy through the cricothyroid membrane. The procedure can be performed using a needle (e.g., 18-gauge or Ravussin needle), or a venous or arterial angiocatheter.[78] Ventilation through the catheter requires a jet injector powered by an oxygen source (Figure 22-45). Needle cricothyrotomy with PTJV may be considered in the cannot intubate and cannot ventilate scenario; however, in the adult patient a surgical cricothyrotomy can be performed quickly and provides a more secure airway with better ventilation. Instead, PTJV should be reserved for those airways where the anatomy is less favorable for placement of a surgical cricothyrotomy (e.g., small children less than 12 years old), or as a temporary means of ventilation.[134]

The procedure can be accomplished quickly using a large-bore intravenous catheter inserted through the cricothyroid membrane (see Figure 22-27) in a caudad direction (Figure 22-46).[135,136] The lungs are ventilated using a high-pressure oxygen source and a regulating valve to control oxygen flow through noncompliant tubing attached to the IV catheter. High-pressure oxygen is delivered reliably through central wall outlets and high-flow (50 to 100 psi) tank regulators. Most jet ventilators have a regulator to allow for a decrease in the inspiratory pressure. Inspiratory pressures should not exceed 50 psi on the regulator, and in most instances, 25 psi is sufficient. A 1-second inspiration at 25 psi with a rate of 20 breaths per minute delivers a 285-mL tidal volume or 5.7 L/min ventilation. Exhalation occurs passively through the upper airway. Obstructions to passive exhalation or excessively large tidal volumes result in hyperinflation and incomplete exhalation of CO_2. Placement of bilateral nasal airways or an oral airway may facilitate exhalation. Use of an in-line pressure gauge and inspiration

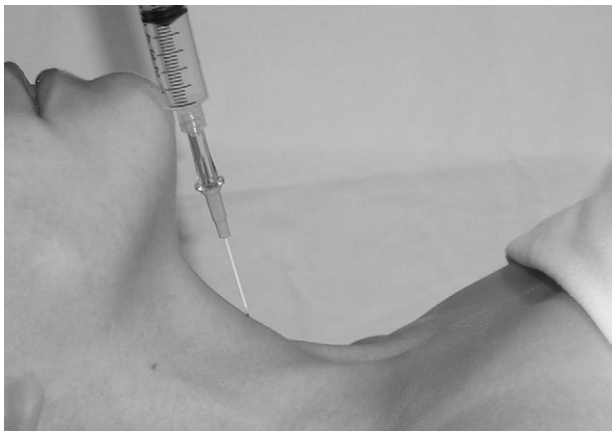


FIGURE **22-46** Insertion of needle for transtracheal jet ventilation.

to expiration ratios of 1:2 or 1:3 help decrease the incidence of barotrauma.

Complications associated with the use of PTJV include barotrauma, subcutaneous emphysema, pneumothorax, pneumomediastinum, hypercarbia, esophageal puncture, airway mucosal damage, blood or mucus obstruction, catheter kinking, and inadvertent removal.[71,134] Bilateral breath sounds should be confirmed frequently to rule out pneumothorax or dislodgement of the catheter.

Retrograde Intubation

A retrograde wire-guided intubation may be considered in a situation in which intubation has failed, but ventilation is possible. A commercial kit is available for retrograde intubation, or the practitioner can choose to insert either a "J-wire" or #2 Mersilene suture via a cricothyrotomy and pass the device cephalad into the oropharynx. This procedure is performed by inserting a 14- to 18-gauge IV catheter or a Cook needle through the cricothyroid membrane and directing it cephalad. After aspiration of air is confirmed, a wire or suture is then inserted through the needle and passed cephalad until it can be visualized in the posterior pharynx. It is then either advanced through the mouth or nose or retrieved using Magill forceps. The distal end of the wire is secured with a clamp at the neck to prevent the wire from being pulled into the trachea prematurely. An ETT is then directed over the wire and passed into the trachea. As the tube enters the larynx, tension is increased on the wire or suture. Once the ETT is through the larynx and cannot pass further, the distal wire is removed at the level of the skin and the ETT is advanced further into the trachea. Placement should be confirmed and the tube secured in place. This procedure is not usually used in an emergency and often can be completed by a skilled practitioner in 5 to 7 minutes.

Surgical Cricothyrotomy

A surgical cricothyrotomy is the establishment of an airway by surgically incising through the cricothyroid membrane and placing a cuffed tracheostomy tube or an ETT. Most airway algorithms and strategies recommend this procedure as a means of providing ventilation for patients who cannot be intubated or ventilated with a facemask or supraglottic airway device.[137] Because of the many surgical cricothyrotomy kits available, this procedure can be performed relatively quickly. One study demonstrated the ability to place a surgical cricothyrotomy in pig tracheas using different cricothyrotomy kits in approximately 1 to 2 minutes.[138] Indications for cricothyrotomy include (1) failed airway (e.g., cannot intubate and subsequently cannot ventilate), (2) traumatic injuries of maxillofacial, cervical spine, head, or neck structures that make intubation through the nose or mouth impossible or difficult and too time consuming, (3) immediate relief of an upper airway obstruction, and (4) the need for a definitive airway for neck or facial surgery, assuming intubation is not possible.

Absolute contraindications are rare; however, the anesthetist should consider avoiding surgical cricothyrotomy in favor of needle cricothyrotomy and PTJV in infants and small children less than 12 years of age. The anatomy of the child's larynx is small, pliable, and movable, which makes cricothyrotomy very difficult.[134] Relative contraindications for cricothyrotomy include preexisting laryngeal or tracheal diseases such as tumors, infections, or abscesses in the location of the cricothyroid membrane, distortion of neck anatomy (e.g., hematoma), bleeding diathesis, and history of coagulopathy.[134]

Complications related to the placement of a surgical cricothyrotomy are similar to those listed under the placement of a needle cricothyrotomy. In addition, initial malplacement (e.g., inferior or superior to the cricothyroid membrane or through the posterior tracheal wall) of a cricothyrotomy is the main complication.[64]

Several cricothyrotomy kits are available, such as the Melker, Quicktrach II, Pertrach, or Portex cricothyrotomy kit (PCK), which can assist the anesthetist with surgical cricothyrotomy placement. The tracheostomy tube is placed percutaneously using these kits by either a cannula over a trocar, or by a Seldinger method. Both the Quicktrach II and PCK devices have a tracheostomy tube loaded over a trocar. The sequence of placing these devices over the trocar includes (1) checking the tube cuff for air leaks; (2) palpation of the cricothyroid membrane and stabilization between the first two fingers (see Figure 22-27); (3) insertion of the trocar/tube through the cricothyroid membrane in a caudad direction; (4) aspiration of air and then advancement of the tracheostomy tube into the trachea; (5) removal of the trocar and inflation of the tube cuff; and (6) securing the tube with a tracheotomy tie and confirming ventilation.

The Melker Universal Emergency Cricothyrotomy Catheter Set (Figure 22-47) by Cook Critical Care is a commonly used technique that contains equipment for both open surgical and Seldinger techniques. The Melker set contains all of the necessary equipment to perform a surgical cricothyrotomy. The set includes an airway catheter (tracheostomy tube) with dilator, scalpel, syringe, introducer needle and catheter introducer needle, stiff guide wire, tracheal hook, forceps, and tie tapes for securing the airway catheter once it is placed in the neck.

The sequence of steps for placing a surgical cricothyrotomy using the Seldinger technique is as follows:

1. Place the patient's head in a neutral position.
2. Open the proper tray and place it in a position that is comfortable and within reach for the person inserting the device. Insert the dilator into the airway catheter.
3. Palpate the cricothyroid membrane, and using the introducer needle with the syringe attached, puncture the neck in a caudad direction while aspirating on the syringe. Once air is aspirated, thread the catheter off of the needle, attach the syringe to the catheter, and again aspirate air (Figure 22-48).
4. Insert the flexible end of the guide wire through the catheter until it is approximately 2 inches beyond the tip of the catheter (Figure 22-49).
5. Using the enclosed scalpel, incise the neck with a single insertion along the guide wire (Figure 22-50).

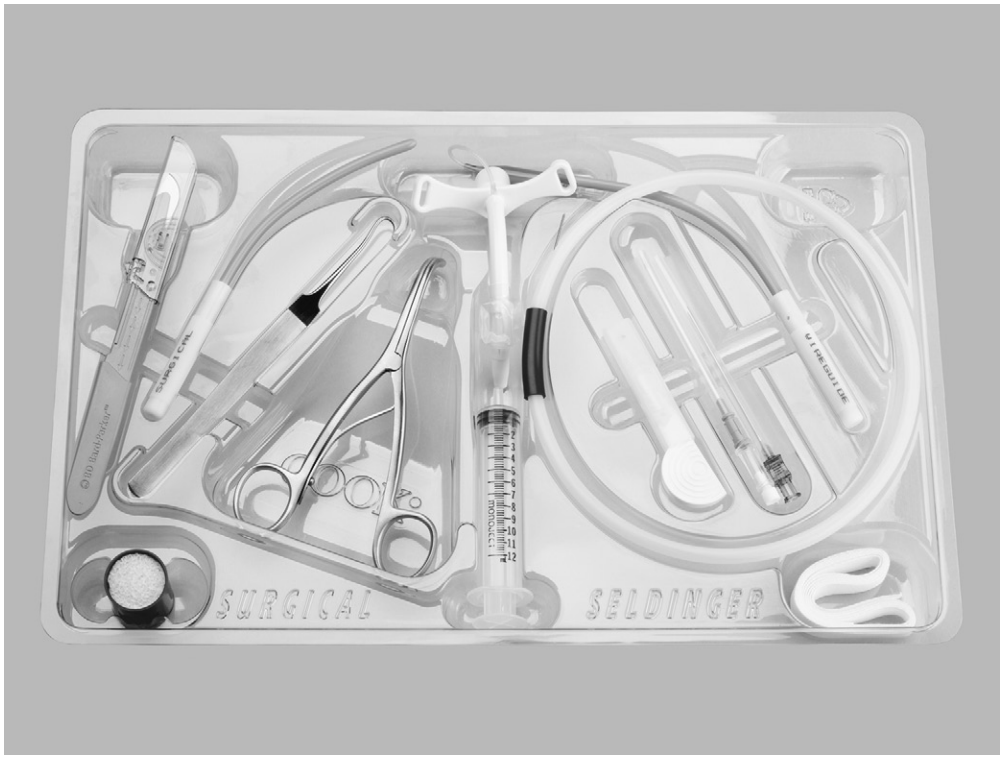


FIGURE **22-47** Melker cricothyrotomy set. (From Cook Medical Incorporated, Bloomington, Indiana.)

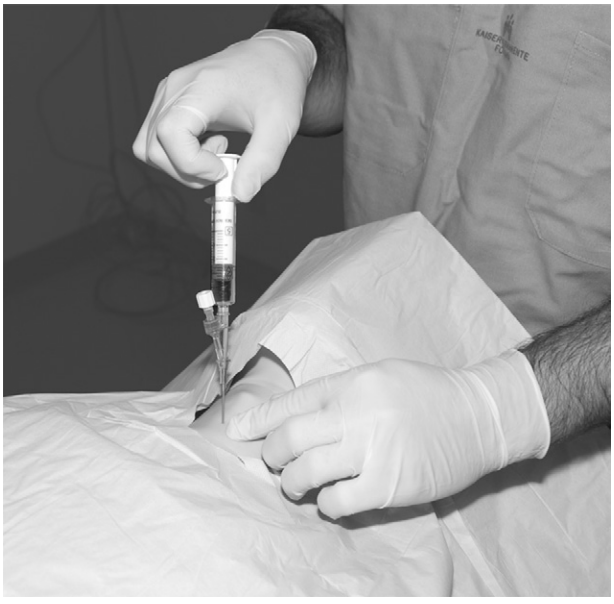


FIGURE **22-48** Needle inserted through cricothyroid membrane in caudad direction aspirating for air.

6. Thread the airway catheter/dilator over the exposed guide wire and advance, applying steady pressure by pushing on the dilator. Once there is loss of resistance, usually preceded by a "pop" as the catheter penetrates the cricothyroid membrane, advance the airway catheter off of the dilator until it rests firmly against the neck. Remove the dilator and assess for appropriate ventilation (Figure 22-51).
7. Using suture or the tape ties, secure the airway catheter onto the neck, while continuously ventilating the patient (Figure 22-52).

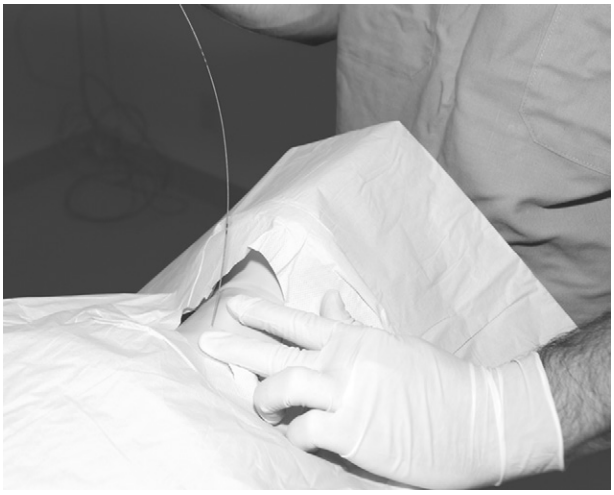


FIGURE **22-49** Guide wire threaded through catheter in neck.

The decision to place a cricothyrotomy should not be delayed when indications are present.[64] Indeed, a review of closed claims data for injuries related to invasive airway access suggested that failure to apply the technique early enough, and before significant hypoxia developed, resulted in death or brain damage in two thirds of the claims reviewed.[71] Researchers advocate for continued training and practice on a regular basis to maintain proficiency with this critical skill.[139-141]

Tracheotomy

An additional surgical airway technique is the tracheotomy. However, this surgical intervention should not be considered in an emergency and is not a procedure performed by an anesthetist. Instead, this surgical airway technique should be performed under

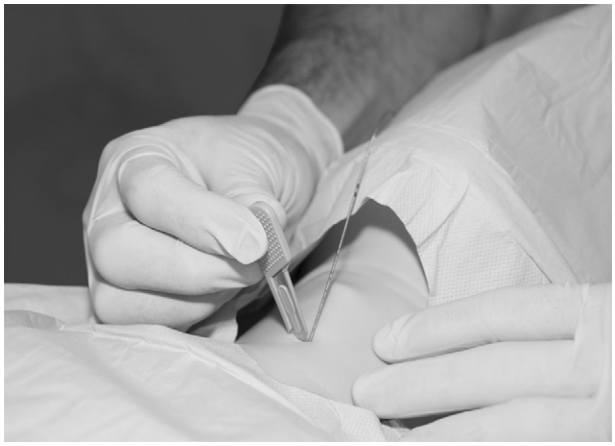


FIGURE **22-50** Neck incised with scalpel along guide wire.

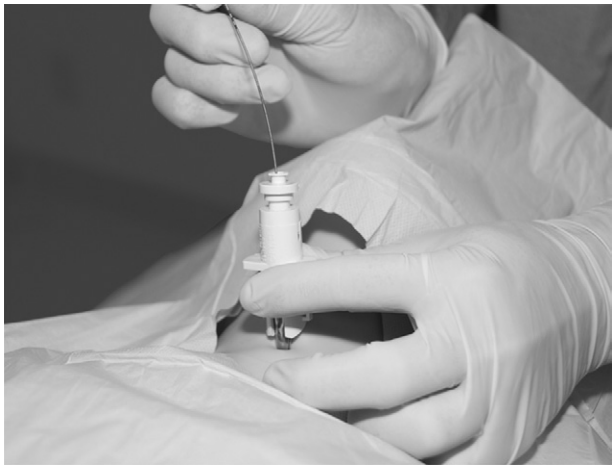


FIGURE **22-51** Airway catheter/dilator threaded over guide wire, through cricothyroid membrane, and into the trachea.

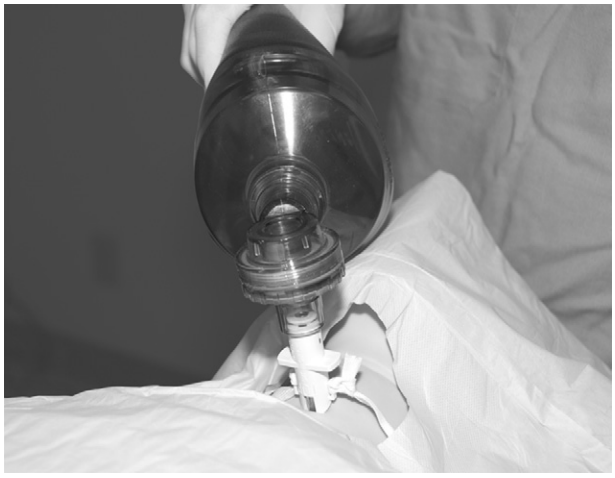


FIGURE **22-52** Dilator and guide wire removed, allowing ventilation.

ideal conditions by a surgeon because of the potential complications (e.g., recurrent laryngeal nerve trauma, damage to large vessels in the neck). If airway difficulty occurs, such as with facial and neck trauma, and ventilation is compromised, then a surgical cricothyrotomy should be the invasive airway technique of choice in an emergency situation. If a need to perform a tracheotomy exists, the airway should be secured first, or the procedure performed with the patient under a local anesthetic. The standard tracheotomy is performed at the level of the fourth to sixth tracheal ring, below the isthmus of the thyroid gland. This procedure can take up to 30 minutes.

TRACHEAL EXTUBATION

Tracheal extubation and continued control of the airway during recovery are cornerstones of perioperative airway management. Tracheal extubation remains a logical corollary of tracheal intubation, in that almost all intubations are performed with the prospect of tracheal extubation at some point during the course of a hospitalization.[12] During the early postoperative period the plan for tracheal extubation should be considered to (1) minimize alterations in cardiopulmonary physiology; (2) decrease the risk of respiratory infection and complications; and (3) reduce the postoperative length of stay while decreasing cost and resource utilization.

Tracheal extubation is not a benign procedure and is associated with significant complications (Box 22-8).[142] Every tracheal extubation is a trial to determine whether a patient's spontaneous ventilation is adequate enough to support cardiopulmonary function. There is no guarantee that tracheal extubation will be tolerated, especially in patients with marginal cardiopulmonary reserve. Standard criteria for tracheal extubation can be divided into two categories: global and respiratory (Box 22-9).[143] It is often impossible and impractical to fulfill the criteria in its entirety. However, the anesthetist should exercise sound judgment in determining which patients are suitable for postoperative tracheal extubation. In addition, the decision to extubate a patient should be based on a methodical and comprehensive evaluation of patient, surgical, and anesthetic-related risk factors for extubation failure (Box 22-10). Patients that require postoperative mechanical respiratory support should remain intubated until standard extubation criteria are met and risk factors for extubation failure are minimized.

Tracheal Extubation Techniques

The same vigilant care taken to secure the airway should be exercised when control of the airway is returned to the patient. Complications of tracheal extubation are increased when extubation is performed during Guedel's stage II of anesthesia (e.g., excitatory plane). Clinically important reflexes, such as laryngospasm, can be readily elicited during stage II by airway stimulation (e.g., laryngoscopy, intubation, or extubation). Tracheal extubation should be performed with the patient in a surgical plane of anesthesia (e.g., deeply anesthetized or Guedel's stage III) or fully awake. Advantages and disadvantages of deeply anesthetized versus fully awake extubation can be found in Table 22-8. In patients with a history of difficult intubation or who are at high risk of aspiration, it would be prudent for the anesthetist to allow full return of the patient's airway reflexes and extubate fully awake. Increased cardiovascular stimulation during awake tracheal extubation can be minimized using beta-blockers, calcium channel blockers, and vasodilators. Furthermore, coughing and straining can be attenuated by judicious use of local anesthetics (e.g., intravenous, topical, intra-cuff lidocaine) and opioids.

Tracheal Extubation of the Difficult Airway

An American Society of Anesthesiologists' closed claims analysis for perioperative difficult airway management revealed that claims for death or brain damage associated with induction of anesthesia decreased from 62% in 1985 to 1992 to 35% in 1993 to 1999. The development of difficult airway guidelines and new

BOX 22-8

Complications of Tracheal Extubation

Respiratory
- Airway obstruction
- Breath holding
- Clearance of secretions, inadequate
- Coughing and straining
- Hypercarbia
- Hypoxemia
- Laryngeal cartilage damage
- Laryngospasm
- Negative-pressure pulmonary edema
- Postextubation laryngeal edema
- Pulmonary aspiration
- Stridor
- Subglottic or supraglottic edema
- Tracheomalacia
- Vocal cord damage (e.g., edema, paralysis, or dysfunction)

Cardiovascular
- Cardiac dysrhythmias
- Hypertension
- Left ventricular failure
- Myocardial infarction
- Myocardial ischemia
- Tachycardia

Neurologic
- Cervical spine injury
- Increased intracranial pressure
- Increased intraocular pressure

Other Considerations
- Damage to dentition
- Inadvertent removal of equipment (e.g., nasogastric tube)
- Self-extubation
- Unintentional extubation

BOX 22-9

Standard Extubation Criteria

Global Criteria
- Acceptable hemodynamic status
- Normothermia
- Ability to maintain patent airway
  1. Return of laryngeal and cough reflexes
  2. Appropriate level of consciousness
- Adequate muscular strength
  1. Reversal of neuromuscular blockade as indicated by train-of-four ratio greater than 0.9, tetanic response to 100 Hz for 5 seconds, and double-burst stimulation without fade
  2. Head lift for more than 5 seconds and strong, constant hand grip
- Acceptable metabolic function indicators
  1. Electrolytes
  2. Acid-base balance
- Acceptable hematologic function indicators
  1. Hemoglobin level consistent with adequate oxygen delivery
- Adequate analgesia for optimal respiratory effort

Respiratory Criteria
- Adequate respiratory mechanics
  1. Vital capacity greater than 15 mL/kg
  2. Maximal negative inspiratory force greater than –20 cm H_2O
- Ability to maintain adequate oxygenation (with F_{IO_2} less than 50%)
  1. SpO_2 greater than 90%
  2. PaO_2 greater than 60 mmHg
- Ability to maintain adequate alveolar ventilation
  1. $Paco_2$ less than 50 mmHg
- Spontaneous respiratory rate (breaths/minute) to tidal volume (liter) ratio (e.g., rapid shallow breathing index) less than 100 breaths/minute/liter

TABLE 22-8 Tracheal Extubation Techniques

	Anesthetized	Awake
Advantages	Decreased cardiovascular stimulation Decreased coughing and straining	Return of airway reflexes Decreased risk of aspiration Maintenance of airway
Disadvantages	Absent or obtunded airway reflexes Increased risk of aspiration Airway obstruction	Increased cardiovascular stimulation Increased coughing and straining

airway adjuncts (e.g., LMA, ILMA, and video laryngoscopy) has greatly improved the safety of anesthesia induction. In contrast, death or brain damage for difficult airway management during maintenance, extubation, and recovery did not differ significantly between the time periods of 1985 to 1992 and 1993 to 1999.[144] This may be attributed to the paucity of literature and guidelines regarding techniques for tracheal extubation of the difficult airway. Therefore a preformulated airway management plan, based on extubation strategies or algorithms (Figure 22-53), may be helpful in decreasing complications of extubation.[142]

Effective strategies for tracheal extubation in high-risk patients include (1) extubation over a flexible fiberoptic bronchoscope, (2) extubation followed by placement of a supraglottic airway (e.g., laryngeal mask airway), and (3) use of an airway exchange catheter (AEC). The placement of these short-term devices serves as a guide for expedited reintubation in the event that oxygenation or ventilation proves inadequate after extubation (e.g., reversible extubation). The anesthetist should select the most appropriate strategy based on patient characteristics and the anesthetist's own experience, judgment, and skill (Table 22-9). Success of these techniques may be aided by judicious use of antisialagogues (e.g., glycopyrrolate), and/or sedative-analgesics (e.g., dexmedetomidine). It is the responsibility of the anesthetist to ensure accessibility to standard and emergency (e.g., cricothyrotomy) airway equipment in the event that these short-term devices fail.

BOX **22-10**

Risk Factors for Difficult Tracheal Extubation

Patient Risk Factors

- Comprehensive airway evaluation indicating possible difficult reintubation or extubation
- Current and past medical illnesses that affect extubation tolerance or with airway implications (e.g., cardiopulmonary disease)
- Difficult intubation or ventilation (e.g., vocal cord paralysis or dysfunction, morbid obesity, obstructive sleep apnea)
- Generalized airway edema (e.g., drug or systemic reactions, angioedema, anaphylactic reactions, anaphylactoid reactions, sepsis, inhalation injury, burns, SIRS)
- Limited cervical spine mobility injury (e.g., hard cervical collar or halo fixation, ankylosing spondylitis)
- Tracheomalacia

Surgical Risk Factors

- Airway surgery (e.g., uvulopalatopharyngoplasty, laryngeal or tracheal surgery, tracheal resection, or reconstruction)
- Head and neck surgery (e.g., maxillofacial surgery, carotid surgery, thyroid surgery, facial and deep neck infections)
- Neurosurgical (e.g., cranial surgery, posterior fossa surgery, stereotactic brain procedures, and cervical fusion)
- Orthopedic surgery (e.g., close proximity to airway)
- Impingement of head and neck venous drainage
- Postsurgical injury (e.g., hematoma, hemorrhage, nerve injury)
- Prolonged surgical duration and intubation
- Prone or Trendelenburg position

Anesthesia Risk Factors

- Depressed neurologic status, muscular strength, or respiratory effort
- Difficult or traumatic intubation (e.g., failure to visualize glottis, intubation requiring multiple attempts or alternative techniques)
- Excessive head and neck movement during procedure
- Excessive volume resuscitation
- Intubation injury causing laryngeal incompetence or arytenoid dislocation
- Lack of cuff leak
- Laryngotracheal edema (e.g., caused by over sized endotracheal tube or dual-lumen tube, excessive cuff pressure, traumatic suctioning)

SIRS, Systemic inflammatory response syndrome.

BOX **22-11**

Benefits of the Airway Exchange Catheter

- Exchangeable 15-mm external diameter connector for manual ventilation and Luer-Lock adaptor for jet ventilation
- Facilitates removal of endotracheal tube while still maintaining continual access to the airway
- Lumen allows for ventilation, oxygenation, tracheal suctioning, administration of medication (e.g., local anesthetic), and carbon dioxide monitoring
- Lumen and side ports ensure adequate airflow, while blunt tip decreases trauma to airway (see Figure 22-38)
- Radiopaque and depth (cm) markers
- Sufficient length and rigidity guides replacement endotracheal tube into position (e.g., Seldinger technique)

The AEC has received considerable attention because of its potential benefits over other similar devices (e.g., gum elastic bougie) (Box 22-11).[145] There are three AECs currently available on the market: (1) the Endotracheal Ventilation Catheter (CardioMed Industries), (2) the Sheridan Tracheal Tube Exchanger (Hudson Respiratory Care), and (3) the Cook Airway Exchange Catheter (Cook Medical) (see Figure 22-38). For adult patients, 11-Fr (external diameter 3.7 mm) and 14-Fr (external diameter 4.7 mm) AECs are generally well tolerated and allow spontaneous breathing, phonation, and the clearance of secretions. After confirmation of placement and depth, the AEC may be secured in situ until it is determined that reintubation will not be required (e.g., up to 72 hours). It is critical that the internal diameter of the reintubation ETT approximate that of the external diameter of the AEC as much as possible to prevent the leading edge of the ETT from impinging on airway structures, causing trauma and preventing passage through the glottis. A laryngoscope can be used to lift and move supraglottic tissue; this minimizes the angle of approach to the glottis and facilitates ETT passage through the glottis. If the ETT encounters an obstruction at the glottic opening, manual rotation 90 degrees counterclockwise can be used to avoid arytenoid or vocal cord impingement.

Complications After Tracheal Extubation

Laryngospasm is the involuntary protective reflex and contraction of the laryngeal musculature (see Table 22-1 and Box 22-1). Laryngospasm is believed to occur as a result of sensory stimulation of the internal branch of the superior laryngeal nerve and afferent responses from both the external branch of the superior laryngeal nerve and the recurrent laryngeal nerve. Laryngospasm can be caused by a number of factors such as airway manipulation, noxious stimuli (e.g., water, blood, or mucus) within the pharynx, or stimulation of the larynx during inadequate anesthetic depth. Tracheal extubation should therefore be performed with the patient in a surgical plane of anesthesia (e.g., deeply anesthetized or Guedel's stage III) or fully awake to minimize the risk of laryngospasm. See Box 22-9 for standard extubation criteria.

Laryngospasm has been described as having two mechanisms. During "glottis shutter closure," intrinsic laryngeal muscles mediate vocal cord adduction, causing partial airway obstruction. In contrast, during the "ball valve closure," extrinsic laryngeal muscles cause contraction of the false vocal cords and supraglottic soft tissue, causing complete airway obstruction. If left untreated, laryngospasm can result in hypoxia, negative-pressure pulmonary edema, and cardiovascular derangements (e.g., cardiac arrhythmias, tachycardia, bradycardia, and cardiac arrest). Treatment of laryngospasm includes (1) administration of 100% oxygen, (2) the application positive-pressure ventilation (10 to 20 cm H_2O pressure), and/or (3) administration of succinylcholine (e.g., 0.2-0.5 mg/kg intravenously or 4-5 mg/kg intramuscularly).

Laryngotracheobronchitis

Laryngotracheobronchitis, or croup, involves inflammation and edema of the airway below the level of the vocal cords. Subglottic edema may manifest as stridor, which is the high-pitched inspiratory and expiratory sound caused by turbulent airflow through a partially obstructed upper airway. A "barking" cough is another

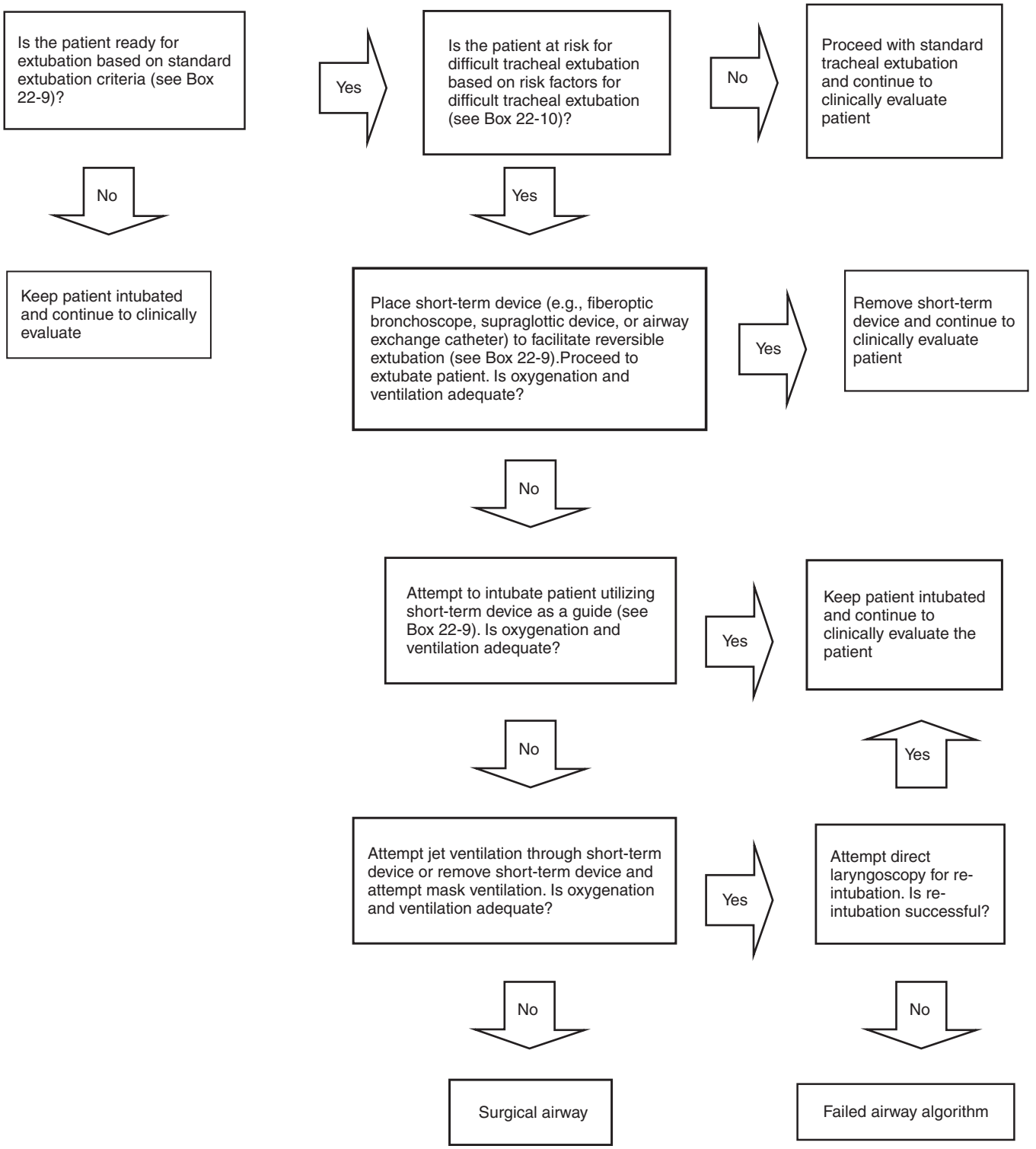


FIGURE **22-53** Extubation algorithm for the difficult airway, using an airway exchange catheter. NOTE: Short-term device refers to fiberoptic bronchoscope, supraglottic device, or airway exchange catheter.

distinctive symptom of croup. Croup can occur in adult and pediatric patients. However, pediatric patients are more vulnerable because of their narrow caliber of airway. Because inflammation greatly increases airway resistance, respiratory failure can occur rapidly. Croup can be caused by (1) postintubation edema around the glottic and subglottic regions, (2) multiple intubation attempts, (3) inappropriately large endotracheal tube, or (4) excessive head and neck movement of the patient. Croup can occur anytime during the postoperative period, but typically occurs within 3 hours of extubation. Treatment of croup is aimed at decreasing inflammation and edema using (1) humidified, supplemental oxygen, (2) racemic epinephrine (e.g., 0.5 mL of a 2.25% solution in 2.5 mL of normal saline), and (3) dexamethasone (e.g., 0.1 to 0.5 mg/kg). Other treatment modalities include the use of a helium-oxygen mixture to facilitate oxygen delivery through narrowed airways.

TABLE 22-9 Tracheal Extubation of the Difficult Airway

	Flexible Fiberoptic Bronchoscope	Supraglottic Airway	Airway Exchange Catheter (AEC)
Advantages	Useful method to evaluate pharyngeal and laryngeal function, injury, pathology, and obstruction	Facilitates fiberoptic bronchoscope evaluation of airway through mask orifice Associated with decreased cardiovascular stimulation, coughing, and straining	Maintains continual access to the airway Lumen allows for ventilation, oxygenation, tracheal suctioning, administration of medication, and carbon dioxide monitoring
Disadvantages	Requires significant skill on the part of the anesthetist May offer only a brief evaluation of the airway May cause carinal irritation	Restricted evaluation of supraglottic and pharyngeal structures if fiberoptic bronchoscope used Periglottic obstruction will impair gas exchange through supraglottic airway	Dislodgement of AEC can occur any time during procedure Complications include trauma from deep placement, barotrauma or pneumothorax with jet ventilation, and carinal irritation
Method for extubation	Tracheal extubation Insertion of bronchoscope prefitted with endotracheal tube Fiberoptic evaluation of airway Bronchoscope is left in place within the trachea and removed when deemed appropriate	Tracheal extubation Insertion of laryngeal mask airway (LMA) LMA is left in place and removed when deemed appropriate	Placement of AEC through endotracheal tube to predetermined depth (e.g., not to exceed 25-26 cm) Tracheal extubation over AEC Confirm depth and tracheal placement of AEC by standard methods, secure with tape AEC is left in place and removed when deemed appropriate
Method for reintubation	Visual confirmation of bronchoscope within trachea Appropriately sized endotracheal tube is passed over bronchoscope Bronchoscope removed Placement of endotracheal tube confirmed by standard methods	Appropriately sized endotracheal tube passed through supraglottic airway tube, blindly or aided by fiberoptic bronchoscope Placement of endotracheal tube confirmed by standard methods	Remove tape and maintain depth of AEC Perform laryngoscopy Appropriately sized endotracheal tube passed over AEC AEC removed Placement of endotracheal tube confirmed by standard methods

COMPLICATIONS OF AIRWAY MANAGEMENT

Complications related to tracheal intubation include (1) airway trauma, (2) aspiration, (3) esophageal intubation, (4) endobronchial intubation, and (5) endotracheal tube complications. Vigilant care must always be undertaken whenever manipulating the airway.

Airway Trauma

Trauma to the airway is a well-recognized complication related to airway management.[142-149] An analysis of the American Society of Anesthesiologists Closed Claims Project (ASA-CCP) indicate that airway trauma was present in 6% of claims. Of these, difficulty with intubation was shown to be a contributing factor in only 38% of claims.[142,148] Structures damaged and sites of injury noted in the analysis included dentition, pharynx, larynx, esophagus, and trachea.[146]

Of the anesthesia-related malpractice claims, dental injury is among the most common with a reported incidence greater than 1:4500.[146] Approximately 50% of dental injuries occur during laryngoscopy and intubation, with the maxillary central incisors most at risk. However, dental injury can also occur after emergence and extubation. Risk factors for dental trauma include: (1) preexisting dental pathology (e.g., carious teeth, periodontitis, paradentosis, or fixed dental work) and (2) one or more indicators of difficult laryngoscopy and intubation (e.g., upper incisor protrusion).

Pharyngeal injury to the airway includes: (1) pharyngeal perforation, laceration, or contusion, (2) localized infection, (3) macroglossia, and (4) edema and necrosis of the uvula.[142,146,147] The cause of pharyngeal injury is often the result of (1) direct trauma (e.g., laryngoscopy or blind pharyngeal suctioning), (2) prolonged mechanical compression and ischemia by an endotracheal tube or oral pharyngeal airway, or (3) pressure-induced nerve injury (e.g., lingual, recurrent laryngeal, or hypoglossal nerve). A malpositioned, oversized, or overinflated laryngeal mask airway (LMA) may also cause trauma to delicate mucosa.[146,147] Lastly, obstruction of the submandibular duct by extreme head flexion, surgical manipulation/trauma, or impingement via endotracheal tube or bike block can cause massive tongue swelling in extreme cases. The incidence of sore throat after intubation is approximately 40% to 65% when blood is observed on the instruments (e.g., laryngoscope) after airway manipulation. Fortunately, pain on swallowing usually lasts no more than 24 to 48 hours.

Trauma to the larynx can be subcategorized into (1) vocal cord paralysis, (2) granuloma formation, and (3) arytenoid dislocation and subluxation. Most susceptible to mechanical injury are the posterior half of the vocal cords, the arytenoids, and the posterior tracheal wall. Unilateral or bilateral vocal cord paralysis can most often be attributed to nerve or mechanical injury and may manifest as partial or complete airway obstruction, respectively. Hoarseness or airway obstruction noted immediately in the postoperative period should be evaluated for possible emergent reintubation or tracheotomy. Granuloma or polyp formation can occur at the vocal process of the arytenoids as well as the posterior wall of the trachea (Figures 22-54 and 22-55), both of which come into intimate contact with the endotracheal tube. Degree of injury and granuloma formation increases with increasing endotracheal tube diameter and with duration of intubation. Arytenoid dislocation (e.g., complete disruption of the cricoarytenoid joint, or malpositioning of the arytenoids cartilages) can be caused by the mechanical force of an endotracheal tube against the arytenoids or by forceful endotracheal tube placement.

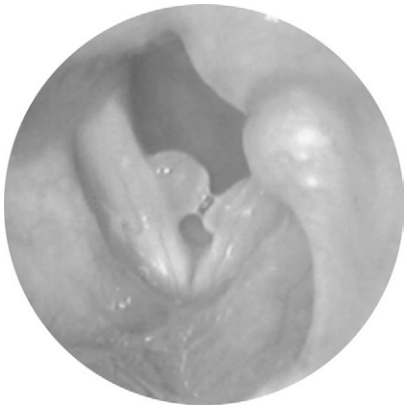


FIGURE **22-54** Fiberoptic view of vocal cord polyps.

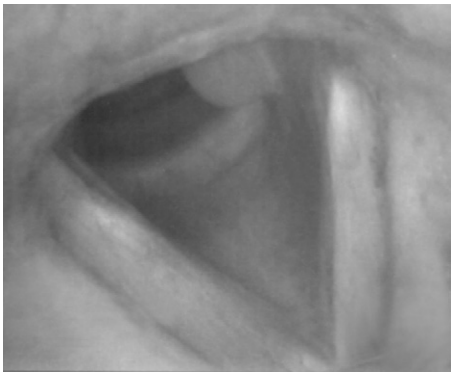


FIGURE **22-55** Fiberoptic view of granuloma.

Esophageal laceration or perforation can occur with any attempt at intubation, especially in patients with a difficult airway or multiple attempts. Esophageal laceration or perforation may manifest as neck erythema, edema, pneumothorax, and subcutaneous emphysema. Mediastinitis associated with esophageal injury is associated with a high degree of morbidity and mortality despite aggressive treatment with surgical drainage and antibiotics.

Tracheal laceration or perforation may be caused by overinflation of the endotracheal tube cuff, overdistention of endotracheal tube cuff by nitrous oxide, multiple intubation attempts, use of an intubating stylet, repositioning of the endotracheal tube without cuff deflation, or inappropriately large endotracheal tube size. The risk of tracheal injury is increased with tracheal distortion (e.g., neoplasm or enlarged lymph nodes), membranous trachea weakness, corticosteroid therapy, and chronic obstructive lung disease. The anesthetist should exercise extreme caution whenever manipulating the airway.

Aspiration

Pulmonary aspiration has two components: the movement of gastric contents from the stomach to the pharynx, followed by the movement of gastric contents from the pharynx into the lungs. Clinically significant aspiration is an uncommon complication of general anesthesia, with a reported incidence of 1 per 35,000 anesthetics.[96] Less than half of all aspirations lead to pneumonia. An analysis of the ASA-CCP indicated that aspiration pneumonitis was present in 3% of claims.[142,148] Patient, anesthetic, and pathologic risk factors for gastric aspiration are reviewed in Box 22-12. The development of pneumonia, with subsequent ventilation perfusion abnormalities, is dependent on the (1) type of aspirate (e.g., contaminated, acidic, particulate, or nonparticulate), (2) volume of aspirate, and (3) the patient's comorbid conditions. Aspiration

BOX **22-12**

Risk Factors for Gastric Aspiration

Patient-Related Risk Factors
- Ascites
- Cardiac arrest
- Emergency surgery
- Full stomach
- Nausea and vomiting
- Obesity
- Scleroderma
- Severe hypotension
- Trauma or stress

Anesthesia-Related Risk Factors
- Cricoid pressure
- Difficult airway management
- Inadequate depth of anesthesia
- Opioids

Gastrointestinal Pathology
- Decreased esophageal sphincter tone
- Diabetic gastroparesis
- Gastroesophageal reflux disease (GERD)
- Gastrointestinal obstruction
- Hiatal hernia
- Increased gastric pressure
- Peptic ulcer disease

Neurologic Pathology
- Decreased airway reflexes
- Decreased level of consciousness
- Head injury
- Seizures

From Nagelhout JJ. Aspiration prophylaxis: is it time for changes in our practice? *AANA J.* 2003;71(4):299-303.

pneumonitis can be divided into two phases: phase 1 (direct chemical injury) and phase 2 (inflammatory mediator release).[96] Acute gastric aspiration can occur whenever the patient's laryngeal reflexes are inhibited. Gastric aspirate contamination into the lungs causes (1) chemical destruction of pulmonary tissue, (2) alveolar capillary membrane edema and degeneration, (3) alveolar type II pneumocyte destruction, and (4) microhemorrhaging leading to hypoxia. Management of this condition includes positive pressure ventilation and intensive physiologic support.

A number of mechanical and pharmacologic measures can be taken to minimize the risk of gastric aspiration. During airway management and mask ventilation, it is imperative to maintain peak airway pressures of less than 15 to 20 cm H_2O, which helps minimize gastric insufflation. If higher peak airway pressures (e.g., greater than 25 cm H_2O) are used for ventilation, gastric insufflation may occur. The application of cricoid pressure during rapid sequence induction may be beneficial in preventing gastric aspiration provided that it is performed properly and does not impede effective airway management. Realistic adherence to fasting guidelines should be instituted, and these guidelines should include consideration of the type of liquid or food consumed, patient age and characteristics, type of anesthesia and surgical procedure planned, and the presence of risk factors for gastric aspiration.[96]

Pharmacologic methods to reduce the acidity and volume of gastric contents may reduce the risk of gastric aspiration.[96] The administration of nonparticulate antacids (e.g., sodium citrate 30 mL) 10 to 20 minutes before induction of anesthesia effectively raises gastric pH. A histamine-blocking agent (e.g., famotidine, cimetidine, or ranitidine) administered 45 to 60 minutes preoperatively either orally or intravenously is also effective in raising gastric pH. The administration of a gastroprokinetic agent (e.g., metoclopramide 10 mg intravenously) 20 to 30 minutes before induction of anesthesia accelerates gastric emptying.

Esophageal Intubation

Esophageal intubation may occur during any intubation procedure. However, during difficult intubation when inadequate visualization

of the glottis is achieved, the possibility of inadvertently placing the endotracheal tube into the esophagus increases significantly. Unrecognized esophageal intubation can lead to severe hypoxia and catastrophic complications including death. An analysis of the ASA-CCP indicated that that 18% of respiratory-related claims involved esophageal intubation.[142,148] It is imperative that confirmation of endotracheal tube placement includes end-tidal CO_2 monitoring. Fiberoptic bronchoscopy is another sensitive method for confirming endotracheal tube placement. It is important to recognize that other traditional methods of confirming endotracheal tube placement such as equal bilateral breath sounds, symmetrical chest wall movement, epigastric auscultation, and observation of tube condensation lack specificity and are potentially misleading. Esophageal perforation, retropharyngeal abscess formation, subcutaneous emphysema, and pneumothorax have been documented after esophageal intubation. Mediastinitis is a potentially lethal consequence after esophageal intubation with a mortality rate of 50%.[146]

Endobronchial Intubation

Endobronchial intubation may occur during any intubation procedure and is sometimes difficult to identify. An American Society of Nurse Anesthetist closed-claims analysis of respiratory events indicated that 9% of respiratory incidents involved endobronchial intubation, which was believed to contribute to inadequate ventilation. The recommendation from the closed-claims analysis was for anesthesia providers to remain vigilant and be aware of tube markings and recommended depths for common patient populations. Endobronchial intubation occurs most commonly within the right mainstem bronchus. It occurs more commonly in infants and children because of the relatively short distance between the glottis and the carina. Signs and symptoms of endobronchial intubation include: (1) increased peak inspiratory pressures, (2) asymmetrical chest expansion, (3) unilateral breath sounds, and (4) hypoxemia. Endobronchial intubation may occur after initial placement of an ETT or following extreme flexion of the neck. The tip of the endotracheal tube can move an average of 3.8 cm (up to 6 cm) toward the carina when the neck is moved from full extension to full flexion.[142] When endobronchial intubation is discovered, the endotracheal tube should be carefully withdrawn into the trachea and the lungs hyperinflated sufficiently to expand any atelectatic areas.

Endotracheal Tube Complications

Complications regarding the endotracheal tube can occur any time during the administration of general anesthesia. In particular, partial or complete obstruction of the endotracheal tube may occur during surgery of prolonged duration or in a patient with predisposing abnormalities of the airway anatomy. Airway obstruction through an endotracheal tube may be caused by (1) mechanical factors (e.g., sharp bend, kinking, or biting), (2) foreign material (e.g., mucus, blood, tissue, foreign bodies, or lubricant), or (3) the endotracheal tube cuff. The expansion of gas bubbles within the endotracheal tube by nitrous oxide or overinflation of the cuff may cause partial or complete airway obstruction. Wire-reinforced endotracheal tubes may be used to decrease the risk of mechanical obstruction. To clear a partially obstructed endotracheal tube, a suction catheter or a fiberoptic bronchoscope should be placed down the lumen of the endotracheal tube. If the endotracheal tube is totally obstructed, passage of a stylet or airway exchange catheter should be attempted. Total obstruction that cannot be treated quickly requires removal of the endotracheal tube followed by reintubation.

SUMMARY

Airway management is a critical component of anesthesia practice. Knowledge of anatomy, equipment, and techniques is paramount if safe airway management is to be provided. Adherence to established standards and protocols including difficult airway strategies and algorithms can minimize complications. Competence and skill with a variety of airway management techniques will facilitate the appropriate management when a difficult airway situation occurs.

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23 CHAPTER Cardiovascular Anatomy, Physiology, Pathophysiology, and Anesthesia Management

◆ *Sass Elisha*

CARDIOVASCULAR SYSTEM

Knowledge of anatomy and physiology of the cardiovascular system is essential to anesthesia practice. Every anesthetic agent has either a direct or an indirect effect on the cardiovascular system. Therefore whether the clinical concern is about a sympathectomy that causes a decrease in blood pressure during neuraxial blockade or about myocardial depression during inhalation anesthesia, a thorough understanding of these effects and their implications with regard to human physiology is vital if excellent anesthesia care is to be provided.

The cardiovascular system is composed of the heart and the vasculature that carries blood to provide nutrients to all cells in the body. In addition, the cardiovascular system transports substances such as hormones and electrolytes from one part of the body to another.

At the center of this network is the heart. The heart pumps unoxygenated blood to the lungs and then supplies oxygenated blood to all parts of the body. This chapter describes the anatomic and physiologic characteristics, as well as pathophysiologic changes, associated with the cardiovascular system.

Heart

Gross Anatomy

The heart is bound anteriorly by the sternum and the costal cartilages of the third, fourth, and fifth ribs and inferiorly by the diaphragm. It is positioned with the apex of the heart projecting anteriorly and inferiorly toward the left fifth intercostal space at the midclavicular line. At this location, the pulsation from the cardiac apex may be palpated. This is known as the *point of maximal impulse*. The first heart sound (S_1) is best auscultated in this area. A third (S_3) or fourth (S_4) heart sound, if present, can also be heard in this location. Heart sounds are generated from the vibrations caused by the closure of the semilunar and atrioventricular (AV) valves.[1]

Cardiac Silhouette

The superior aspect of the cardiac silhouette is formed by the transverse and ascending aortas. The right lateral border is composed of the right atrium (RA), and the mass of the right ventricle (RV) constitutes most of the inferior border. The left ventricle (LV) comprises the majority of the apex and the lower left lateral border. The left atrial appendage lies superior to the LV and to one side of the pulmonary artery. This appendage may be seen radiographically between the LV and the pulmonary outflow tract. The heart is rotated on its base such that the anterior surface is almost entirely made up of the RV. The base of the heart is the most superior portion of the cardiac silhouette.

Pericardium

The heart is situated within the mediastinum and surrounded by a fibrous, double-walled sac called the *pericardium*,[2] which envelops the heart and the roots of the great vessels. It consists of a visceral portion, which is in intimate contact with the outer surface of the heart (epicardium), and an outer parietal portion, and adheres to the fibrous pericardium (Figure 23-1).

The fibrous pericardium is pierced superiorly by the aorta, the pulmonary trunk, and the superior vena cava. The base of the fibrous pericardium is fused with the central tendon of the diaphragm. The visceral pericardium and parietal pericardium are separated by a thin potential space known as the *pericardial cavity*. This space normally contains approximately 10 to 25 mL of serous fluid, which provides lubrication for the free movement of the heart within the mediastinum. In disease states, the pericardial space can fill with blood and or serosanguinous fluid, compress the heart, and decrease cardiac output (CO). In acute cardiac tamponade, the volume rapidly increases, producing myocardial dysfunction. In contrast, in chronic cardiac tamponade, the degree of pressure exerted on the heart increases slowly because the pericardial sac stretches over time to accommodate the blood that accumulates. However, the pressure may eventually increase as much as 10-fold before symptoms of cardiac tamponade occur.[3]

The pericardium receives its arterial blood supply from the branches of the internal thoracic arteries and through the bronchial, esophageal, and superior phrenic arteries. Venous drainage from the pericardium occurs through the azygos system and the pericardiophrenic veins, which anastomose with the internal thoracic veins. Nervous innervation to the pericardium is derived from the vagus nerve, the phrenic nerves, and the sympathetic trunks.

Surface Anatomy

The atria are separated from the ventricles by the coronary sulcus (AV sulcus), as seen in Figure 23-2, *A*. The right coronary artery travels within this sulcus. The circumflex artery arises from the left coronary artery and travels in the coronary sulcus until it branches posteriorly. The RV and LV are separated by the interventricular sulci, which descend from the coronary sulcus to the apex. The interventricular sulci are composed of an anterior interventricular sulcus and a posterior interventricular sulcus. The anterior interventricular sulcus contains the left anterior descending (LAD) artery, which courses over the interventricular septum and continues in the posterior interventricular sulcus.

The crux of the heart is the place at which the coronary and the posterior interventricular sulci meet. Internally, it is where the atrial and ventricular septa meet (Figure 23-2, *B*). This anatomic crux is important in determining coronary artery dominance.

Cardiac Skeleton

Essential to a discussion of the chambers of the heart is a description of the fibrous skeleton, the annulus fibrosus (Figure 23-3). Tough fibrous rings surround the AV valves and act as points of

attachment for the valves. Two additional fibrous annuli develop in relation to the bases of the aorta and the pulmonary trunk. The aortic fibrous annulus is connected to the pulmonary annulus by a fibrous band called the *tendon of the conus*. The aortic annulus is connected to the AV annuli by the small left fibrous trigone and the larger right fibrous trigone, also called the *central fibrous body*. The four annuli and their interconnections constitute the fibrous cardiac skeleton.

The annulus fibrosus is the fixation point for the cardiac musculature and plays an important role in the structure, function, and efficiency of the heart. The annulus acts as an insulator to prevent aberrant electrical conduction from the atria to the ventricles so that AV conduction moves through one pathway only: the AV node to the bundle of His. This element increases the electromechanical efficiency of the heart and helps prevent dysrhythmias.

Chambers of the Heart

Right Atrium. The atria act as the priming chambers for the ventricles. As such, the RA acts as a reservoir for the RV and has unique anatomic characteristics. It has a muscle wall thickness of approximately 2 mm.

The RA receives blood from several sources: the superior vena cava, the inferior vena cava, and the coronary sinus (Figure 23-4). The RA consists of two parts: an anterior, thin-walled trabeculated portion and a posterior, smooth-walled portion called the *sinus venarum*. The sinus venarum receives blood from the vena cava and the coronary sinus. The auricle projects to the left from the root of the superior vena cava and overlaps the root of the ascending aorta.

The superior vena cava returns blood to the RA from the upper body. The inferior vena cava returns blood to the RA from the lower body. The entrance of the inferior vena cava into the RA is protected by a rudimentary valve called the *eustachian valve*.[4]

The entrance from the coronary sinus into the RA is located between the AV orifice and the valve of the inferior vena cava. This opening is protected in part by a rudimentary valve of the coronary sinus called the *thebesian valve*.[5] Other distinguishing structures in the RA include the interatrial septum and the fossa ovalis cordis, which is the remnant of the fetal foramen ovale within the septum.

Right Ventricle. The RV ejects blood into the pulmonary arterial system for oxygenation and removal of carbon dioxide by the lungs. The RV communicates with the RA through the AV orifice, which is separated by the tricuspid valve. The RV also communicates with the pulmonary outflow tract through the pulmonary orifice, which is guarded by the pulmonic valve (see Figure 23-4).

The walls of the RV are much thicker (4 to 5 mm) than those of the RA because of the increased pressures required to generate forward blood flow into the pulmonary circulation. The superior portion of the RV as it approaches the pulmonary orifice has a conical appearance and is called the *conus arteriosus* or *infundibulum*.[6]

The inner wall of the conus is smooth, but the remainder of the right ventricular wall has a rough appearance because of the

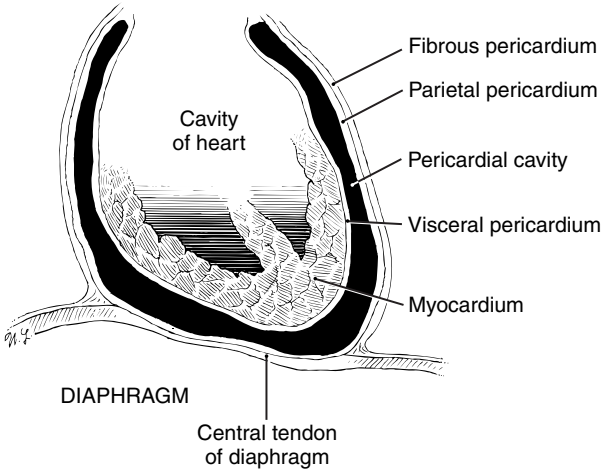

FIGURE **23-1** The pericardium.

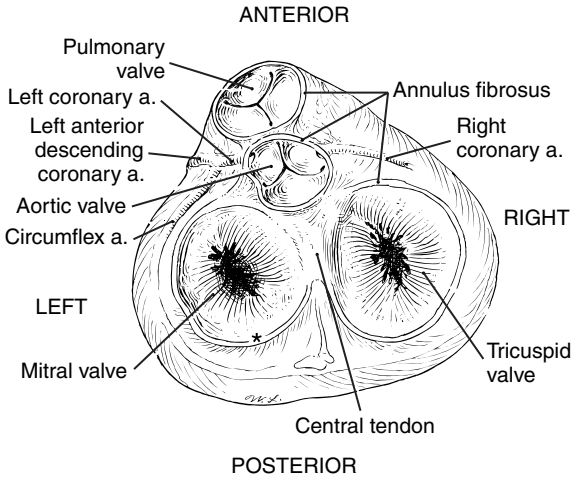

FIGURE **23-3** The annulus fibrosus. *a.*, Artery.

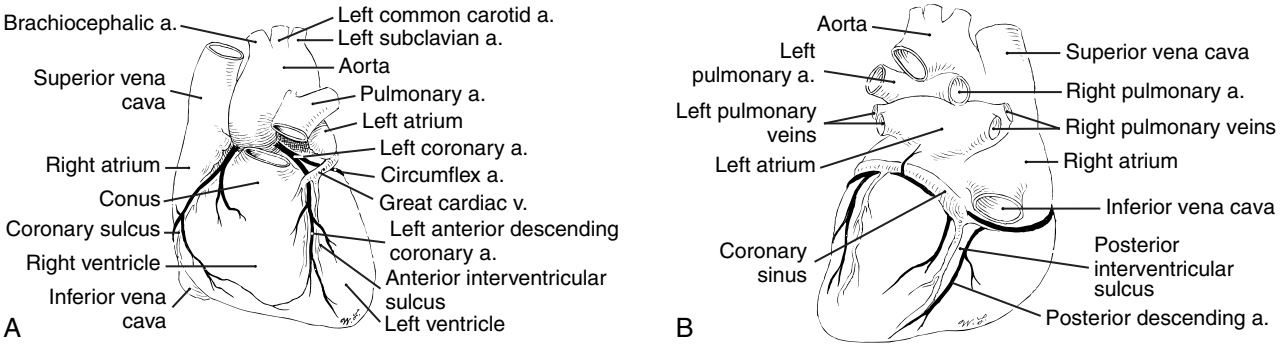

FIGURE **23-2** **A,** Surface anatomy of the heart (anterior view). **B,** Surface anatomy of the heart (posterior view). *a.*, Artery; *v.*, vein.

presence of several irregular muscular bundles called the *papillary muscles* and the *trabeculae carneae*. One of the trabeculae carneae (the moderator band) crosses the cavity of the ventricles and carries the right branch of the AV bundle. The papillary muscles have attachments to the ventricular walls and to the chordae tendineae. The chordae tendineae are attached to the cusps of the tricuspid valve; together with the papillary muscles, they help prevent eversion of the tricuspid valve into the RA during ventricular systole.[7]

Left Atrium. The left atrium (LA) acts as a reservoir for oxygenated blood as it receives blood from the four pulmonary veins and also serves as a pump during atrial systole. It provides a 20% to 30% increase in left ventricular end-diastolic volume (LVEDV), which is known as the *atrial kick*. A person who has normal myocardial performance does not rely on this increase in ventricular filling to achieve adequate CO. However, in certain cardiovascular or respiratory pathologic conditions, compromised patients do rely on this atrial kick to maintain an adequate CO. The LA is located superiorly and posteriorly to the other cardiac chambers. The walls of the LA are slightly thicker (3 μm) than those of the RA. The LA connects to the LV through the left AV orifice, which contains the mitral valve. The atrial septum is smooth but may contain a central depression that corresponds to the location of the fossa ovalis cordis.

Left Ventricle. The apex of the LV is positioned within the mediastinum in an anterior and inferior orientation. The LV receives blood from the LA and ejects it into the aorta. Left ventricular wall thickness is approximately 8 to 15 mm, or two to three times the thickness of the RV. This additional muscle mass is required to overcome the systemic vascular resistance (SVR), or afterload, to maintain CO.

The ventricular septum separates the right and left ventricular cavities.[8] The upper third of the septum is smooth endocardium. The remaining two thirds of the septum and the rest of the ventricular wall are covered with trabeculae carneae.

Two large papillary muscles are present within the LV. The anterior papillary muscle attaches to the anterior part of the left ventricular wall, and the posterior papillary muscle arises from the posterior aspect of the inferior wall. The chordae tendineae of each muscle are attached to the cusps of the mitral valve and prevent eversion of the valve during ventricular systole.

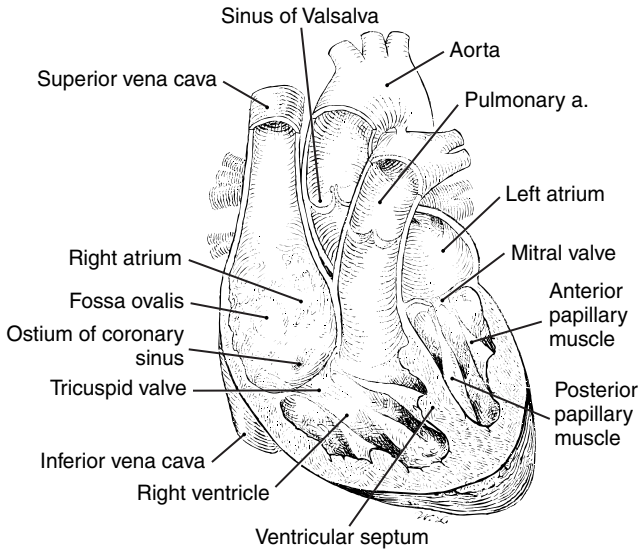

FIGURE **23-4** Internal anatomy of the heart chambers. *a.*, Artery.

Myocardium

The cardiac musculature is arranged in three distinct layers: an outer epicardium, a middle muscular myocardium, and an inner endocardium. The epicardium is composed of mesothelium, connective tissue, and fat. The middle muscular myocardium consists of two muscle layers—a superficial and a deep layer. These layers are arranged in a spiral fashion and appear on cross section to run at right angles to each other. It has been postulated that the superficial and deep layers of the myocardium are not two separate layers but one tortuous and continuous layer. The arrangement of the muscle layers provides strength during contraction of the myocardium and efficient propulsion of blood toward the semilunar valves. The endocardium consists of endothelium and a layer of connective tissue.

Valves

The cardiac valves increase the heart's efficiency by ensuring a one-way flow of blood through the circuit. They open and close in response to pressure gradients that exist above or below the valves. These valves may be categorized as AV or semilunar in configuration.

One of the most accurate ways to determine the presence of valvular pathology is by calculating valve area. The standard method for determining valve area is by cardiac catheterization. A cardiologist is able to determine valve gradients using the Gorlin formula or its correction, which can provide information regarding the degree of pathology that exists.[9]

$$\text{Valve area} = \frac{\text{Flow across valve}}{K \times \sqrt{\text{Mean transvalvular gradient}}}$$

Where valve area is expressed in cm^2, blood flow across the mitral valve is expressed in mL/s, K is a hydraulic pressure constant, and mean transvalvular gradient is expressed in mmHg.

Echocardiography is a noninvasive method of determining valve area and is used in the diagnosis of valvular heart disease. The use of echocardiography is discussed later in this chapter.

Atrioventricular Valves

Tricuspid Valve. The tricuspid valve is situated within the right AV orifice, which lies between the RA and the RV. The tricuspid leaflets are thinner and more translucent than the mitral valve and more easily separated into well-defined leaflets. Three leaflets of unequal size exist: the anterior, septal, and posterior leaflets. The leaflets are attached to the chordae tendineae, which are attached to the papillary muscles.[10] The normal tricuspid valve area is approximately 7 cm^2. Symptoms associated with tricuspid valve stenosis occur when the valve area is less than 1.5 cm^2.

Mitral Valve. The mitral valve is situated in the left AV orifice between the LA and the LV. Two major leaflets, the anteromedial leaflet and the posterolateral leaflet, are connected by commissural tissue. The normal mitral valve area is 4 to 6 cm^2. When the surface area of the valve is decreased by half, clinical symptoms may appear. Like the tricuspid valve, the mitral valve has papillary muscles and chordae tendineae attached to the leaflets to prevent eversion of the valve during ventricular systole.[11]

Semilunar Valves. The configuration of the aortic and pulmonary valves is similar. The cusps of the aortic valve are slightly thicker because it is subjected to greater pressures, which are created by left ventricular ejection. The semilunar valves are situated within the outflow tracts of their corresponding ventricles. Each valve is composed of three cusps. Above the aortic valve is a dilation known as the *sinus of Valsalva*, which allows the valve to open efficiently without occluding the coronary ostia or openings

that communicate with the coronary arteries. Eddy currents form behind the valve leaflets and prevent contact between the valve leaflets and the walls of the aorta. Normal aortic valve area is 2.5 to 3.5 cm^2. Reduction of the valve area by one third to one half is associated with an increase in the symptoms caused by aortic stenosis.

Coronary Circulation

The heart is an aerobic organ that depends on a constant supply of oxygen to meet its high metabolic demand. It requires an elaborate arterial and venous network to ensure that myocytes are adequately supplied with oxygen. The arterial system consists of epicardial and subendocardial vessels. The epicardial vessels are located superficially and most commonly become obstructed at areas of bifurcation where the blood flow is turbulent rather than laminar. Significant obstruction (50% to 70% reduction in luminal diameter) can result in myocardial ischemia or infarction as a result of increased resistance to flow across the stenotic areas.

Coronary Arteries. The coronary ostia are the entrance points by which blood flows through the coronary circulation and they are located behind the aortic cusps near the superior part of the sinus of Valsalva. The ostium of the left coronary artery is superior and posterior to the right coronary ostium. The coronary arteries act as end arteries, and each supplies blood to its respective capillary bed[12] (Figure 23-5).

Left Main Coronary Artery. The left main coronary artery travels anteriorly, inferiorly, and leftward from the left coronary sinus to emerge from behind the pulmonary trunk. Within 2 to 10 mm of its emergence, the left main coronary artery divides into two or more branches of near-equal diameter. The branches include the LAD artery, the left circumflex coronary artery, and possibly the diagonal branch.

Left Anterior Descending Coronary Artery. The LAD is a continuation of the left main coronary artery. The branches of this vessel include the first diagonal branch, the first septal perforator, the right ventricular branches (not always observed), other septal perforators, and other diagonal branches. The LAD provides blood flow to the anterior two thirds of the interventricular septum, the right and left bundle branches, the anterior and posterior papillary muscles of the mitral valve, and the anterior lateral and apical walls of the LV. The LAD also provides collateral circulation to the anterior wall of the RV.

Left Circumflex Coronary Artery. The left circumflex artery arises from the left main coronary artery at an obtuse angle, and it is directed posteriorly as it travels around the left side of the heart within the left AV sulcus. Branches are variable and may include the sinus node artery (40% to 50% of the population), the left atrial circumflex artery, the anterolateral marginal artery, the distal circumflex artery, one or more posterolateral marginal arteries, and the posterior descending artery (10% to 15% of the population). The circumflex artery supplies blood to the left atrial wall, the posterior and lateral LV, the anterolateral papillary muscle, the AV node in 10% of the population, and the sinoatrial (SA) node in 40% to 45% of the population.

Right Coronary Artery. The right coronary artery supplies blood to the SA and AV nodes, the RA and RV, the posterior third of the interventricular septum, the posterior fascicle of the left bundle branch, and the interatrial septum. In approximately 90% of the population, the right coronary artery leaves the right coronary sinus and descends in the right AV groove. At the crux, the right coronary artery courses inferiorly in the posterior AV groove and terminates as a left ventricular branch.

The branches of the right coronary artery include the conus artery, the sinus node artery (50% to 60% of the population), several anterior right ventricular branches, the right atrial branches, the acute marginal branch, the AV node artery (90% of the population), the proximal bundle branches, the posterior descending artery, and the terminal branches to the LA and LV.

Coronary Artery Dominance. Dominance of one coronary artery is determined by the location of the coronary artery that crosses the crux and provides blood flow to the posterior descending artery. The dominant coronary artery in 50% of the general population is the right coronary. In addition, 10% to 15% of the general population are left coronary dominant, and 35% to 40% of the general population have mixed right and left dominance.

Venous Drainage. An extensive venous system exists in the heart. The three major systems include the coronary sinus, the anterior cardiac veins, and the thebesian veins (Figure 23-6).

The coronary sinus is located in the posterior AV groove near the crux. It collects approximately 85% of the blood from the LV, and for this reason it is catheterized when metabolic studies of the LV are performed. It may also be cannulated during cardiopulmonary bypass to deliver cardioplegia. The coronary sinus receives blood from the great, middle, and small cardiac veins; the posterior left ventricular veins; and the left atrial vein of Marshall.

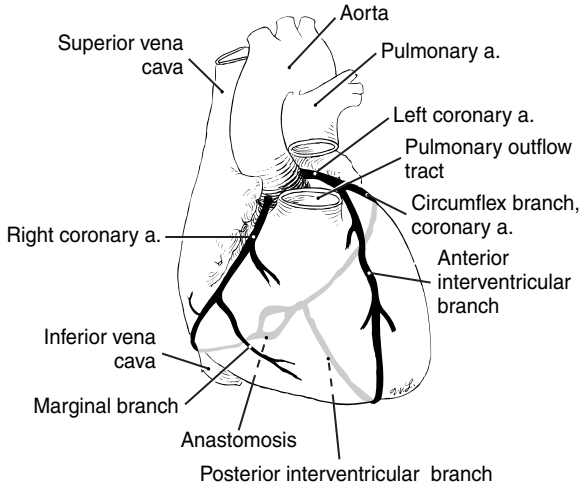

FIGURE **23-5** The coronary arterial circulation. *a.*, Artery.

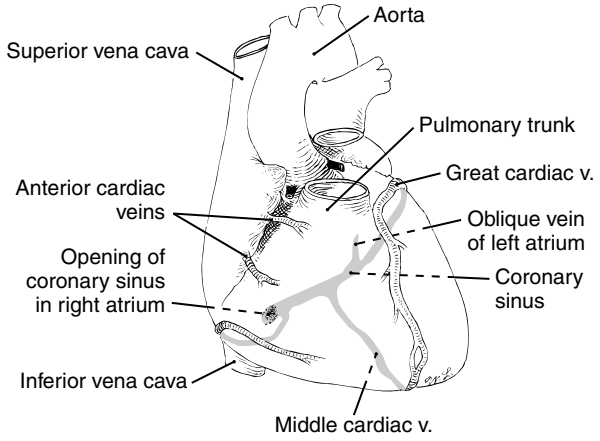

FIGURE **23-6** The coronary venous system. *v.*, Vein.

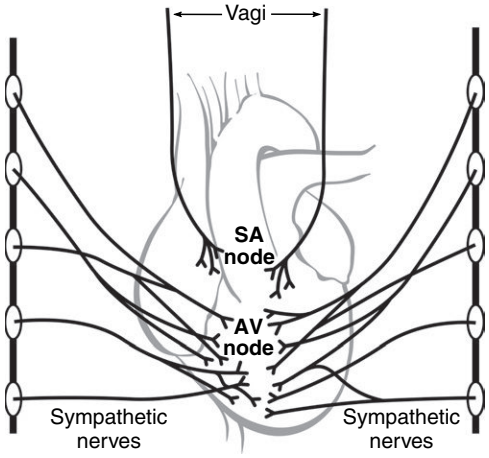

FIGURE **23-7** Distribution of sympathetic and parasympathetic innervation to the heart.

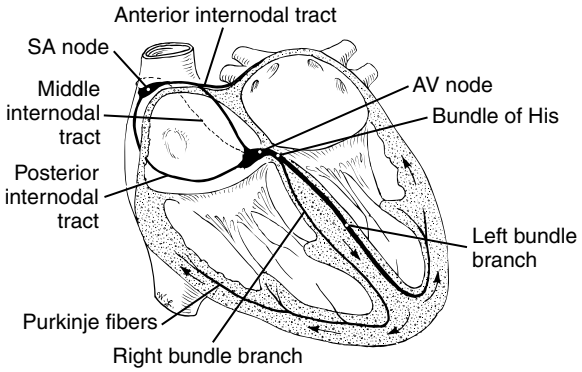

FIGURE **23-8** The cardiac conduction system. *AV*, Atrioventricular; *SA*, sinoatrial.

Two to four anterior cardiac veins drain the anterior right ventricular wall. These veins may enter the RA directly, or they may empty into the coronary sinus.

The thebesian veins traverse the myocardium and drain into the various cardiac chambers, especially the RA, the RV, and to a lesser extent the LV. The thebesian veins may carry up to 40% of the blood that is returned to the RA.

Cardiac Innervation

The autonomic nervous system is divided into the sympathetic and parasympathetic nervous systems. Efferent impulses are transmitted from the brainstem and hypothalamus to numerous body systems, including the heart. The neurologic innervation to the heart originates from the autonomic nervous system, as well as from sensory fibers. The myocardium also has a specialized conduction system that is discussed in this chapter.

Increased sympathetic nervous system tone increases heart rate (chronotropic), force of myocardial contraction (inotropic), and rate of sinus node discharge (dromotropic). Sympathetic nervous system activation results in the mobilization of myocardial fat-free acids and glycogen for energy use by the myocardial cells. The preganglionic sympathetic nervous system fibers originate from the cells in the intermediolateral columns of the higher thoracic segments of the spinal cord and synapse at the first through the fourth or fifth thoracic paravertebral ganglia. These spinal cord segments are known as the *cardioaccelerator fibers*. The postganglionic fibers then travel as the superior, middle, and inferior cardiac nerves and the thoracic visceral nerves. These fibers form an epicardial plexus and are distributed over the entire ventricular myocardium. There is greater distribution of sympathetic nerves that innervate the ventricles, resulting in increased ventricular contractility, as is shown in Figure 23-7. Catecholamines released during sympathetic stimulation bind with adrenergic receptors on the heart (primarily B_1) and change the biochemical properties within the myocyte. This process is discussed later in this chapter.

Some of these postganglionic sympathetic fibers also join with the postganglionic parasympathetic fibers from the cardiac plexus and primarily innervate the SA and AV nodes and the atrial myocardium. Suppression or blockade of this thoracic portion of the spinal cord by regional anesthesia causes bradycardia and hypotension as a result of the blockade of these sympathetic ganglia parasympathetic nervous system predominance.

The preganglionic parasympathetic fibers originate in the dorsal motor nucleus of the medulla. Short postganglionic fibers primarily innervate the SA and AV nodes and the atrial muscle fibers (see Figure 23-7). For this reason, increased parasympathetic tone decreases heart rate (HR). The function of the parasympathetic nervous system is primarily to slow the HR and secondarily to decrease contractility. In fact, maximal vagal (parasympathetic) stimulation reduces contractility by only 30%, whereas maximal sympathetic stimulation increases contractility by 100%. Acetylcholine is the neurotransmitter of the parasympathetic nervous system. Acetylcholine binds to muscarinic receptors on the heart and decreases the rate of sinus node discharge and slows conduction velocity through the AV node. The physiologic effects of parasympathetic nervous system stimulation occur because of increased permeability of cardiac muscle cell membranes to potassium, resulting in hyperpolarization. As a result, SA and AV node cells are less excitable.

Sensory innervation to the heart originates in the nerve endings in the walls of the heart, the coronary artery adventitia, and the pericardium. These nerve endings synapse with ascending fibers in the posterior gray columns of the spinal cord, where the fibers synapse with second-order neurons. From these neurons, the fibers ascend in the ventral spinothalamic tract and terminate in the posteroventral nucleus of the thalamus.

Cardiac Conduction System

Within the myocardium lies the specialized conduction system whose purpose is to automatically initiate and coordinate the cardiac rhythm. The cells of this system differ from the other myocardial cells because they are more variable in shape, contain fewer myofibrils, and have a characteristic pale staining of the cytoplasm. The conductive system consists of the following components: the sinoatrial (SA) node, the internodal tracts, the AV node, the AV bundle, and the Purkinje system (Figure 23-8).

Sinoatrial Node. The SA node (the Keith-Flack node) is a small mass of specialized cells and collagenous tissue located along the epicardial surface at the junction of the superior vena cava and the RA. It has a prominent central artery that is a branch of the right coronary artery. The SA node is derived from the junction of the right horn of the sinus venosus and the primitive atrium. The SA node consists of two cell types: P cells (pacemaker cells), which are pale and ovoid with large round nuclei, and intermediate or transitional cells, which are elongated. These transitional cells are intermediate between ovoid and ordinary cells. They conduct impulses within and away from the SA node.

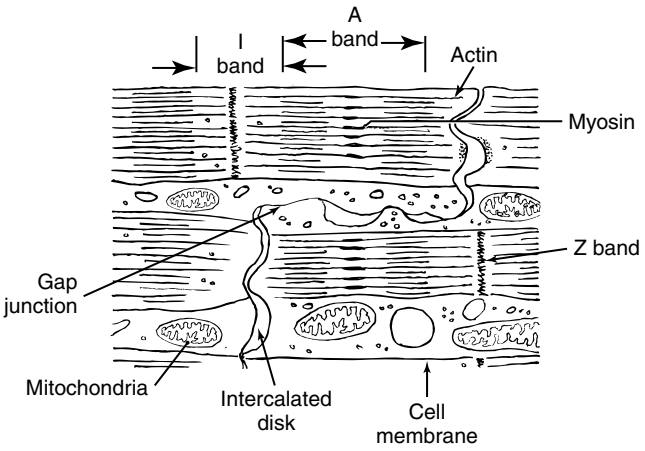

FIGURE **23-9** The myocardial sarcomere.

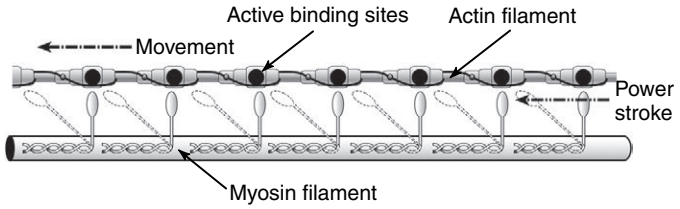

FIGURE **23-10** Interaction between actin and myosin that initiates cardiac muscle contraction.

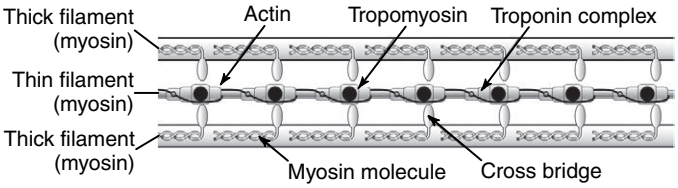

FIGURE **23-11** Arrangement of actin and myosin in cardiac muscle.

Internodal Tracts. The internodal tracts are located within the atria and are the preferential conduction pathways between the SA and the AV nodes. They are composed of a combination of closely packed parallel myocardial fibers and large pale-staining cells with a perinuclear clear zone. They have large nuclei and sparse myofibrils that resemble the Purkinje cells. Like the SA node, the internodal tracts contain P cells and transitional cells.

Three major internodal tracts exist: the anterior, middle, and posterior internodal tracts. The anterior internodal tract, or Bachmann bundle, sends fibers to the LA and then travels down through the atrial septum to the AV node. The middle internodal tract, or Wenckebach tract, curves behind the superior vena cava before descending to the AV node. Finally, the posterior internodal tract, or Thorel tract, continues along the terminal crest to enter the atrial septum and then passes to the AV node.

Atrioventricular Node. The AV node is located beneath the endocardium on the right side of the atrial septum, anterior to the opening of the coronary sinus. The AV node is supplied by an abundance of nerve endings, as well as vagal (ganglionic) cells. The AV node causes a delay in the transmission of action potentials. This delay may be attributed to several factors, such as the size of the AV nodal cells (smaller than the surrounding atrial cells), a decreased distribution of gap junctions between cells, a resting membrane potential that is *more negative* than the normal resting membrane potentials of the surrounding cells, and the paucity of gap junctions. Greater resistance to the transmission of an action potential exists within the AV node.

Atrioventricular Bundle. The AV bundle (bundle of His) extends from the lower end of the AV node and enters the posterior aspect of the ventricle and the Purkinje system. This AV bundle is the preferential channel for conduction of the action potential from the atria to the ventricles.

Purkinje System. The Purkinje system consists of the bundle branch system and its terminal branches. The left bundle branch extends outward under the endocardium and forms several fascicles, which innervate various parts of the LV. The anterior fascicle innervates the anterolateral wall of the LV and the anterior papillary muscle. The posterior fascicle innervates the lateral and posterior ventricular wall and the posterior papillary muscle. The anterior and posterior fascicles join to form the septal fascicle, which innervates the lower ventricular septum and the apical wall of the LV.

The right bundle branch travels under the endocardium along the right side of the ventricular septum to the base of the anterior papillary muscle.

Structural and Regulatory Proteins. The myocardium has characteristics of both skeletal and smooth muscle. Like smooth muscle, cardiac muscle fibers are interconnected (syncytial), which allows for an action potential to rapidly spread to adjacent cells. Because of this characteristic of cardiac muscle fibers, action potential propagation and muscle contraction occur as an "all-or-none" response.

The myocardial cell is similar to skeletal muscle in that it is composed of sarcomeres (Figure 23-9). These sarcomeres contain all the microfilaments and structures that are consistent with the skeletal muscle sarcomere. The sarcomere stretches from Z line to Z line. The A bands consist of the actin filaments, which contain a bilayer filament of F-actin and tropomyosin. Along the actin filament, many active sites exist that can attach to the head of the myosin molecule. A troponin complex is necessary to inhibit actin and myosin from interacting and initiating muscle contraction. The other microfilament in the cardiac muscle is the myosin molecule. This molecule is made up of two major parts: a light meromyosin chain and a heavy meromyosin chain. The heavy meromyosin chain consists of two hinged ends and a head that plays a role in the "ratchet theory" of muscle contraction (Figure 23-10).[1]

During sympathetic nervous system stimulation, catecholamines (primarily epinephrine and norepinephrine) are released from the central nervous system and the adrenal medulla. Increased cardiac conduction velocity, increased force of contraction, and increased heart rate are primarily mediated by beta$_1$ (β_1)-adrenergic receptors. When catecholamine hormones interact with β_1 receptors, they stimulate G protein activation. Adenyl cyclase activity increases and catalyzes the formation of cyclic adenosine monophosphate (cAMP). A specific protein kinase is formed, and phosphorylation occurs, increasing myocardial cell permeability to calcium and sodium. Threshold potential is reached, and depolarization occurs, which increases the concentration of calcium from the sarcoplasmic reticulum and the transverse tubular system. Calcium interacts with the troponin tropomyosin complex to initiate cardiac contraction. The force of myocardial contraction is dependent on the quantity of calcium present in the cardiac cell.

Evidence indicates that the troponin-tropomyosin complex inhibits the binding of the heads of the myosin filaments with the active sites on the actin molecule (Figure 23-11). During the initiation of contraction, calcium is released from the sarcoplasmic reticulum. Calcium binds to the troponin-tropomyosin complex

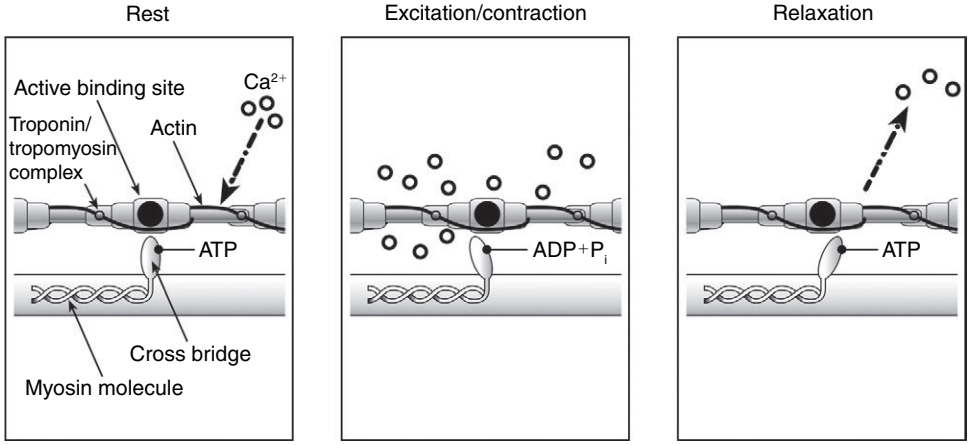

FIGURE **23-12** Phases of cardiac muscle contraction.

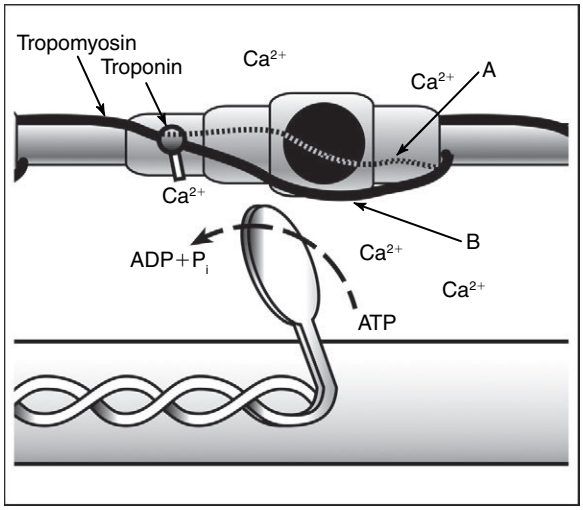

FIGURE **23-13** Letter A *(dotted line)* indicates that the troponin tropomyosin complex blocks the active binding site and inhibits contraction. Letter B *(solid line)* indicates that when calcium interacts with troponin, there is a conformational change. The troponin tropomyosin is displaced, and interaction between actin and myosin initiates muscle contraction. Note that ATP is used during the binding, the power stroke, and the unbinding process. *ADP,* Adenosine diphosphate; *ATP,* adenosine triphosphate.

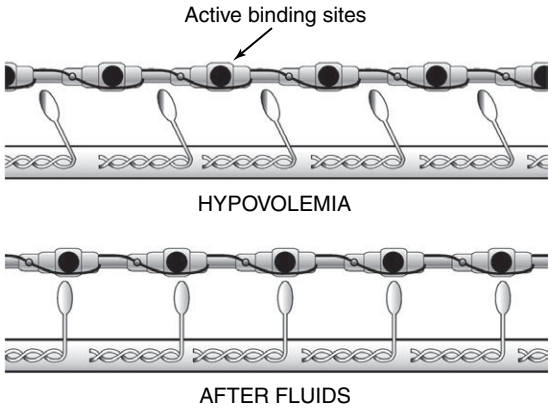

FIGURE **23-14** Greater alignment of actin binding sites and myosin cross bridges causes increased myocardial contractility.

and causes a conformational change so that the active binding sites on the actin filaments become exposed. The myosin cross bridges bind to the active filament and move along the actin filament by alternately attaching and detaching from the active sites, thereby causing shortening of the Z lines (Figure 23-12). This is known as the *sliding filament theory*. When the actin filaments and myosin cross bridges intermingle, muscle contraction occurs. Inhibition of calcium influx into the cardiac muscle cells is the proposed mechanism whereby the inhaled anesthetic agents cause depression of myocardial contractility. Cellular energy or adenosine triphosphate (ATP) is required for this process, known as *excitation-contraction coupling*, to occur, as shown (Figure 23-13). For muscle contraction to cease, calcium reuptake into the sarcoplasmic reticulum occurs as a result of active transport. The troponin-tropomyosin complex reinhibits the interaction between actin and myosin. That this process occurs constantly and within milliseconds is the primary reason for the heart's high metabolic demands (see Figure 23-13). With a limited supply of oxygen and substrate (primarily fatty acids), such as with patients with coronary artery disease or an increased energy demand caused by tachycardia from sympathetic nervous system stimulation, myocardial dysfunction and infarction can occur.

Similar length-force relationships exist within the myocardium and in skeletal muscle. The resting sarcomere length at which the muscle cell is most efficient is 2.0 to 2.4 μm. At greater lengths, the interdigitation of the actin and myosin is compromised, and at shorter lengths the sarcomere is unable to generate an efficient contraction.

Clinically this concept is demonstrated by having the ideal filling pressure of the LV necessary to achieve adequate CO. Filling pressures are used to reflect the filling volumes of the ventricles and (indirectly) the amount of stretch on the ventricular muscle at rest. Filling pressures are measured by the use of the pulmonary capillary wedge pressure (PCWP) or the pulmonary artery diastolic pressure. It has been demonstrated that at excessively high filling pressures (as in congestive heart failure) and at excessively low filling pressures (as in hypovolemia), the CO can be compromised as a result of either excessive or inadequate stretch of the left ventricular myocardium. The greater the degree of stretch of myocardial muscle fibers, the greater the number of actin filaments and myosin cross bridges that are more completely approximated. This will result in an increase in the force of cardiac contraction, as shown in Figure 23-14. This concept is the basis for the Frank-Starling law of the heart, which is discussed later in this chapter.

TABLE 23-1 Equilibrium Potential of Various Ions

Ion	Intracellular Concentration (mmol)	Extracellular Plasma Concentration (mmol)	Equilibrium Potential E_m (mV)
Na^+	10	145	60
K^+	135	4	–94
Cl^-	4	114	–97
Ca^{2+}	10^{-4}	2	132

Differences Between Skeletal and Cardiac Muscle Cells. Several differences exist between myocardial muscle cells and skeletal muscle cells (see Figure 23-9). At the junctions between the fibers in the myocardial muscle mass, many branching, interconnected fibers are intercalated disks and gap junctions, or nexi. Areas of low resistance facilitate the conduction of the action potential from one myocardial cell to another.

The myocardial sarcomeres also contain higher concentrations of mitochondria than do other types of muscle cells. The cardiac cells are aerobic and cannot tolerate oxygen deficiency. Skeletal muscles can function both aerobically and anaerobically.

The myocardial sarcomere system has a rich capillary blood supply (one capillary per fiber) that allows for efficient diffusion and perfusion. The T-tubular system and the sarcoplasmic reticulum are extensive within the cardiac sarcomere. This situation allows for the rapid release and reabsorption of calcium from the cells. It also serves to highlight the important role extracellular calcium plays in the contractile process of the myocardial cell.

Generation of Membrane Potentials

Resting Membrane Potentials. The myocardial sarcomere is not merely a contractile entity. It also possesses properties common to neural tissue, such as the generation of a resting membrane potential, the ability to generate an action potential, and the conduction of the action potential from one sarcomere to the next.

The resting cell membrane is relatively permeable to potassium and relatively impermeable to both sodium and calcium. The resting membrane potential is caused by a chemical force, an electrostatic counterforce, and the sodium-potassium active transport pump.

The chemical force relies on the potential difference in ion concentration between one side of the cell membrane and the other. The ions primarily responsible for this force are sodium, potassium, and calcium.[13] The electrostatic counterforce results from the negative potential generated by the ion difference of the interior of the cell. This force can pull ions into the cell, especially potassium.

The sodium-potassium pump requires an energy source (active transport) and involves the magnesium-dependent enzyme adenosine triphosphatase located in the cell membrane. Three molecules of sodium are pumped out of the cell into the extracellular fluid for every two molecules of potassium pumped into the intracellular fluid.

Calculation of the equilibrium potential (E_m, measured in millivolts) has been accomplished by examining the concentration of an ion inside the cell versus outside the cell (see the Nernst equation that follows). Table 23-1 lists the equilibrium potentials of the most physiologically important ions. The ion most responsible for the resting membrane potential is potassium.

$$E_m = (-RT/FZ) \times \log [K]_i / [K]_o$$

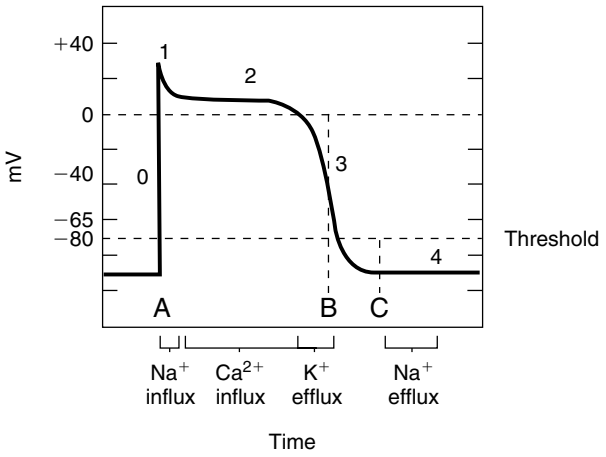

FIGURE 23-15 The ventricular muscle action potential. *A* to *B*, Absolute refractory period; *B* to *C*, relative refractory period; *0*, depolarization; *1*, overshoot; *2*, plateau; *3*, repolarization (rapid); *4*, repolarization (complete).

where R is a gas constant, T is temperature in Kelvin, F is Faraday's constant, $[K]_i$ is the intracellular concentration of potassium, and $[K]_o$ is the extracellular concentration of potassium.

If a temperature of 310° K is assumed for a living human, the Nernst equation reduces to the following in a human heart:

$$E_m = (-61.5/FZ) \times \log [K]_i / [K]_o$$

The Nernst potential is useful only in discussions of a single ion. The membrane potentials are generated because the cell membrane is permeable to several different ions. Three factors affect the calculation of the effect of these different ions on the resting membrane potential: the electric charge of each ion, the permeability of the membrane to each ion, and the concentration gradient across the membrane. The following equation, the Goldman-Hodgkin-Katz equation, is a modification of the Nernst equation that accounts for these factors.

$$EMF = 61.5 \times \log ([Na]_i P_{Na} + [K]_i P_K + [Cl]_o P_{Cl}) / ([Na]_o P_{Na}\ [K]_o P_K\ [Cl]_i P_{Cl})$$

where $[K]_i$ is the intracellular ion concentration of potassium, $[K]_o$ is the extracellular ion concentration of potassium, P_{Na} is the membrane permeability of sodium, P_{Cl} is the membrane permeability of chlorine, and P_K (when calculated) is the membrane permeability of potassium.

Ventricular Muscle Fiber Action Potential

Gate Theory. Several electrostatic gates have been elucidated for the various ions. These gates open (activated) and close (inactivated), depending on the electrical potential of the cell membrane. An electrostatic gate exists for each of the major cardiac ions (sodium, potassium, calcium, and chloride).

Phases of the Action Potential. The action potentials of the various parts of the conduction system vary according to their locations and functions.[14] The action potential of the ventricular muscle fiber is separated into five phases (Figure 23-15). Phase 0, or upstroke, is represented by depolarization and involves the fast sodium channels. The fast sodium channel activation gates (M gates) open between −70 and −65 mV (threshold potential). At 0 mV, both the activation and the inactivation gates (H gates) are open. The rapid upstroke velocity of phase 0 gives a relative

TABLE 23-2 Cardiac Action Potential

Phase	Name	Cation Movement	Effect
0	Upstroke	Na^+ ECF to ICF	Sodium channels open Potassium permeability decreased
1	Initial repolarization	K^+ ICF to ECF	Sodium channels close Potassium channels open
2	Plateau	Ca^{2+} ECF to ICF	Calcium channels open
3	Final repolarization	K^+ ICF to ECF	Calcium channels close Potassium channels open
4	Resting potential	K^+ ICF to ECF	Resting membrane permeability restored, sodium and potassium leak to ICF to increase threshold potential
		Na^+/Ca^{2+} ECF to ICF	

ECF, Extracellular fluid; *ICF*, intracellular fluid.

indication of the conductivity of the myocardial cell. Local anesthetics such as lidocaine have an inhibitory effect on phase 0 by decreasing the influx of sodium. Table 23-2 describes the phases and events of a cardiac action potential.

At *phase 1*, or early rapid repolarization (+2 to +30 mV), the sodium gates close, the rapid influx of sodium stops, and the slower influx of calcium begins. Also, potassium gates open and potassium moves out of the interior of the cell into the extracellular fluid.

One of the characteristics of the action potential unique to ventricular muscle is *phase 2*, or the plateau phase. The plateau phase exists because the slow calcium channels open at −30 to −40 mV and allow an influx of calcium. This inward calcium flux delays repolarization and prolongs the absolute refractory period. Toward the end of phase 2, a decreased permeability to potassium occurs that accounts for a small outward leakage of potassium balanced by the calcium and sodium influx that maintains a membrane potential near 0 mV. Calcium channel blockers exert their pharmacologic effect during phase 2. The physiologic effects include decreased contractility, decreased heart rate, and decreased cardiac conduction velocity.[15]

The terminal repolarization phase, *phase 3*, is initiated as the slow calcium channels become inactivated, and this phenomenon is sustained by an accelerated potassium efflux. These events return the transmembrane potential to its resting membrane value.

The sodium-potassium pump, which is dependent of ATP, reestablishes the proper intracellular-to-extracellular ionic concentrations during *phase 4* (diastolic repolarization phase). Phase 4 lasts from the completion of repolarization to the next action potential. Lidocaine lengthens the duration of phase 4 by decreasing the cardiac cell membrane's permeability to potassium ion, thereby decreasing the efflux of potassium and delaying the onset of the resting membrane potential.[15]

The cardiac glycoside digoxin inhibits the sodium-potassium ATP-dependent pump, decreasing sodium efflux into the extracellular fluid. As intracellular sodium concentrations increase, the exchange between sodium and calcium is decreased. The result is a higher concentration of calcium remains within the cardiac cell, and this effect is believed to be responsible for the increased inotropic effect.[15]

Refractory Periods. The extended duration of the action potential of the myocardial cell protects it against premature excitation. This period of quiescence is known as the *refractory period* and can be divided into absolute and relative periods. The refractory periods are a result of the properties of the sodium channels during the action potential.

The term *effective or absolute refractory period* is used to describe the time during which a conducted action potential may not be evoked, even if an active response is elicited by a stimulus at the cellular level. This period lasts from phase 0 to the middle of phase 3, when the membrane potential drops below −60 mV. The relative refractory period is the time during the action potential when a second stimulus can result only in an action potential with decreased amplitude, upstroke velocity, and conduction velocity. The relative refractory period extends from this middle part of the phase 3 range to the beginning of phase 4, when the membrane potential ranges from −60 to −90 mV. This information can be clinically related to synchronized cardioversion. The shock will not be delivered during the T wave on the electrocardiogram, which represents ventricular repolarization. The relative refractory period occurs during the T wave, and electricity delivered to the chest during this time can cause electrical disorganization in cardiac cells, resulting in ventricular tachycardia or ventricular fibrillation.

Sinoatrial Node Action Potential. The myocardium has among its characteristics contractility, automaticity, and conductivity. Each of the various myocardial masses has its own intrinsic automaticity and rate of action-potential initiation. The SA node is the primary pacemaker of the heart and has several unique characteristics (Figure 23-16). As a result of its higher resting membrane potentials, the SA node membrane is more permeable to sodium than other atrial myocardial cells. This "leakiness" gradually raises the membrane potential closer to threshold potential (−55 to −60 mV), at which point an action potential may be initiated. Therefore the action potential originating within the SA node differs from the action potential generated within the ventricular muscle mass. For this reason, the SA node is the primary pacemaker of the heart.

The SA node and the other automatic cells exhibit only phase 4, phase 0, and phase 3 of the action potential. Because rapid depolarization does not occur, phase 1 or phase 2 (plateau phase) does not occur.

If the SA node fails, the area of the heart with the next highest intrinsic rate, the AV node, replaces the SA node as the pacemaker of the heart. The intrinsic firing rate of the AV node is 40 to 60 beats per minute. If both the SA and the AV nodes fail, the ventricular cells take over and become automatic, firing at a rate of 15 to 30 beats per minute.

Physiology of the Heart

Cardiac Cycle. To understand the cardiac cycle, one must have a firm understanding of the basics of the anatomy of the heart and the pressures and volumes generated within the various chambers during the cardiac cycle. An appreciation for the valves and their positions during the phases of the cycle is essential (Figure 23-17). Additionally, notice that the electrocardiogram impulse generation precedes the mechanical action of the heart. This delay between the electrical impulse and the mechanical event occurs

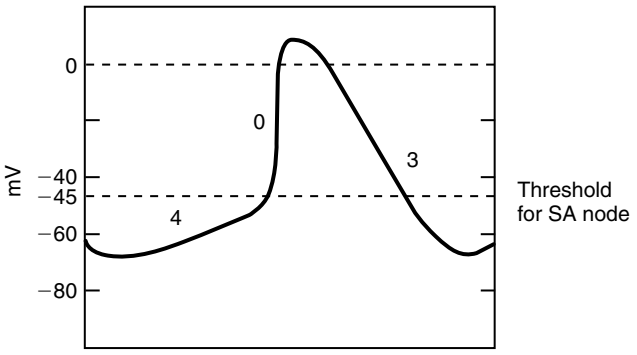

FIGURE **23-16** The sinoatrial nodal action potential.

because time is needed for the wave of depolarization to spread across the myocardium before contraction can begin. In relation to the electrocardiogram, the P wave represents atrial systole, the QRS complex signifies ventricular systole, and the T wave represents ventricular repolarization.

The cardiac cycle extends from one ventricular contraction to the next. It may be divided into two main phases—systole and diastole. Usually the cardiac cycle is described in relation to the left side of the heart. However, similar conclusions about the function of the right side of the heart may be drawn in the absence of cardiopulmonary pathology.

Diastole. During ventricular systole, the atria fill and blood returns from the venous system to the right side of the heart and from the pulmonary circulation to the left side of the heart. The first phase of diastole is the period of isovolumetric relaxation. The ventricular muscle mass relaxes, and the aortic and mitral valves are closed as long as the ventricular pressure remains higher than the atrial pressure. The true filling phase is divided into three periods: (1) rapid inflow, or diastasis, (2) reduced inflow, and (3) atrial systole. Once the ventricular pressure drops below atrial pressure, the mitral valve opens, and the period of rapid inflow to passively fill the ventricle begins. The second period of diastole is diastasis, in which minimal changes occur in volume and in pressure.

Atrial systole provides another period of rapid filling that is commonly referred to as the *atrial kick*. This phenomenon increases ventricular filling by 20% to 30%. In patients who have severe mitral stenosis, the atrial kick may be responsible for up to 40% of the ventricular filling. During periods of strenuous exercise or in patients with many pathologic conditions such as shock or congestive heart failure, the additional ventricular filling is critical to maintaining CO.

Systole. After atrial systole, the isovolumetric phase, or isovolumetric contraction, which is the phase at the beginning of ventricular contraction, occurs. The myocardial fibers shorten, and pressure is generated within the ventricle but only enough to close the mitral valve. Therefore during this period, an increase in left ventricular pressure occurs without a change in ventricular diastolic volume. Isovolumetric contraction begins with closure of the mitral valve and lasts until opening of the mitral valve.

Systolic ejection begins with the opening of the aortic valve and occurs when the ventricular pressure exceeds the aortic pressure. This phase of the cardiac cycle is divided into two periods, with the period of rapid ejection taking the first third of systole and the period of reduced ejection taking the last two thirds of systole. During rapid ejection, ventricular systolic pressures reach their maximum, and the largest amount of volume is ejected. Therefore systole is composed of isovolumetric contraction, rapid ejection, and reduced ejection. The dicrotic notch or incisura on the

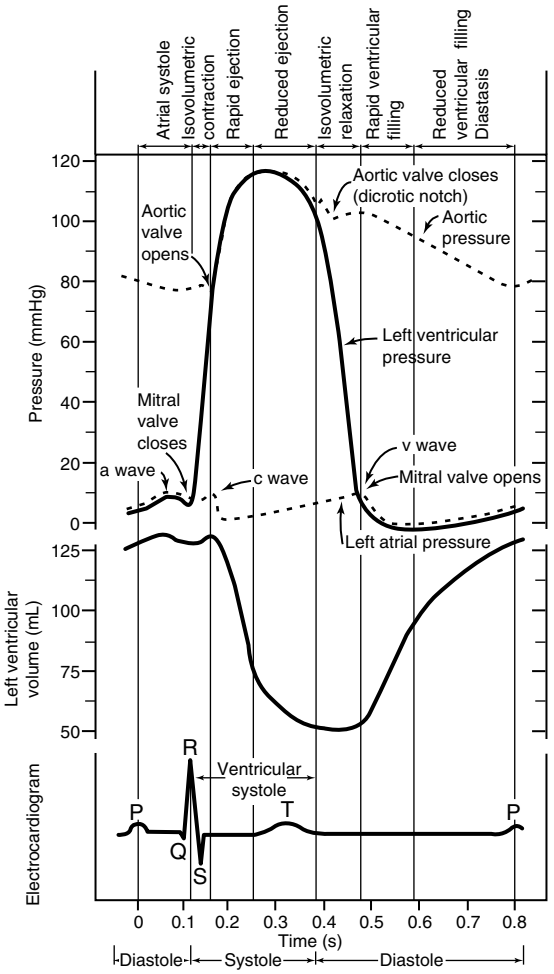

FIGURE **23-17** The cardiac cycle.

arterial pressure tracing occurs within the period of isovolumetric relaxation. This segment represents retrograde blood flow back into the LV before aortic valve closure. Three waveform segments are present on the left atrial pressure tracing: the *a* wave, *c* wave, and *v* wave. The specific waveforms correspond to their position within the cardiac cycle. The *a* wave represents atrial systole as it ends just before mitral valve closure. The *c* wave represents ventricular contraction and is produced by bulging of the mitral valve caused by increasing left ventricular pressure. The *v* wave represents increased pressure in the LA caused by blood return from the pulmonary artery before mitral valve opening.

Physiology of Coronary Circulation. The anatomy of the coronary circulation has already been discussed. A description of the physiologic determinants of coronary blood flow follows.

Coronary Blood Flow. The rate of blood flow is determined by a change in the pressure within the vessel divided by resistance of the system. Alterations of the radius of a vessel change the flow to the fourth power of the radius. This phenomenon is an extension of Poiseuille's law, which determines the flow of a fluid through a tube.

At rest, approximately 4% to 5% of the CO, or 225 mL/min of blood, passes through the coronary vasculature. Phasic changes have been documented during coronary blood flow. A greater amount of coronary flow in the LV occurs during diastole. During systole, left coronary artery blood flow ceases to the subendocardium due to compression of the subendocardial vessels by the myocardium; flow through the epicardial vessels is not affected

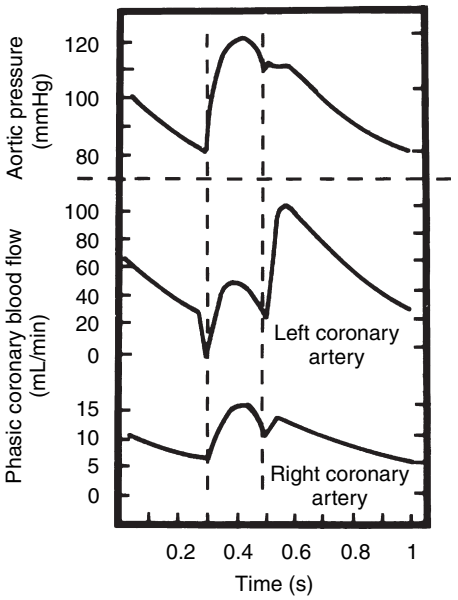

FIGURE **23-18** Blood flow in the left and right coronary arteries. The right ventricle is perfused throughout the cardiac cycle. Flow to the left ventricle is largely confined to diastole. (From O'Brien ER, Nathan HJ. Coronary physiology and atherosclerosis. In: Kaplan JA, Reich DL, Savino JS, eds. *Kaplan's Cardiac Anesthesia: The Echo Era*. 6th ed. Philadelphia: Saunders; 2011.)

during systole to this extent. The flow to the left coronary artery is greatest during diastole as a result of the decreased resistance to flow from decreased myofibril tension that occurs as the intracavitary pressure decreases (Figure 23-18).

Control of Coronary Circulation and Oxygen Supply and Demand. Coronary blood flow is regulated by intrinsic and extrinsic factors that affect coronary artery tone. Intrinsic factors include the anatomic arrangement and perfusion pressure of the coronary vessels. Extrinsic factors include compressive factors within the myocardium, as well as metabolic, neural, and humoral factors. Blood flow through the coronary circulation is primarily controlled by the factors that determine oxygen demand and oxygen supply. Myocardial oxygen supply is determined by arterial blood content, diastolic blood pressure, diastolic time as determined by HR, oxygen extraction, and coronary blood flow. Myocardial oxygen demand is determined by preload, afterload, contractility, and HR (Figure 23-19).

The factors that increase myocardial oxygen consumption ($M\dot{V}O_2$) are listed in Table 23-3. Notice in Figure 23-19 that heart rate appears on both the supply (diastolic time) side and demand side of the balance. Increasing heart rate not only increases demand but also decreases diastolic time, which is when 80% to 90% of coronary filling and myocardial perfusion occurs. Increased heart rate is the most important factor that negatively affects $M\dot{V}O_2$. Doubling the heart rate doubles $M\dot{V}O_2$.[16] This phenomenon most dramatically affects patients with coronary artery disease, because the supply of blood is compromised and may not be able to meet the oxygen demands caused by tachycardia. As a result, myocardial dysfunction or infarction can occur. By slowing HR and decreasing contractility, β-blocking medications increase supply and decrease demand, protecting the heart from ischemia.[17]

Because at rest the myocardium extracts 65% to 70% of the available oxygen, the only way to increase oxygen delivery to the myocardium is by increasing blood flow. During periods of increased myocardial oxygen demands, flow through the coronary

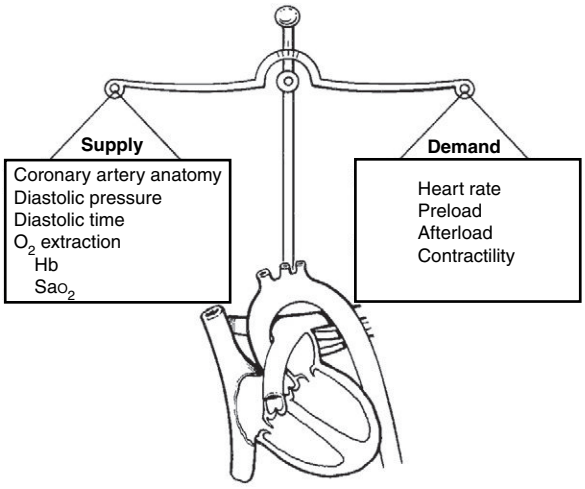

FIGURE **23-19** The heart's oxygen supply and demand must be balanced by the anesthetist, who should increase the former and reduce the latter. *Hgb*, Hemoglobin; *Sao_2*, arterial oxygen saturation.

TABLE 23-3 Components and Effects on Myocardial Oxygen Consumption

A 50% Increase in	Resultant Increase in $M\dot{V}O_2$
Heart rate	50%
Pressure work	50%
Contractility	45%
Wall stress	25%
Volume work	4%

$M\dot{V}O_2$, Myocardial oxygen consumption.

arteries can increase by three to four times. Several vasodilator substances have been identified and are released from the myocardium in response to decreased oxygen delivery or concentration. Among these substances are adenosine, adenosine phosphate compounds, potassium ions, hydrogen ions, carbon dioxide, bradykinin, and prostaglandin. Experts believe that adenosine is the primary substance responsible for coronary vasodilation.

The normal physiologic parameters of the heart are given in Table 23-4. The determinants of $M\dot{V}O_2$ include myocardial contractility, myocardial wall tension (preload), HR, and mean arterial pressure (MAP; afterload). Oxygen extraction is determined by measurement of the difference between the oxygen tension in the pulmonary arterial blood and that in the coronary sinus.

Oxygen supply relies on the blood oxygen content (see following equation), which is affected by both the oxygen carried on the hemoglobin (Hgb) molecule (1.34 mL of oxygen per gram of Hgb) and to a lesser extent the oxygen dissolved in the plasma (0.003 mL of oxygen per milliliter of plasma).

$$O_2 \text{ content (mL } O_2 \text{/ mL plasma)} = (PaO_2 \times 0.003) + (\text{Hgb content} \times \text{Hgb} - O_2 \text{ saturation } \%)$$

Other factors that have an influence on coronary circulation include the direct and indirect effects of the sympathetic nervous system and the effect of certain substrates of cardiac metabolism.

Autoregulation. Under normal physiologic conditions, the coronary circulation, like other tissue beds in the body, exhibits *autoregulation*, which is the ability to maintain coronary blood flow through a range of MAPs by dilating or constricting. Coronary

TABLE 23-4 Normal Physiologic Parameters

Heart size	230-280 g (female) 280-340 g (male)
Coronary blood flow	225-250 mL/min or 4%-7% total cardiac output
Myocardial O_2 consumption	65%-70% extraction 8-10 mL O_2/100 g/min
Normal autoregulation	60-140 mmHg (MAP)
Coronary filling	80%-90% during diastole

MAP, Mean arterial pressure.

blood flow is maintained at a constant rate through a MAP range of 60 to 140 mmHg. When arterial blood pressure is less than or exceeds these pressure limits, coronary blood flow becomes pressure dependent. Therefore during hypotension, when the coronary arteries are maximally dilated, coronary blood flow is determined by the MAP minus the right atrial pressure.

A method for directly estimating coronary perfusion pressure (CPP) can be calculated by subtracting left ventricular end-diastolic pressure (LVEDP) from diastolic blood pressure (DBP)—that is, CPP = DBP − LVEDP. Because under normal conditions LVEDP (10 mmHg) is significantly less than DBP (80 mmHg), the major determinant of CPP is DBP.

Coronary vascular reserve is the difference between the maximal flow and the autoregulated flow. The closer these two values, the lower the coronary reserve of the patient. Factors that increase myocardial oxygen demand and limit supply decrease coronary reserve flow and can result in myocardial dysfunction.

The concept of "coronary steal" has emerged, especially in reference to the use of agents such as adenosine, nitroglycerin, and isoflurane. If vasodilator treatment is used in a patient who has both an ischemic area of the heart that is supplying a stenotic vessel with collateral flow and another area that has an intact autoregulated vessel, only the autoregulated vessel dilates further and has the ability to increase its flow. Constant maximal coronary artery dilation exists in an area where stenosis is present. Therefore only the areas of the heart with intact autoregulation respond to vasodilators and receive preferential flow over the stenotic area. The existence of this phenomenon is questionable. As long as adequate CPP is maintained, coronary steal and myocardial ischemia caused by isoflurane do not occur.[18,19] A second factor that could result in this phenomenon is coronary steal–prone anatomy. This has been defined as complete occlusion of one coronary artery and at least 50% occlusion of a second coronary artery that supplies collateral blood flow to the area in which the complete occlusion exists.[18] In addition, recent evidence suggests that the inhaled anesthetics isoflurane, desflurane, and sevoflurane produce myocardial protection during periods of ischemia in humans by decreasing the formation of free radicals, preserving myocardial ATP stores, and inhibiting increased intracellular calcium.[19,20] This is referred to as *anesthetic preconditioning*.

Cardiac Output. Cardiac output is the amount of blood ejected from the LV during 1 minute. Comparing various CO values among several patients requires a method for calculating output in relation to the size of the patient. The CO is measured in liters per minute. Cardiac output is indexed, because a CO of 3.5 L/min may be adequate for a patient who is 5 feet tall and weighs 95 lb, but it is less than optimal for a patient who is 6 feet 7 inches tall and weighs 300 lb. The average CO is 5 L/min, and the average cardiac index (CI) is 2.5 L/min or more per square meter of body surface area (BSA). The formula for this relationship is CI = CO/BSA.

The primary determinants of CO are stroke volume (SV) and HR. CO is derived by using the equation CO = HR × SV. The SV is the amount of blood ejected from the LV with each beat. The average SV is approximately 70 mL. If the average HR is 70 to 80 beats per minute, a CO of 5 L/min results.

Several key factors affect SV, including preload, afterload, and myocardial contractility. Preload is the effective tension of the blood on the ventricle or the wall tension at the end of diastole. Preload can either be passive (the flow of blood from the atria to the ventricles during diastole) or active (the volume contributed by the atrial kick). With increased preload, there is an associated increase in contractility. This phenomenon is known as the *Frank-Starling law* of the heart, which states that the greater the wall tension (preload), the greater the compensatory increase in myocardial contractility. This mechanism allows the heart to immediately compensate for increased preload and avoid overdistention of the cardiac chambers by increasing SV, which facilitates chamber emptying. However, there is a point at which progressive increases in preload no longer increase contractility but can contribute to decreased myocardial performance. Increased preload increases myocardial oxygen demand. Clinically, preload can be estimated by using the PCWP and the pulmonary artery diastolic pressure. In patients with normal mitral valve and ventricular muscle function, either of these measures provides an estimate of the preload or LVEDP and volume.

Cardiac output can be determined indirectly by applying the Fick principle (see the following equation). Assuming normal respiratory function, CO is equal to the amount of oxygen absorbed by the lungs divided by the arteriovenous oxygen difference.

$$\text{CO (L/min)} = \frac{\text{Oxygen absorbed per minute by the lungs (mL/min)}}{\text{Arteriovenous oxygen difference (mL of blood)}}$$

Right-sided heart pressures (central venous pressure) that are obtained clinically can be estimates of left ventricular volumes in patients with good left ventricular function.[21]

Afterload is the wall tension the myocardium needs to overcome to eject the SV. It is the pressure within the LV during peak systole. Factors affecting LV afterload include the state of the ventricular chamber and the compliance of the arterial vasculature. The shape, size, and wall thickness of the ventricle play an important role in afterload. The vascular component of the afterload includes SVR and MAP because these variables relate to the vascular compliance of the aorta. Thus increases in blood pressure increase afterload.

Afterload is most often estimated clinically by determining the SVR. The SVR may be calculated once the CO and the difference between the MAP and the central venous pressure (CVP) are known (see the following equation). The normal SVR is 800 to 1500 dyn.s/cm^5.

$$\text{SVR} = (\text{MAP} \times \text{CVP}) / \text{CO} \times 80$$

The problem with equating afterload with SVR is that ventricular wall tension, which is an integral part of the afterload, is not considered.

Contractility of the myocardium is the state of inotropy that is independent of either preload or afterload. It may be altered by many cardiovascular disease states. Factors such as rate of pressure changes over time (dP/dt [first derivative of pressure measured over time]), force-velocity or Starling ventricular function curves, pressure-volume loops, ejection fraction (EF), and velocity

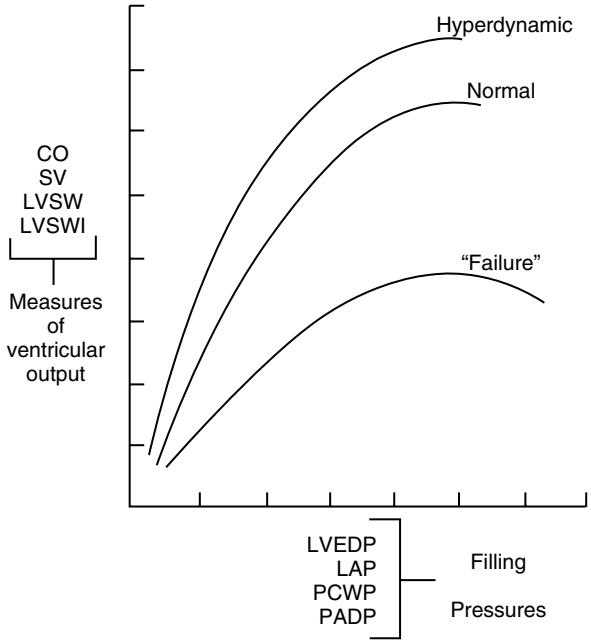

FIGURE **23-20** The ventricular function curve. *CO*, Cardiac output; *LAP*, left atrial pressure; *LVEDP*, left ventricular end-diastolic pressure; *LVSW*, left ventricular stroke work; *LVSWI*, left ventricular stroke work index; *PADP*, pulmonary artery diastolic pressure; *PCWP*, pulmonary capillary wedge pressure; *SV*, stroke volume.

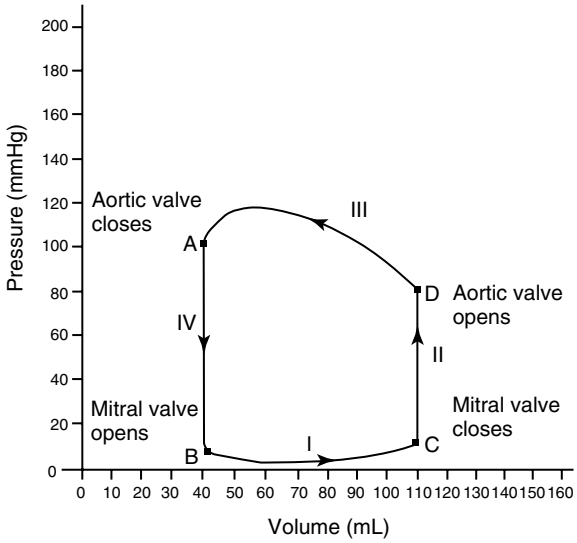

FIGURE **23-21** Phases of the left ventricular (LV) pressure-volume loop, which is a continuous cycle divided into four phases. Phase I represents diastolic filling. Left ventricular filling begins at point *B* and ends at point C. Note the increase in volume of 70 mL and the upward movement of the curve at point C, representing a slightly increased pressure in response to the increased volume. Point C or mitral valve closure represents end-diastolic volume (EDV). Phase II represents isovolumetric contraction. Note there is a significant increase in pressure but no change in volume. Cardiac muscle fibers are shortening and increasing the pressure on the LV volume until point *D*, where the LV pressure exceeds aortic pressure. Phase III represents systolic ejection. Note the decrease in LV volume throughout LV systolic ejection. Phase IV represents isovolumetric relaxation. At point *A* the aortic pressure exceeds LV pressure, and the aortic valve closes. Point A represents end-systolic volume (ESV). The LV relaxes, and the pressure decreases significantly. At maximal LV relaxation, the mitral valve opens and the process starts again.

of circumferential fiber shortening have all been used to estimate contractility.

Left ventricular dP/dt measurements require a high-fidelity recording system, and for this reason these measures are not readily available in the clinical setting. A wide range of normal values exists (800 to 1700 mmHg/sec), making patient-to-patient comparisons difficult. Assessment of the acute change in contractility of a single patient over time is still the common method of using this measurement.

Ventricular function curves[22] (Figure 23-20), define the relationship between the left ventricular filling pressure (left ventricular diastolic pressure, left atrial pressure, PCWP) and the left ventricular stroke work index (LVSWI), which is calculated by use of the following equation:

$$\text{LVSWI (in g/m}^2\text{ per beat)} = 0.0136 \times \text{SVI} \times (\text{MAP} - \text{PCWP})$$

where SVI = CI/HR.

Each left ventricular function curve has a steep upstroke that has a plateau at higher filling pressures. To apply the Frank-Starling mechanism to Figure 23-20, notice in the "normal" and "hyperdynamic" curves that as pressure (horizontal axis) increases, so does LV output (vertical axis). However, at the top of these curves, there is a plateau where increasing the filling pressures no longer increases performance and can then decrease ventricular output. Symptoms may be elicited by either high or low filling pressures. On the "failure" curve, with compromised cardiac function, increases in filling pressures do not dramatically increase myocardial performance and can lead to cardiogenic shock. The clinical determination of LVSWI is worthwhile because it contains many of the factors that contribute to CO, and it gives measures of both systolic and diastolic performance.

Left ventricular pressure-volume loops have been mentioned before as conceptual models depicting phases of the cardiac cycle. They may also be used as tools to determine myocardial performance. Left ventricular pressure-volume loops simultaneously measure chamber pressures and the resultant volumes (Figure 23-21). Movement from left to right on the horizontal axis represents increased volume. Movement from right to left on the horizontal axis represents decreased volume. Movement up and down on the vertical axis represents increases and decreases in pressure, respectively. The distinct phases of the left ventricular pressure-volume loop are represented in Figure 23-22.

The interior of the curve (distance between the two vertical lines of the LV pressure-volume loop) is representative of SV. In this diagram, SV is calculated by subtracting end-systolic volume (ESV) from end-diastolic volume (EDV), or EDV (110 mL) − ESV (40 mL). Thus in this example, stroke volume is 70 mL. Ejection fraction (EF) can then be estimated using the following equations:

$$\text{EF} = (\text{EDV} \times \text{ESV}) / \text{EDV} \times 100$$

or

$$\text{EF} = (\text{SV} / \text{EDV}) \times 100$$

The EF is the percentage of the end-diastolic volume ejected during systole, as seen in Figure 23-23. The normal EF is 60% to 70%. An EF of less than 40% is associated with significant left ventricular impairment.

Deviations from the normal left ventricular pressure-volume loops occur as a result of many causes. Factors that alter the normal loop include increases and decreases in LV preload, LV afterload, and LV contractility. These factors can be acute and transient, such as during the administration of vasoactive medications, or

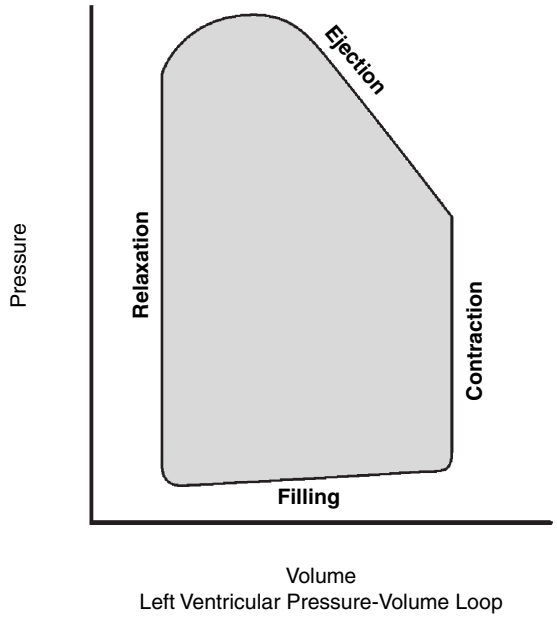

FIGURE **23-22** Phases of the cardiac cycle represented by a left ventricular pressure-volume loop.

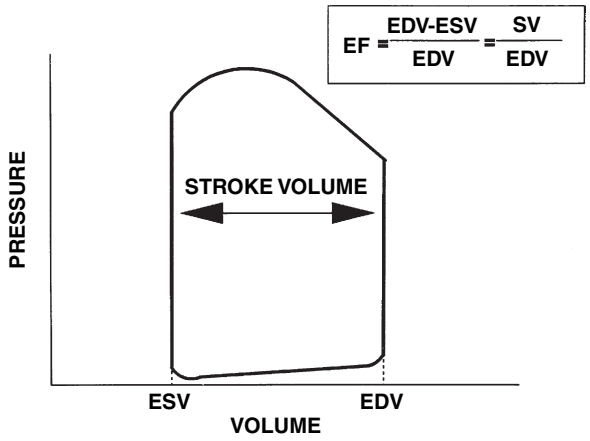

FIGURE **23-23** Pressure-volume diagram indicating end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume (SV), and the equation for ejection fraction (EF). (From Johnson B, et al. Cardiac physiology. In: Kaplan JA, Reich DL, Savino JS, eds. *Kaplan's Cardiac Anesthesia: The Echo Era.* 5th ed. Philadelphia: Saunders; 2006:73.)

chronic as a result of myocardial compensation caused by valvular heart disease. In Figure 23-24, these changes are consistent with valvular heart disease. Because many factors contribute to variations in pressure and volume from beat to beat within the LV, each pressure volume loop is distinct, represents one LV systolic ejection, and is different for each contraction. A discussion of these pathologic curves is presented later in this chapter.

A clinically useful tool is two-dimensional transesophageal echocardiography (TEE). When this technology is appropriately used, real-time movement of all four chambers of the heart, as well as that of the valves, may be visualized.

TEE can be used to detect valvular function and blood flows in both regurgitant and stenotic lesions. It is also useful in determining areas of hypokinesis, dyskinesis, or akinesis caused by myocardial infarction, ischemia, or injury. It can be useful in determining myocardial contractility, and it is a more direct measure of intraventricular volume status than pulmonary artery catheter

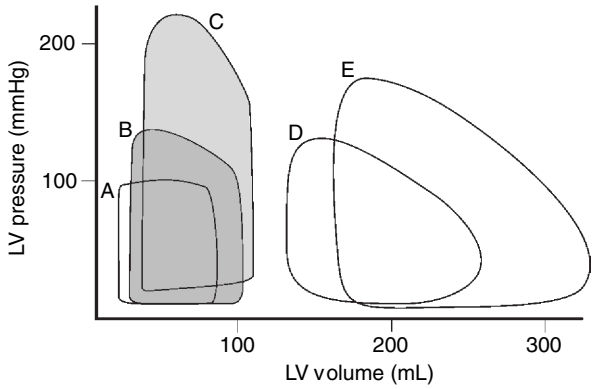

FIGURE **23-24** Pathologic left ventricular pressure-volume loops. *A*, Mitral stenosis; *B*, normal curve; *C*, aortic stenosis; *D*, mitral regurgitation; *E*, aortic regurgitation.

pressure measures. TEE has also proven useful in directing fluid and pharmacologic therapy in patients who have undergone coronary bypass and other surgical procedures. Ventricular dysfunction or reperfusion injury, as well as the presence of intraventricular air, can be determined with TEE. This diagnostic tool is the gold standard for assessing intraoperative myocardial performance. The practical problems associated with the clinical use of TEE entail acquiring the skills necessary for accurate interpretation of the visual data, the possibility of esophageal rupture, and the cost associated with its use.

Cardiovascular Reflexes

Cardiac Output Regulation. A direct interplay exists between CO and venous return. As long as neither the contractility nor the HR is compromised, maintenance of a constant return of blood flow to the heart ensures an adequate CO. The body's regulation of CO depends on its ability to regulate HR and contractility of the myocardium, as well as constriction and distention of the vascular tree.

Many of the factors that affect CO also affect the MAP and are addressed in the section on regulation of MAP. Some of the more common reflexes that can alter the CO are described in this section or in the section on regulation of MAP.

Valsalva Maneuver. The Valsalva maneuver occurs as a result of forced expiration against a closed glottis. The reflex is mediated through the baroreceptors located near the bifurcation of the internal and external carotid arteries (carotid sinus) and the aortic arch. The afferent pathway is directed via Hering's nerve and either the glossopharyngeal nerve (carotid sinus) or the vagus nerve (aortic arch), as shown in Figure 23-25. Stimulation of either of these areas inhibits the vasomotor center in the medulla. The response inhibits the sympathetic nervous system and stimulates the parasympathetic nervous system, producing a decrease in HR, a decrease in myocardial contractility, and vasodilation, resulting in a decrease in blood pressure. The Valsalva maneuver also increases intrathoracic pressure, which decreases venous return and thereby decreases CO.

Baroreceptor Reflex. The baroreceptors respond to fluctuations in arterial blood pressure. Afferent and efferent impulse transmission travels along the same pathway as the Valsalva maneuver. Decreases in arterial blood pressure are sensed by the baroreceptors, increasing sympathetic tone, which results in increased myocardial performance and vasoconstriction. Acute hypertension causes the opposite cardiovascular response. A more in-depth explanation of the baroreceptor response and its role

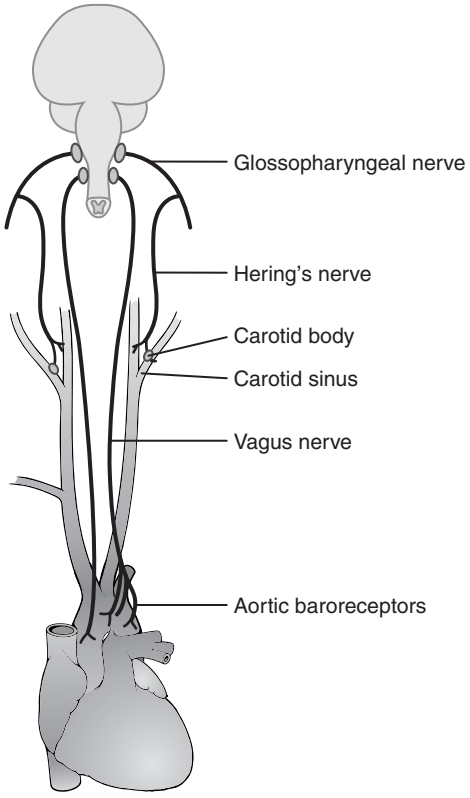

FIGURE **23-25** Afferent and efferent neural pathways from carotid and aortic baroreceptors. (From Hall JE. *Guyton and Hall Textbook of Medical Physiology.* 12th ed. Philadelphia: Saunders; 2011:206.)

in short- and long-term blood pressure control is presented later in this chapter. The baroreceptor response is inhibited by volatile anesthetic agents in a dose-dependent manner and results in decreased ability of the baroreceptors to respond to blood pressure changes when these agents are used.

Oculocardiac Reflex. Traction on the extraocular muscles (especially the medial rectus), conjunctiva, or orbital structures causes hypotension and a reflex slowing of the HR, as well as arrhythmias. The oculocardiac reflex may also be elicited during retrobulbar block, ocular trauma, or pressure on the tissue that remains after enucleation. The afferent path of the reflex is mediated by the long and short ciliary nerves to the ciliary ganglion of the oculomotor nerve and then the ophthalmic division of the trigeminal nerve (cranial nerve V) to the gasserian ganglion. The efferent branch of the reflex is mediated by the vagus nerve (cranial nerve X). This reflex may be blunted by the use of retrobulbar block or the release of the offending stimulus. The resulting vagal response to the heart can be inhibited by an anticholinergic agent (atropine or glycopyrrolate).

Celiac Reflex. The celiac reflex is elicited by traction on the mesentery or the gallbladder or stimulation of the vagus nerve in other areas of the body, such as the thorax and abdominal cavity. Stimulation of this reflex causes bradycardia, apnea, and hypotension. Clinically, the celiac reflex can be initiated indirectly as a result of a pneumoperitoneum. As with the oculocardiac reflex, the celiac reflex is frequently resolved by stopping the initiating stimulus.

Bainbridge Reflex (Atrial Stretch Reflex). The Bainbridge reflex is elicited as a result of an increased volume of blood in the heart, which causes sympathetic nervous system stimulation. Stretch receptors are located in the right atrium, junction of the vena cava, and pulmonary veins. The sinoatrial node is also involved in this process and can increase heart rate by 10% to 15%. This reflex helps to prevent sequestration of blood in veins, atria, and pulmonary circulation. Antidiuretic hormone secretion from the posterior pituitary gland is decreased, resulting in decreased circulating blood volume. Atrial natriuretic peptide is increased, which also promotes diuresis.

Cushing Reflex. This physiologic response to central nervous system (CNS) ischemia caused by increased intracranial pressure is called the *Cushing reflex*. It is triggered as a result of an elevation of intracranial pressure to a value greater than the MAP, thereby decreasing cerebral perfusion and cerebral-causing ischemia. An intense sympathetic nervous system response is initiated by the vasomotor center, resulting in intense vasoconstriction. These compensatory physiologic changes attempt to restore adequate cerebral perfusion. However, if cerebral ischemia is not relieved, cerebral infarction results. When the vasomotor area becomes ischemic as a result of hypotension (MAP less than 50 mmHg), maximal stimulation of the vasomotor center occurs. The Cushing's triad is a late sign of high and sustained intracranial pressure prior to cerebral herniation. The signs include hypertension, bradycardia, and respiratory irregularity.

Chemoreceptor Reflex. The central chemoreceptors are located beneath the ventral surface of the medulla and are directly stimulated primarily by increased hydrogen ion concentrations. The peripheral chemoreceptors are located at the bifurcation of the internal and external carotid arteries (carotid body) and within the aortic arch (aortic body) and are primarily stimulated by decreased arterial oxygen concentration. The response elicited from hypoxia, hypercarbia, and acidosis is increased minute ventilation and increased sympathetic nervous system stimulation, resulting in increased blood pressure. Like the baroreceptor reflex, the chemoreceptor response is inhibited by the volatile anesthetic agents in a dose-dependent manner. Thus if residual volatile agent is present during the emergence from anesthesia, the threshold for breathing will be increased, necessitating a higher $Paco_2$ prior to spontaneous respirations. Table 23-5 provides a summary of the cardiovascular reflexes.

VASCULAR SYSTEM

Anatomy

Vascular Anatomy

The vascular circulation is divided into the pulmonary circulation and the peripheral systemic circulation (Figure 23-26). This vascular system is composed of several functional parts.

Arteries

Arteries transport blood to the tissues under high pressure. Arteries have an average diameter of 4 mm and a wall thickness of 1 mm. They have a thick layer of elastic tissue, smooth muscle, and fibrous tissue. Arteries are able to maintain the flow of blood because of their large internal diameter.

Arterioles

Arterioles are the last small branches of the arterial system, and they act as control valves for the release of blood into the capillary beds. Arterioles have an average diameter of 30 μm and a wall thickness of 20 μm. Like arteries, arterioles have a thick layer of elastic tissue, smooth muscle, and fibrous tissue. Constriction of the arterioles, compared with that of other structures within the vascular system, causes the greatest increase in SVR. Because of this contribution, arterioles exhibit the greatest pressure drop in the vascular system across the length of their vessels.

TABLE 23-5 Cardiac Reflexes

Reflex	Stimulus	Response
Baroreceptor reflex	Hypertension resulting in baroreceptor stimulation; carotid baroreceptors send afferent response via Hering and glossopharyngeal nerves (CN IX); aortic baroreceptors send afferent response via the vagus nerve (CN X)*	Decreased heart rate, decreased contractility, peripheral vasodilation from efferent response via the vagus nerve (CN X)
Valsalva maneuver	Forced expiration against a closed glottis mediated via baroreceptors; see baroreceptor reflex for neural pathways	Decreased heart rate, decreased contractility, peripheral vasodilation from efferent response via the vagus nerve (CN X)
Cushing reflex	Increased intracranial pressure resulting in cerebral ischemia	Sympathetic nervous stimulation resulting in increased blood pressure
Chemoreceptor reflex	Decreased oxygen saturation, increased carbon dioxide, increased hydrogen ion concentration; peripheral chemoreceptors located in the carotid body and aortic arch; see baroreceptor reflex for neural pathways	Increased respiratory drive, increased blood pressure
Atrial stretch reflex (Bainbridge reflex)	Hypervolemia, increased venous return causes stimulation of atrial stretch receptors	Increased heart rate, decreased blood pressure, decreased systemic vascular resistance, diuresis
Oculocardiac reflex	Traction on the extraocular muscles (especially medial rectus) or pressure on the globe causes an afferent response via the trigeminal nerve (CN V) and results in an efferent vagal response via the vagus nerve (CN X)	Bradycardia, hypotension, and arrhythmias
Celiac reflex	Traction or pressure on structures within abdominal and thoracic cavities causes vagal nerve stimulation	Bradycardia, hypotension, and apnea

*Efferent response increases parasympathetic tone via the vagus and sympathetic nerves.
CN, Cranial nerve.

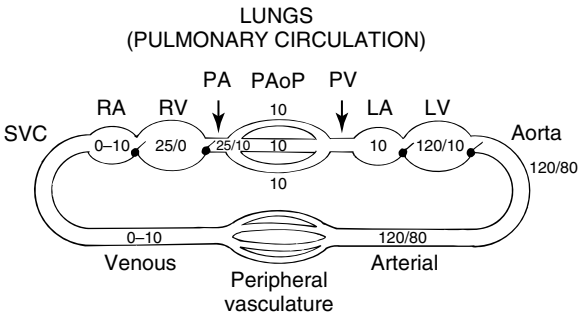

FIGURE 23-26 The vascular circuit. *LA,* Left atrium; *LV,* left ventricle; *PA*, pulmonary artery; *PAOP*, pulmonary artery occlusion pressure; *RA*, right atrium; *RV*, right ventricle; *SVC*, superior vena cava.

Capillaries

The exchange of fluids, nutrients, electrolytes, hormones, and other substances occurs between the blood and the interstitial fluids in the capillaries. Capillaries have an average diameter of 8 μm and a wall thickness of 1 μm. The walls of capillaries are only one cell thick and have no elastic tissue, smooth muscle, or fibrous tissue. The capillary cell membrane is semipermeable to water and other small molecules.

Venules

Venules collect blood from capillaries and gradually coalesce into progressively larger veins. Venules have an average diameter of 20 μm and a wall thickness of approximately 0.5 mm. They do not have an elastic or smooth muscle layer but have a thin fibrous layer.

Veins

Veins act as conduits for the transport of blood back to the heart. They also act as a large reservoir because they are very distensible. They have an average diameter of 30 mm and a wall thickness of 1.5 mm. The venous system contains approximately 60% of the blood volume, as opposed to the 20% contained within the arteries (Figure 23-27). The elastic tissue and the fibrous tissue layers are similar in size to those of the arterioles, but the smooth muscle layer in the veins is smaller than that in the other large vessels.

Arterial Circulation

Knowledge of the anatomy of the arterial circulation is an important part of anesthesia practice. Such information is essential for obtaining intraarterial access, assessing HR and pulse quality, understanding the anatomic relationships for the purpose of regional blocks, and understanding the physiologic implications of blood flow in shock states.

Microscopic Anatomy of the Arterial Circulation. Arteries are classically divided into two types: conducting, or elastic, arteries and distributing, or muscular, arteries. Conducting arteries include the major arteries, such as the aorta, and their major branches, such as the brachial, radial, and ulnar arteries. The walls of the arteries are thicker than the walls of veins and consist of three major layers: the tunica intima, the tunica media, and the tunica adventitia.

Thoracic Aorta. The thoracic aorta is divided into three sections: the ascending aorta is the portion that leaves the LV; the transverse aorta, or arch, is the portion that levels off; and the descending aorta is the portion that descends into the thorax. After the thoracic aorta penetrates the diaphragm, the vessel is called the *abdominal aorta* (Figure 23-28).

The first branches of the ascending aorta are the right and left coronary arteries. From this point, three major branches of the thoracic aorta exist: the brachiocephalic (innominate) artery, the left common carotid artery, and the left subclavian artery.

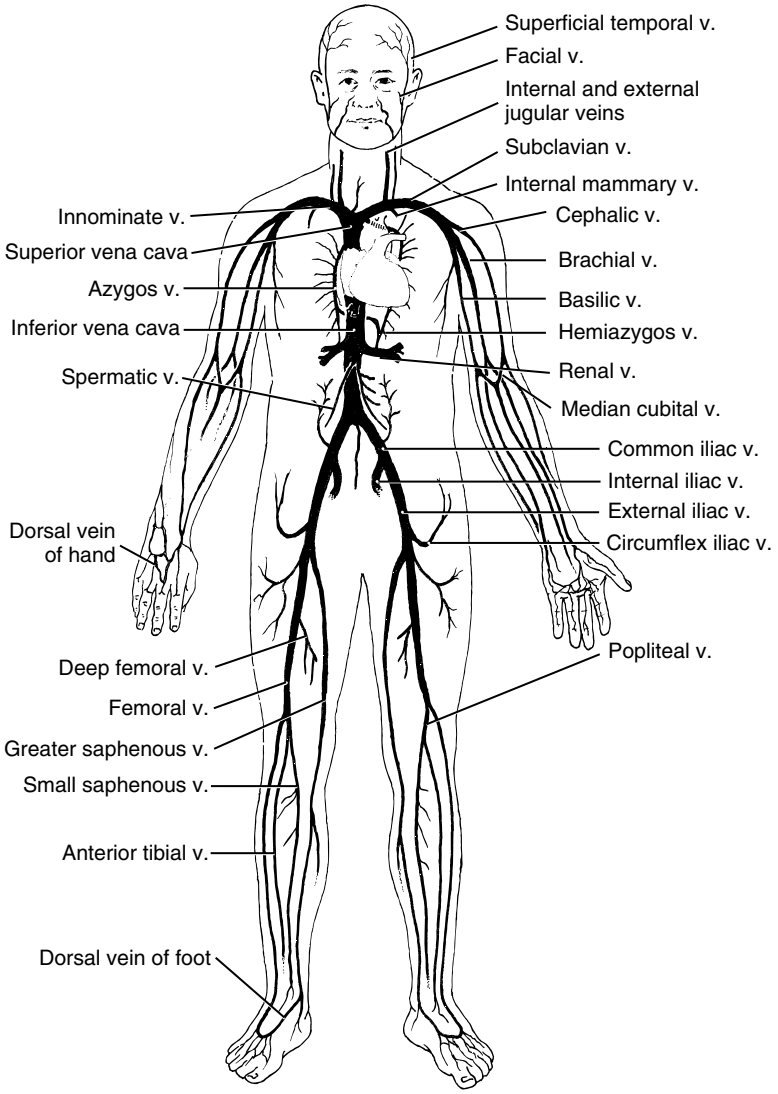

FIGURE **23-27** The venous system. *v.*, Vein.

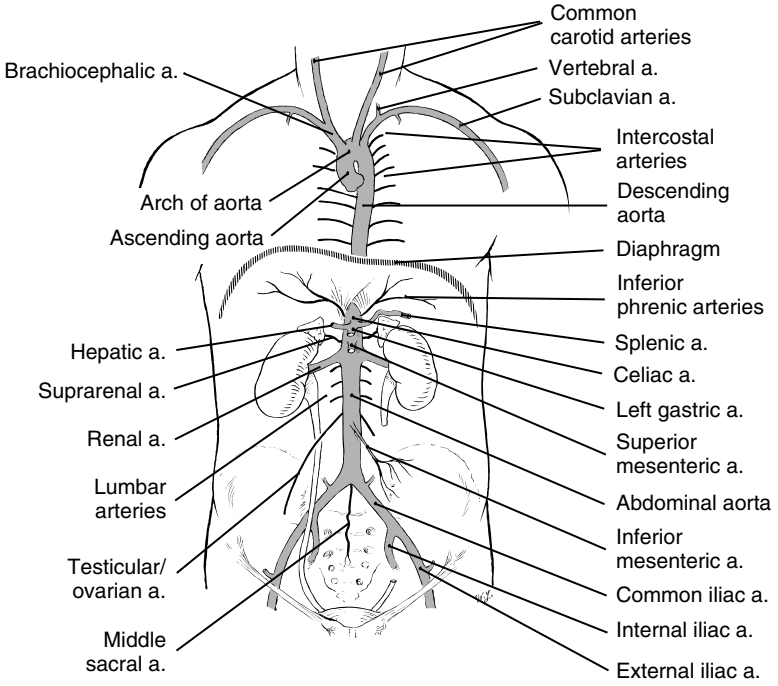

FIGURE **23-28** Thoracic aorta and abdominal aorta and their branches. *a.*, Artery.

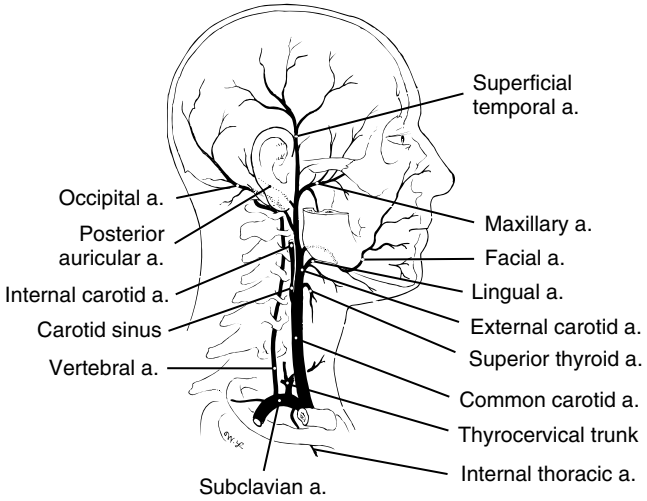

FIGURE **23-29** Arterial supply to the face. *a.*, Artery.

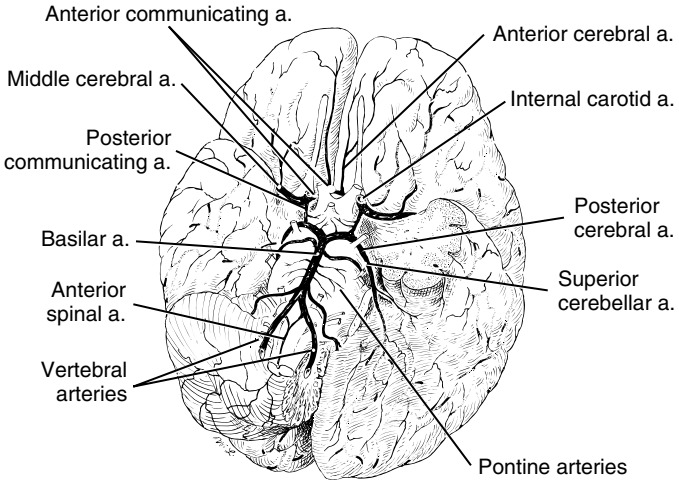

FIGURE **23-30** The circle of Willis. *a.*, Artery.

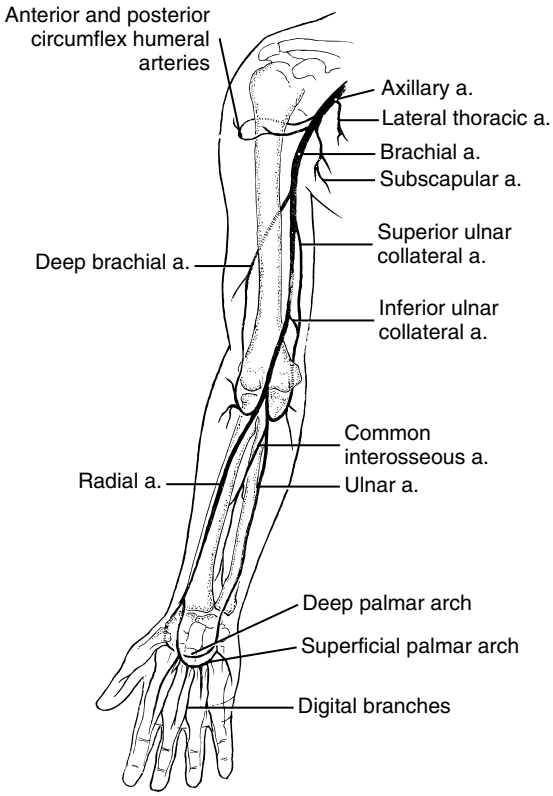

FIGURE **23-31** Arterial supply to the upper extremity. *a.*, Artery.

The brachiocephalic artery branches and becomes the right common carotid artery and the right subclavian artery. The left and right common carotid arteries branch into internal and external carotid arteries. The external carotid arteries supply blood to the face and neck, and the major branches are the superior thyroid artery, the lingual artery, the facial artery, the posterior auricular artery, the maxillary artery, the transverse facial artery, the middle temporal artery, and the superficial temporal artery (Figure 23-29).

The internal carotid arteries supply 80% of blood to the brain via the circle of Willis and to the eyes via the ophthalmic arteries (Figure 23-30). The circle of Willis also receives a major part of its blood supply from the vertebral branches of the subclavian artery.

Upper Extremity Arteries. The subclavian arteries branch before entering the upper arm. These branches include the vertebral arteries, as noted earlier; the thyrocervical trunk, which supplies blood to the thyroid gland as well as other structures in the neck; the internal thoracic artery, which supplies blood to the anterior chest; and the costocervical trunk, which supplies blood to the first two intercostal spaces and the muscles of the neck.

The subclavian artery continues at the border of the first rib as the axillary artery (Figure 23-31). Branches from the axillary artery supply blood to the axillary region and include the highest thoracic artery, the thoracoacromial artery, the lateral thoracic artery, the subscapular artery, and the anterior and posterior circumflex humoral arteries.

The brachial artery begins at the terminal end of the axillary artery at the inferior border of the teres major muscle. The artery continues until the neck of the radius, where it ends by dividing into the radial and ulnar arteries. The radial artery forms the deep palmar arch, and the ulnar artery supplies blood to the superficial palmar arch.

Descending Thoracic Aorta. The descending thoracic aorta passes caudad through the posterior mediastinum on the left side and at the level of the twelfth thoracic vertebra passes through the aortic opening in the diaphragm and becomes the abdominal aorta. Branches of the descending thoracic aorta include the lower nine posterior intercostal arteries, the subcostal arteries, the pericardial arteries, the esophageal arteries, and the bronchial arteries.

Abdominal Aorta. As the thoracic aorta passes through the aortic hiatus of the diaphragm, it becomes the abdominal aorta. The first branches of the abdominal aorta are the inferior phrenic arteries, which supply blood to the underside of the diaphragm and the adrenal glands (see Figure 23-28).

The next major branch of the abdominal aorta is the celiac trunk, which supplies blood to many of the organs in the upper abdomen. Its branches include the splenic artery, the left gastric artery, the gastroduodenal artery, and the hepatic artery. The cystic artery, which supplies blood to the gallbladder, is a branch of the hepatic artery.

Below the celiac trunk of the aorta lies the superior mesenteric artery, which arises at the level of L1. This artery supplies blood to the jejunum, the ileum, and the transverse colon by means of an anastomosis with the middle colic artery. The jejunal and ileal branches unite to form the arterial arcades of the colon.

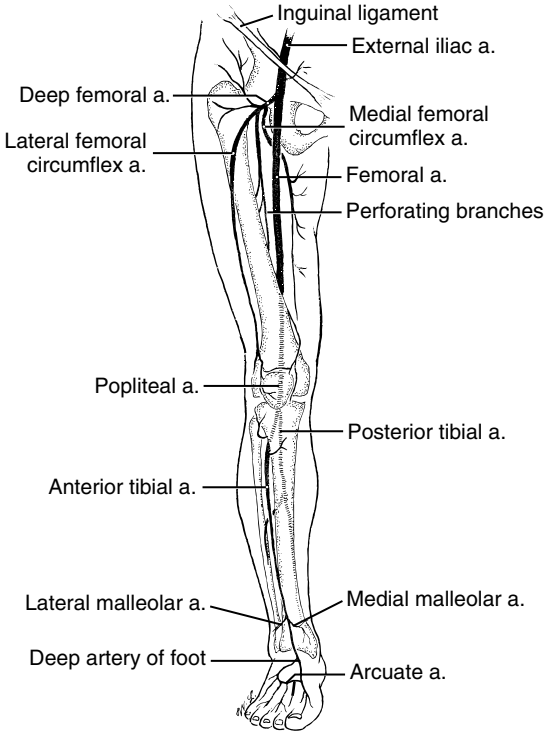

FIGURE **23-32** Arterial supply to the lower extremity. *a.*, Artery.

Below the superior mesenteric artery are the right and left renal arteries. The right renal artery branches to the right adrenal gland, where it is called the *middle suprarenal artery*. Below the renal arteries are the testicular or ovarian arteries. Inferior to the renal arteries lies the inferior mesenteric artery. This artery has branches to the transverse colon, the descending colon, and the sigmoid colon and rectum.

Iliac Arteries. The abdominal aorta terminates at the common iliac arteries in the pelvis. These arteries divide into internal and external iliac arteries. The internal iliac arteries supply blood to structures within the pelvis, whereas the external iliac arteries supply blood to the legs.

Lower Extremities. The external iliac artery continues as the femoral artery and the deep femoral artery (Figure 23-32). The femoral artery becomes the popliteal artery behind the knee and then divides into the anterior and posterior tibial arteries. The anterior tibial artery continues as the dorsal artery of the foot. The posterior tibial artery continues and supplies blood to the plantar arches. Clinically, the dorsal artery of the foot is not only an important landmark for the assessment of lower extremity circulation but can also be used for arterial cannulation if the radial artery catheter insertion is not possible.

Venous Circulation

An understanding of the anatomy of the venous system is essential in the practice of anesthesia, not only for vascular access but also for identification of significant landmarks to help locate nerve bundles when performing nerve blocks. Evaluation of venous distention is an important assessment tool for fluid overload and cardiovascular dynamics.

Head and Neck. In the head and neck, venous drainage returns to the heart via the internal and external jugular veins. The drainage from the brain comes from the sagittal, transverse, and sigmoid sinuses. These sinuses drain into the internal jugular vein, whereas the more superficial structures of the face and head drain into the external jugular vein.

Upper Extremities. Superficial veins of the upper extremities include those that drain into the axillary vein, the cephalic vein laterally, and the basilica vein medially. The axillary vein drains into the subclavian vein on the right and then into the right brachiocephalic vein. The left subclavian vein drains into the left brachiocephalic vein. The right and left brachiocephalic veins empty into the superior vena cava and account for the venous drainage that occurs from the upper extremities. Pressure and occlusion of the superior vena cava from a mass can result in a decrease in venous drainage, causing superior vena cava syndrome.

Thorax. Venous drainage of the chest comes from the branches of the superior and inferior vena cava and the azygos and hemiazygos systems. These systems are an important alternative blood return route if a major obstruction of the inferior vena cava occurs. These vessels include the intercostal vessels, the bronchial veins, and the pericardial veins.

Abdomen, Pelvis, and Lower Extremities. The deep femoral and femoral veins receive superficial and deep venous drainage from the legs and join to form the external iliac veins. The internal iliac veins drain blood from the pelvis. The common iliac vessels receive blood from the internal and external iliac veins and drain into the inferior vena cava. In this region, the common iliac vessels are joined by branches from the abdomen and the hepatic portal system.

Microcirculation

The function of the microcirculation is to control the delivery of nutrients to the capillary tissue beds, remove waste products, maintain ionic concentrations, and transport hormones to the tissues.

Anatomy. In general, a main nutrient artery enters an organ, where it branches six to eight times until the vessels are small enough to be called *arterioles* (less than 20 μm in diameter). Arterioles then branch two to five times and reach diameters of 5 to 9 μm, small enough to supply blood to the capillary bed.

In the capillary bed, the blood enters through an arteriole that has a muscular coat. Arterioles are connected to metarterioles, which have many interconnections to the true capillaries and whose branches are protected by precapillary sphincters. These sphincters can control blood flow through the capillary bed.

The capillary wall is a unicellular layer of endothelium surrounded by a basement membrane. The total wall thickness is 0.5 μm, and the diameter of the capillaries is 4 to 9 μm. In the capillary membrane, intercellular clefts allow the diffusion of water-soluble ions and small solutes. Plasmalemmal vesicles form channels in the cell membrane.

The diffusion of substances through the cell membrane is determined by several factors: lipid solubility, water solubility, size of the molecule, and concentration difference from one side of the membrane to the other.[1]

Movement of fluid volume from the plasma and the interstitial fluid is determined by four factors: capillary pressure, interstitial fluid pressure, plasma colloid osmotic pressure, and interstitial fluid colloid osmotic pressure. Excess fluid from the interstitial space is transported through the lymphatic system, which plays an important role in the prevention of pulmonary edema formation when pulmonary artery pressures are elevated.

Local Control of Capillary Blood Flow. Blood flow to the various capillary beds is regulated by local tissue metabolic requirements. Therefore capillary blood flow may be controlled by the delivery of oxygen and other nutrients, the removal of end products of metabolism, or the maintenance of ionic balance of pH in the tissues.

Two major theories regarding regulation of capillary blood flow are the vasodilator theory and the oxygen-demand theory. According to these theories, the vessels dilate to increase the blood flow as a result of either hypoxemia or release of a vasodilator substance in response to hypoxemia. Some of the vasodilator substances that have been suggested are adenosine, carbon dioxide, lactic acid, adenosine phosphate compounds, histamine, potassium ions, and hydrogen ions. These theories assume an active microcirculatory process exists that responds to tissue metabolic needs.

Certain tissue capillary beds do not function as explained by the vasodilator and the oxygen-demand theories of microcirculatory blood flow. Blood flow to the skin is dependent on external temperature and dissipation of body heat, whereas blood flow to the kidneys is dependent on the amount of fluid and sodium that needs to be excreted.

Autoregulation is another process demonstrated by certain organ tissues; it keeps blood flow through the capillary bed constant, despite the normal changes in MAP. Autoregulation has been demonstrated in such tissues as the brain, the kidney, and the coronary circulation. Autoregulation keeps the blood flow to an organ constant by way of vasodilation or vasoconstriction as occurs in response to fluctuations in MAP.

A substance that causes secondary vasodilation of the large arteries in response to increased flow has been isolated and was once called the *endothelium-derived relaxing factor*.[23] Currently it is referred to as *nitric oxide*. This factor is synthesized by the endothelial lining of the arterioles and the small arteries. Shear stress on the walls of the vessels accelerates the release of this substance and allows larger vessels to dilate when blood flow to the tissues increases.

Growth of Collateral Circulation

Microcirculation is a good example of vascular growth that can occur to provide collateral circulation. The growth of new vessels results in part from angiogenesis and the release of angiogenic factors. These substances are released from ischemic tissues, rapidly growing tissues, and tissues with high metabolic rates.

Several angiogenic factors have been identified, including endothelial cell growth factor,[24] fibroblast growth factor,[25] and angiogen.[26] These factors act by the dissolution of the basement membrane of the endothelial cells, followed by the rapid dissolution of new endothelial cells that stream out of the vessels into cords. The cells in these cords divide and then gradually fold over into a tube. The tubes then connect with other tubes to form a vascular network.

Vascular flow is dependent on neurologic as well as hormonal regulation. Some vasoconstrictor hormones include epinephrine and norepinephrine from the central nervous system (CNS) and the adrenal medulla, angiotensin from the adrenal cortex, and vasopressin from the posterior pituitary. Some vasodilator substances include bradykinin, serotonin, histamine, and the prostaglandins. Various other ionic and chemical factors can produce vasoconstriction and vasodilation as well and have an effect on the flow of blood that is delivered to tissues.

Blood Pressure

Pressure, Flow, and Resistance Interrelationships

Ohm's Law. Ohm's law correlates the flow of electricity (current), the applied electrical pressure (voltage), and the resistance to this flow (resistance). A modification of this law is used in medicine to describe the flow of a fluid (blood) through a tube (blood vessel), even though the vessels are dynamic rather than static. Ohm's law and fluid flow are described by the following equation:

$$Q = (P_1 \times P_2) / R$$

where the flow through a cylinder (Q) is equal to the change in pressure from one end of the tube to the other ($P_1 \times P_2$) divided by the resistance (R) of the tube. Therefore either a decrease in resistance or an increase in pressure change across the tube increases the flow of fluid through the tube.

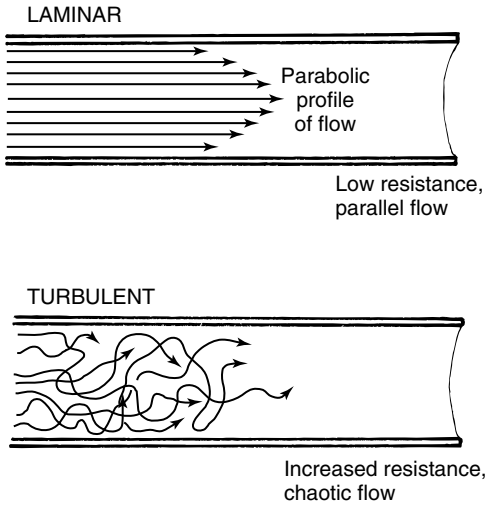

FIGURE **23-33** Laminar and turbulent flow.

Blood Flow. Blood flow is the quantity of blood that passes a given point in a given amount of time. Clinically, CO may be inserted into the equation as blood flow. Two types of flow exist: laminar and turbulent (Figure 23-33).

Laminar flow has a parabolic profile that illustrates the parallel movement of molecules. Conversely, turbulent flow is described as a whirlpool and does not move as easily, thereby increasing resistance to flow. Reynolds number (Re) is a means of determining the type of flow in a tube and uses the diameter of the blood vessel (d) and the velocity (v), density (ϱ), and viscosity (n) of the fluid to determine whether turbulence occurs.

The formula for calculating Reynolds number includes the velocity of blood flow in centimeters per second multiplied by the diameter of the tube in centimeters, multiplied by the density of the fluid in grams per cubic centimeter, divided by the viscosity (see the following equation). A Reynolds number below 200 indicates laminar flow. A Reynolds number of 200 to 400 indicates that turbulence occurs at bends in the tube, and a Reynolds number above 2000 indicates turbulent flow, even in straight, smooth vessels.

$$Re = (v \times d \times \rho) / n$$

Reynolds number demonstrates that in large vessels with high velocities, such as the aorta and large arteries, turbulent flow occurs even in the straight portions of these vessels.

Poiseuille's Law. Poiseuille's law (see the following equation) describes the amount of fluid flowing through a tube (Q) in relation to the pressure drop across the tube ($P_1 - P_2$), the radius of the tube (r), the length of the tube (l), and the viscosity of the fluid (n):

$$Q = ([P_1 - P_2]\, r^4) / (8 \times n \times 1)$$

One of the most important factors in determining fluid flow is the radius of the vessel.

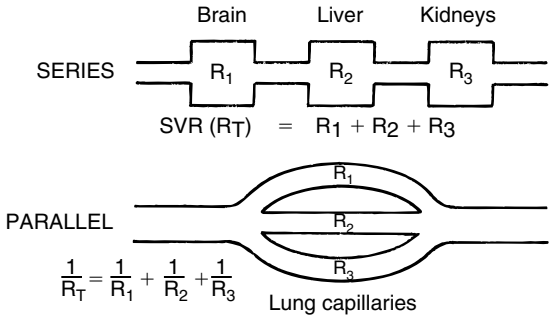

FIGURE **23-34** Resistance in series and parallel systems. *R*, Resistance; *SVR*, systemic vascular resistance. R_T, total resistance.

Clinical applications of Poiseuille's law include selection of intravenous catheter size and endotracheal tube size and determination of vascular distention and constriction in response to pharmacologic agents.

Resistance. Resistance is the impediment to blood flow in a blood vessel. Clinically it cannot be measured directly but is calculated from measures of blood flow (CO) and pressure differences in the vessels.

The units of measure most commonly used in the clinical area are centimeter-gram-second units. The normal SVR is 800 to 1500 dyne/sec per centimeter^{-5}, and the normal pulmonary vascular resistance is approximately one tenth of that number, or between 50 and 150 dyne/sec per centimeter^{-5}.

Resistance of Systems. Resistance is calculated for two major systems (Figure 23-34). In a series system, such as the systemic vasculature, the total resistance (R_T) is equal to the sum of the resistances for the individual tissue beds within the system (see the following equation):

$$R_T = R_1 + R_2 + R_3 + \ldots R_n$$

In a parallel system, such as a capillary bed, the total resistance is less than any of the individual resistances (see the following equation). Therefore the blood flow through a capillary bed such as the pulmonary capillaries is less than the resistance through any of the individual capillaries of the pulmonary system.

$$1/R_T = 1/R_1 + 1/R_2 + 1/R_3 + \ldots 1/R_n$$

Regulation of Mean Arterial Blood Pressure

Regulation of arterial blood pressure is an important function in maintaining homeostasis for patients receiving anesthesia. Mean arterial pressure is an important indicator of perfusion of the tissue beds.

Blood pressure regulation can be categorized as either short term or long term. The choice of category depends on the onset of action, the duration of action, and the intensity of action to return the MAP to normal values.

Short-Term Regulation. The short-term blood pressure regulators are those that respond to rapid changes in MAP and attempt to rapidly (within 30 minutes) return the MAP back to normal range. These reflexes rely on an intact autonomic nervous system, and this interaction is responsible for the rapid onset of action of these blood pressure regulators. The reflexes include the baroreceptor response, the chemoreceptor response, atrial stretch reflex, and CNS ischemic mechanism. All of these reflexes are initiated rapidly in response to acute changes in MAP.

It is important to understand the role of the cardiovascular (vasomotor) center that is located in the medulla and pons. This center regulates four basic actions: vasoconstriction, vasodilation, cardiac excitation, and cardiac inhibition. These areas activate the sympathetic and parasympathetic nervous systems in response to certain stimuli. Under normal conditions, the vasomotor center maintains peripheral vascular tone.

Baroreceptors are located in the internal carotid arteries and the aortic arch and are called the *carotid and aortic sinuses*. They are spray-type nerve endings that increase impulse production when they are stretched. Impulses from the baroreceptors affect the inhibitory centers of the vasomotor center. At MAP of less than 60 mmHg, the baroreceptors do not transmit impulses. However, as the MAP increases to between 60 and 180 mmHg, impulses sent to the inhibitory area of the vasomotor center incrementally increase. The baroreceptors are most efficient in responding to rapid changes in blood pressure. They are not as efficient in long-term blood pressure regulation, because they adapt to the higher pressures, in effect by being reset. Therefore the baroreceptors act as a buffer system to prevent extreme short-term swings in blood pressure. Two clinically significant examples of stimulation of the baroreceptor reflex during surgery include carotid sinus manipulation during carotid endarterectomy and aortic baroreceptor stimulation from pressure exerted on the aortic arch during mediastinoscopy.

Chemoreceptors are chemosensitive cells located within the carotid and aortic bodies. These are known as the *peripheral chemoreceptors*. Each area is supplied by a small nutrient artery and thereby maintains constant contact with the internal environment. Chemoreceptors send impulses to excite the vasomotor center, primarily in response to decreases in Pa_{O_2}. Chemoreceptors play a greater role in respiratory system regulation than in blood pressure regulation.

Low-pressure receptors, or stretch receptors, are located in many areas of the vasculature, especially within the atria and pulmonary arterial tree. They act in conjunction with the baroreceptors to buffer changes in the blood pressure caused by changes in volume status.

The *atrial stretch reflex* is initiated by input from low-pressure receptors. Stretching of the atria caused by an increase in volume results in a dilation of the peripheral arterioles, which decreases SVR, MAP, and CO. Furthermore, hypervolemia causes the release of the atrial natriuretic factor by the atria as a result of increased stretch.[27] This factor causes a reflex dilation of afferent arterioles in the kidney, a phenomenon that increases the glomerular filtration rate and decreases the secretion of antidiuretic hormone via signals to the hypothalamus. The combination of these events causes an increase in urine formation and an attempt to change the MAP by decreasing vascular volume.

The CNS ischemic mechanisms are another rapidly acting blood pressure control system. When hypotension exists, this reflex is initiated in an attempt to restore the MAP to adequate levels for CNS perfusion and especially for perfusion to the vasomotor center. The reflex is most intensely initiated when MAP is less than 20 mmHg and results in one of the most powerful sympathetic vasoconstrictor responses within the human body.[1] The stimulation persists for approximately 10 minutes, by which time either the ischemia has been relieved or the vasomotor center has infarcted, and the stimulation ceases.

Several hormones are instrumental in the short-term regulation of MAP. The onset of action is not as rapid as that of neural control mechanisms, but activation occurs within a short time of stimulation. Norepinephrine and epinephrine are released from the central nervous system and the adrenal medulla during times of sympathetic stimulation and cause vasoconstriction.

Angiotensin I is converted to angiotensin II in the lungs by angiotensin-converting enzyme. This substance is one of the most potent vasoconstrictive substances secreted by the body. It takes approximately 20 minutes to become fully activated. Angiotensin II also plays a role in the secretion of aldosterone from the adrenal cortex. Aldosterone has a role in the long-term regulation of MAP.

The antidiuretic hormone vasopressin has both short-term and long-term effects on blood pressure control. The short-term effect of antidiuretic hormone causes potent and direct vasoconstriction. The long-term control effects of antidiuretic hormone decrease urine output from the kidneys.

Two short-term systems for maintenance of blood pressure that could be classified as intermediate mechanisms are the capillary fluid shift and the stress-relaxation mechanism. Both of these mechanisms depend on an intact vascular system.

The capillary fluid shift is a simple mechanism. As the hydrostatic pressure (MAP) increases within the capillaries, a larger movement of fluid occurs across the capillary membrane as increased pressure. This phenomenon lowers the fluid volume within the vasculature and results in a decrease in MAP.

The stress-relaxation mechanism is an example of the ability of the vasculature to compensate for hypervolemia and hypovolemia as a result of alterations of smooth muscle tone within the vasculature. As intravascular fluid volume increases, tension on the blood vessels results in dilation of the vasculature to compensate for increased volume. Conversely, as the blood volume decreases, the vessels constrict to compensate for the decreased volume in order to maintain MAP.

Long-Term Regulation. Long-term regulation of MAP includes mechanisms that eventually regulate blood volume to within normal range. The renal body fluid system is one of the major long-term regulators of MAP. Renal homeostasis of blood pressure occurs as the kidneys preferentially excrete sodium and water to maintain a normal fluid balance.

It is important to understand the concept of fluid balance and its effect on arterial blood pressure. A chronic increase in blood volume leads to increases in mean filling pressure, venous return, CO, and SVR. The combination of an increased CO and an increased SVR can increase the arterial blood pressure by more than 30%. This causes an increase in myocardial oxygen demand.

Several factors govern the effectiveness of the renal body fluid system, including the renin-angiotensin system, aldosterone secretion, and the nervous system. As fluid intake and blood pressure increase, the secretion of renin by the kidneys decreases. This decreased renin secretion causes a reduced secretion of aldosterone as a result of the decreased production of angiotensin II, which is a potent vasoconstrictor. A decrease in sympathetic nervous system response to the kidney also occurs. The net effect is an increased renal output of sodium and water.

Physiology of the Venous System

In the past, the venous system has been described as simply the return conduit for the arterial system, and it was not thought to play a very active role in the maintenance of circulation and CO. The modern view gives the venous system an integral role in support of the circulation.[28]

The venous system's ability to accommodate large volume changes helps to buffer the intravascular volume during periods of hypervolemia or hypovolemia and thereby helps to maintain CO. In addition, the venous system is well innervated by the autonomic nervous system, and therefore it has the ability to respond to the wide variations in intravascular volume that occur over the course of long surgical procedures and during times of intensive fluid resuscitation.

Knowledge of the anatomy and physiology of the cardiovascular system is essential for safe anesthesia practice. This section discussed issues of concern to the anesthesia provider and offered reference material for the integration of that knowledge into clinical practice.

HYPERTENSION

Extent, Definition, and Etiology

The pathophysiologic cardiovascular condition that is most commonly encountered in patients who require surgery is hypertension. Hypertension affects approximately 70 million people in the United States, and the frequency increases with age. It is vital for the anesthesia provider to understand the pathophysiology of the condition and its relation to the cardiovascular system and other body systems. Only then can a comprehensive anesthesia plan be constructed.[29]

Patients frequently do not exhibit signs or symptoms associated with hypertension. Chronic uncontrolled hypertension affects specific target organs, including the heart, brain, and kidney. Hypertension accelerates and exacerbates the onset of atherosclerotic changes in the arterial vessels of the target organs. It is a primary risk factor for the development of coronary artery disease. Hypertension is a significant cause of congestive heart failure and cardiomyopathy because of increased afterload from chronic vasoconstriction. Because hypertension increases the likelihood of the development of atherosclerosis, it has been implicated as a causative factor responsible for the development of stroke and renal failure.[29]

Hypertension is classified on the basis of its causes. Essential hypertension, also referred to as primary and idiopathic, has no identifiable cause, accounts for 95% of all cases of the disease, and its diagnosis is determined on the basis of exclusion. The relationship between an individual's genetic predisposition and environmental factors most probably influences the potential development and severity of essential hypertension. Theoretic physiologic causes of essential hypertension include sympathetic nervous system hyperactivity and/or increased activity of the renin, angiotensin, and aldosterone system. Remedial (secondary) hypertension has an identifiable and potentially curable cause. Examples of pathophysiologic conditions that cause remedial hypertension include pheochromocytoma, coarctation of the aorta, renal artery stenosis, primary renal diseases (e.g., pyelonephritis, glomerulonephritis), primary aldosteronism (Conn disease), and hyperadrenocorticism (Cushing disease).

Guidelines regarding blood pressure values that constitute hypertension have been published by the National Institutes of Health (NIH). The classification of hypertension is listed in Table 23-6. To determine accurate blood pressure measurements, two readings taken 5 minutes apart with the patient in the sitting position are necessary. The risk of cardiovascular disease doubles with each increment of 20/10 mmHg above 115/75 mmHg. The NIH has coined the term *prehypertension* to refer to those patients who would benefit from lifestyle modifications that decrease the likelihood of developing the pathophysiologic changes associated with hypertension.[30] It is estimated that the implementation of antihypertensive therapy is associated with a 25% decrease in cardiovascular complications and a 38% decrease in stroke.[31] If lifestyle modifications are unsuccessful in decreasing blood pressure to acceptable levels, then antihypertensive therapy should be prescribed.[32] In many instances, patients may have developed advanced atherosclerotic vascular

TABLE 23-6 Classification of Blood Pressure for Adults Age 18 Years and Older

Category	Systolic (mmHg)		Diastolic (mmHg)
Normal	<120	and	<80
Prehypertension	120-139	or	80-89
Hypertension, stage 1	140-159	or	90-99
Hypertension, stage 2	≥160	or	≥100

From National Institutes of Health, National Heart, Lung and Blood Institute, National High Blood Pressure Education Program. *Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (NIH Publication No. 03-5233:3)*. Washington, DC: U.S. Government Printing Office; 2003.

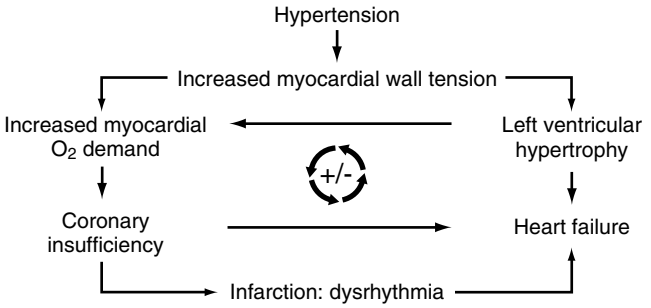

FIGURE 23-35 Schematic representation of the relationship between hypertension and heart failure. (Modified from Matei VA, Haddadin AS. Systemic and pulmonary arterial hypertension. In: Hines RL, Marschall KE, eds. *Stoelting's Anesthesia and Co-Existing Disease*. 6th ed. Philadelphia: Saunders; 2012:106.)

disease or target-organ dysfunction before the start of treatment for hypertension.[33,34]

Pathophysiology

Systemic blood pressure is regulated by interactive feedback mechanisms involving the sympathoadrenal axis and baroreceptors in the heart and great vessels. It is accepted that some degree of sympathetic hyperactivity is responsible for essential hypertension. Dysfunction of the sympathetic nervous system leads to a state of chronic vasoconstriction. In an attempt to maintain normal intravascular volume, the renal juxtaglomerular apparatus secretes renin. All of the vascular and hormonal effects of renin are caused by its conversion of angiotensin I to angiotensin II. Angiotensin II is the major stimulus for the secretion of aldosterone by the adrenal cortex.

Deposition of collagen and metalloproteinases within the intima of arteries leads to vascular stiffness, and this occurs normally as part of the aging process. Narrowing of the vascular lumen and endothelial dysfunction causing inability of complete vasodilation decreases blood flow, especially within the microvasculature. Furthermore, vascular stiffness increases afterload and myocardial oxygen demand and can cause LV hypertrophy, myocardial ischemia/infarction, and/or congestive heart failure.

Anesthesia Management for the Patient with Hypertension

Preoperative Evaluation

The most important issues to be addressed in the preoperative evaluation of the hypertensive patient are the identification and the adequacy of treatment. A number of otherwise healthy patients scheduled for elective procedures are determined to have hypertension, even though they had no prior need for medical treatment. The goal of antihypertensive therapy is to maintain normotension on a consistent basis. Effective antihypertensive therapy that renders the patient normotensive on a routine basis may not necessarily prevent episodes of perioperative hypertension. However, patients whose condition is optimized before surgery have a more stable perioperative course and a lower incidence of cardiovascular system–related morbidity. Although not ideal, if perioperative diastolic blood pressure is maintained below 110 mmHg, the risk of perioperative cardiac morbidity does not increase significantly.[29,35]

It is imperative for anesthesia providers to have an adequate understanding of the pharmacology and side effects of the drugs used for treating hypertension. For a complete discussion of antihypertensive drugs, see Chapter 13, which discusses some of the drugs used to treat hypertension block or depress homeostatic sympathetic reflexes. The depression of these reflexes may prevent homeostatic compensatory mechanisms from functioning at normal levels during the course of anesthesia. Subsequently, compensatory mechanisms (tachycardia and vasoconstriction) associated with blood loss may be diminished or may not occur. Patients treated with antihypertensive medication do not lose their responsiveness to vasoactive drugs but instead may respond to these substances in an exaggerated manner. Even with depression of the sympathetic reflexes, no predominance of the parasympathetic system occurs.

The clinician should carefully obtain a thorough history of the cardiovascular system to elicit any symptoms of ischemic cardiovascular disease. Hypertension is a major risk factor for coronary artery disease. Any symptoms related to coronary artery disease should be further investigated. In addition to being a risk factor for coronary artery disease, hypertension directly affects myocardial function. The chronic increase in myocardial wall tension caused by long-standing hypertension results in left ventricular hypertrophy (LVH) (Figure 23-35). Ventricular diastolic dysfunction occurs before the development of hypertrophy. This diastolic dysfunction is not clinically apparent, and the patient may appear to have normal cardiac function except under stressful physiologic conditions. A delayed rate of passive ventricular filling is evidence of ventricular diastolic dysfunction. The rate of ventricular filling from atrial contraction becomes predominant in hypertensive patients. This represents the inverse of normal ventricular filling patterns. Other information and results from preoperative tests that will help the nurse anesthetist evaluate and create an individualized anesthetic plan for patients with cardiac dysfunction includes determining exercise tolerance, electrocardiogram (ECG), Doppler ultrasound, stress test, and cardiac catheterization results.

Left ventricular hypertrophy is a consequence of chronic hypertension and increased afterload that results in an enlargement of myocardial mass. This compensatory process increases myocardial oxygen demand. Hypertrophy that occurs in response to chronic increases in intracardiac pressure is termed *concentric hypertrophy*. Ventricular hypertrophy also may produce subendocardial ischemia at perfusion pressures that would normally be adequate in a healthy ventricle. Concomitant development of coronary artery disease coupled with increased myocardial oxygen demand hastens and exacerbates the development of ischemic symptoms. As a rule, all patients with chronic hypertension should be suspected of having some degree of coronary artery disease.

Hypertensive cardiomyopathy and systolic ventricular dysfunction are the direct result of the pathophysiologic changes

associated with chronic hypertension. This hypertensive cardiomyopathy manifests as a decrease in both EF and SV. Increasing diastolic dysfunction results in ventricular dilation in conjunction with systolic dysfunction. The subsequent replacement of myocardial cells with fibrous tissue results in a cardiomyopathy.[4]

Long-standing hypertension that has remained either untreated or inadequately controlled has adverse consequences on brain, kidney, and ocular function, and patients with long-standing disease have a higher incidence of strokes than do patients whose blood pressure has been controlled.[29] Inadequate control of hypertension can lead to alterations in cerebrovascular and coronary artery autoregulation. For example, normal physiologic coronary artery autoregulation occurs at a MAP between 60 and 140 mmHg. However, a patient with chronic hypertension and coronary artery disease may develop ischemic changes at a MAP of 60 mmHg or greater. The cerebral and coronary autoregulation curves are shifted to the right in patients with chronic hypertension, necessitating higher perfusion pressures to ensure adequate organ blood flow. Therefore cerebral and myocardial ischemia may occur with significant decreases in MAP in patients with hypertension and coronary artery disease. This phenomenon makes patients with uncontrolled hypertension more susceptible to cardiac and cerebral ischemia, compared with normotensive individuals.[34] Chronic untreated hypertension can cause nephrosclerosis, which can impair renal function. Nephrosclerosis can produce proteinuria and a gradual decrease in renal function. Early treatment of hypertension results in little change in renal function and spares the kidneys. Signs of target organ involvement must be investigated in the hypertensive patient who is to undergo anesthesia.

Anesthesia Management

An individualized anesthetic plan must be created by taking into account the type and extent of cardiac pathophysiology, other disease states, and the surgical procedure. To maintain a stable intraoperative course, administration of antihypertensive medications should be continued on schedule until the time of surgery. All oral medications can be given with one or two sips of water without increased risk of aspiration.[33] It should be noted that acute hypertensive rebound can occur with abrupt cessation of antihypertensive medications. Tachycardia, hypertension, angina, and myocardial infarction can result from interruption of therapy with β-blockers, clonidine, and other cardiac agents. All cardiac drugs should be continued up to and including the day of surgery.

Determining whether to proceed with elective surgery in a patient in whom hypertension is untreated and poorly controlled remains controversial. However, evidence suggests that patients with diastolic blood pressures greater than 110 mmHg have a significantly increased risk of perioperative cardiac morbidity.[34] This caveat may be modified in patients with hypertension in whom diastolic blood pressures greater than 110 mmHg occur frequently, despite aggressive antihypertensive drug therapy (e.g., patients with end-stage renal disease).

To attenuate sympathetic responsiveness, preoperative sedation may be indicated for patients with hypertension. Establishing control of the blood pressure before induction should result in a more stable hemodynamic course during the induction, maintenance, and emergence from anesthesia. A fluid bolus and incremental titration of anesthetic induction agents may help decrease the degree and duration of hypotension.

Induction of Anesthesia

Patients with hypertension may react in an exaggerated manner to induction agents and the stimulation associated with laryngoscopy and tracheal intubation. This response is highly variable and may result in hypertension or hypotension. It is dependent on the individual's physiology, degree of stimulation, adequacy of preoperative antihypertensive therapy, and amount and type of induction agents administered. Hypertensive patients are hypovolemic, either as a result of renal-compensatory mechanisms, extreme vasoconstriction, or pharmacologic therapy (diuretics). Increased vasoconstriction as a consequence of hypertension results in volume contraction and a greater susceptibility to hypotension from the vasodilating and cardiac-depressant effects of anesthetic agents. Of the anesthetic induction agents, etomidate, propofol, or dexmedetomidine can be used in patients with hypertension. Etomidate offers an advantage in patients with cardiac pathology, as compared to propofol, because it preserves stroke volume and cardiac output.[15] Due to the sympathomimetic response that occurs with the administration of induction doses of ketamine, this drug should be not be used routinely for patients with cardiovascular disease.

The stimuli of laryngoscopy and tracheal intubation can result in an exaggerated hypertensive response, despite postinduction hypotension. An existing hypertensive state is further compounded by intense stimulation caused by airway manipulation. Suppressing the exaggerated hypertensive response to intubation requires that a greater depth of anesthesia be achieved. However, the depth of anesthesia at induction necessary to suppress this response may produce a more profound hypotensive state. Administration of adjunct medications before induction (e.g., β-blockers or arterial dilators) can reduce the hyperdynamic sympathetic response to tracheal intubation. Hypotensive episodes can be treated with fluid administration, decreasing anesthetic depth, and administration of vasoconstrictors. Numerous strategies have been suggested for the management of this hyperdynamic response. The pressor response to laryngoscopy and intubation could be significantly reduced by laryngotracheal or intravenous administration of lidocaine.[36] Reducing the duration of airway manipulation to 15 seconds or less may be helpful. Use of a β-blocker before induction has been shown to reduce the hyperdynamic sympathetic responses.[33] Administration of fentanyl (2 to 3 mcg/kg) just before induction also helps attenuate the pressor response.

With regard to suppression of marked hemodynamic responses, a smooth induction followed by a rapid and atraumatic intubation is imperative. Maintaining an adequate depth of anesthesia at induction that produces extreme hypotension may be more detrimental to both coronary and cerebral perfusion than the hypertensive response it was intended to prevent. Because the hypertensive patient is frequently hypovolemic as compared with the normotensive patient, adequate hydration before induction may help prevent postinduction hypotension.[29,33]

Most intravenous induction agents are appropriate for the hypertensive patient. The propensity for these agents to cause vasodilation in a comparatively hypovolemic patient is a concern. In light of this, a combination of low doses of more than one agent in addition to titration of medications may prove a better choice than a full dose of a single agent. In emergency cases in which rapidly securing the airway is of paramount importance, the choice of agents may be limited, and hyperdynamic pressor responses become a secondary issue.

Maintenance of Anesthesia

A general hemodynamic goal during anesthetic management for the hypertensive patient undergoing general anesthesia is to maintain blood pressure stability within 20% of the normal mean arterial pressure (MAP). Intraoperative events that cause wide

TABLE 23-7 Hemodynamic Goals for Management of Coronary Artery Disease

Parameter	Goal
Preload	Decrease/Maintain
Afterload	Maintain
Contractility	Decrease/Maintain
Heart rate	Slow
Heart rhythm	Normal sinus rhythm

fluctuations in blood pressure should be anticipated and treated immediately. The most common event that precipitates intraoperative hypertension includes surgical stimulation. This induces increased sympathetic tone causing release of catecholamines, cortisol, and aldosterone, which is representative of the physiologic stress-induced response caused by surgical stimulation. Volatile and opioid agents given alone and in combination have the ability to attenuate this response.[2,33,34] Altering the depth of anesthesia to suppress maximal surgical stimulation may not be adequate for achieving rapid and complete control of hypertensive responses. The adjunct use of drugs such as β-antagonists, nitroprusside, angiotensin-converting enzyme inhibitors, and others may be necessary for achieving control. These drugs offer the advantage of continued control of hypertensive response in the immediate postanesthesia recovery period. Table 23-7 lists hemodynamic goals for patients with coronary artery disease.

The onset of profound hypotension during anesthesia maintenance should be immediately recognized, diagnosed, and treated. Prolonged severe hypotension has predictive significance in perioperative cardiac morbidity.[35] Treatment of hypotension may require reduction of the amount of volatile agent used and infusion of adequate volume. Should these measures prove inadequate or untimely, a rapid-acting vasopressor such as phenylephrine or ephedrine may be administered as a temporizing measure until the cause of the hypotension can be diagnosed. It is important to realize that hypertensive patients may have exaggerated responses to vasopressor agents. The goal of intraoperative anesthesia management is maintenance of hemodynamic stability, which includes anticipation of intraoperative events that may affect cardiovascular stability and thereby prevent extreme fluctuations in blood pressure.

Postoperative Considerations in the Hypertensive Patient

Termination of anesthesia results in hyperdynamic, hypertensive responses, even in patients with well-controlled hypertension. Intraoperative control of blood pressure should continue into the immediate postoperative period. Initiation of adjunct administration of antihypertensive medications should be anticipated at the end of surgery and early in the postoperative period. Adequate control of pain represents a primary antihypertensive consideration. The hypertensive patient is more susceptible to perioperative cardiac morbidity than the normotensive patient during the postoperative period. Adequate control of blood pressure in the postoperative period reduces the incidence of cardiovascular complications.[29,37] Maintenance of normothermia is helpful as well.

Pericardial Disease

In reviewing the anesthetic management of patients with pericardial disease, this section focuses on the pathophysiology, clinical presentation, and anesthetic implications of three primary disease processes: acute pericarditis, constrictive pericarditis, and cardiac tamponade.

The pericardium surrounds the heart and anchors it to its anatomic position, concomitantly reducing contact between it and surrounding structures. It consists of an inner visceral layer, which envelops the surface of the heart, and an outer parietal layer. The pericardial space between these layers usually contains 20 to 25 mL of clear fluid that under normal circumstances can accommodate gradual volume fluctuations. Rapid accumulation of pericardial fluid in the pericardial space can result in cardiac tamponade and cardiovascular collapse.[38]

Acute Pericarditis

Acute inflammation of the pericardium is caused by a number of disorders.[38] The most common cause of acute pericarditis is viral infection. Postmyocardial infarction syndrome (Dressler syndrome), postcardiotomy, metastatic disease, irradiation, tuberculosis, and rheumatoid arthritis represent the remaining primary predisposing conditions that contribute to the development of this process.[39]

Pathophysiology. It is common for a serofibrinous inflammatory reaction associated with a small intrapericardial exudative effusion to evolve. This may result in adherence of the two layers of the pericardium. The sequelae are largely dependent on the severity of the reaction, as well as on the specific cause. Most often when the condition is left untreated or undiagnosed, complete resolution is the end result. Infrequently, however, extended organization of fibrinous exudate within the pericardial sac may lead to encasement of the heart by dense fibrous connective tissue (chronic constrictive pericarditis) or to the accumulation of a large amount of pericardial fluid and consequent cardiac tamponade, usually when fluid levels exceed 1 L. Constrictive pericarditis and cardiac tamponade result in impaired diastolic filling, which results in decreased CO.[38,39]

Clinical Presentation. The principal symptom associated with acute pericarditis is chest pain with sudden onset. Although similar in nature to that experienced during myocardial infarction, this pain is differentiated by the inclusion of a pleural component, which includes increased discomfort associated with postural changes and relief on sitting or leaning forward. Other signs that are characteristic of acute pericarditis include fever with a pericardial friction rub, absence of elevation of cardiac enzymes levels, and diffuse ST-segment elevation in two or three limb leads and in most of the precordial leads. Echocardiography is another reliable method for diagnosing pericarditis and pericardial effusion.

Anesthetic Management. Acute pericarditis in the absence of an associated pericardial effusion or scarring does not alter cardiac function. Specific considerations for anesthetic management are directed toward the underlying illness.

Chronic Constrictive Pericarditis

Chronic constrictive pericarditis results from pericardial thickening and fibrosis. In the past, tuberculosis was the most common cause of pericardial constriction. Currently the most common causes are idiopathic and include complications following cardiac surgery, neoplasia, uremia, radiation therapy, and rheumatoid arthritis.[39,40]

Pathophysiology. Stiff, fibrous tissue encircles the heart and limits its ability to expand during diastole. The fundamental hemodynamic abnormality in chronic constrictive pericarditis is abnormal diastolic filling. Reduced myocardial compliance impairs filling of both ventricles. Consequently, filling pressures increase, and as a result, pulmonary and peripheral congestion

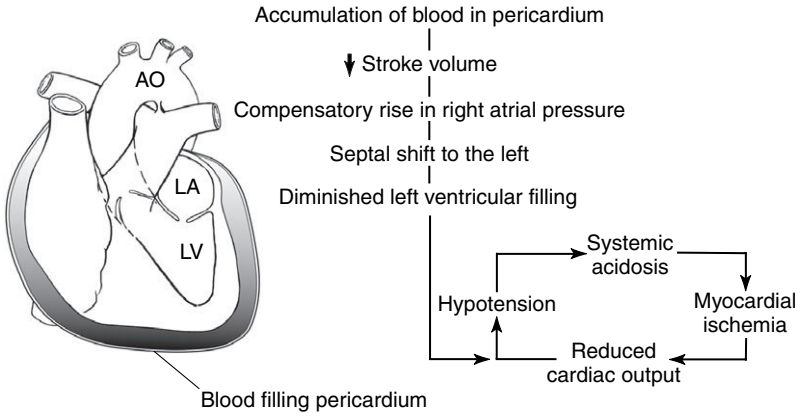

FIGURE **23-36** Pathophysiology associated with cardiac tamponade.

occurs. SV and CO can also be decreased. Equilibration of pulmonary artery diastolic pressure, PCWP, and right atrial pressure commonly occurs. Initially, ventricular systolic function is normal. However, over time the underlying myocardial tissue may atrophy, and systolic function may decrease.

Clinical Presentation. Clinical features representative of chronic constrictive pericarditis include gradually increasing fatigue and dyspnea. Typical signs of increasing venous pressure and congestion are engorgement of neck veins, hepatomegaly, ascites, and peripheral edema. In approximately 50% of patients, the fibrous enclosure becomes calcified and is visible on a chest radiograph.[33] The electrocardiogram may reveal diffuse low-voltage QRS complexes, T-wave inversion, and notched P waves. As many as 25% of patients have atrial dysrhythmias because of the involvement of atrial conduction pathways. Diagnosis is confirmed by demonstration of pericardial thickening with echocardiography or computed tomography.

The treatment used for patients with hemodynamically significant constrictive pericarditis is pericardiotomy. Unfortunately, the surgical removal of adherent pericardium may precipitate malignant cardiac dysrhythmias and massive bleeding. Consequently, pericardiotomy is associated with relatively high perioperative morbidity and mortality rates, ranging from 6% to 19%.[41,42]

Anesthetic Management. Large-bore intravenous lines must be established preoperatively because of the potential for sudden, rapid hemorrhage. A cardiopulmonary bypass circuit should be readily available. Invasive hemodynamic monitoring is essential. Arterial catheterization allows beat-to-beat blood pressure monitoring and assists in the evaluation of significant cardiac dysrhythmias. A pulmonary artery catheter is useful because it permits measurement of filling pressures on both the right and left sides of the heart, as well as determination of CO.

The anesthetic agents chosen for management of patients with constrictive pericarditis should preserve myocardial contractility, HR, preload, and afterload. Among these parameters, HR is of greatest concern. Cardiac output is dependent on HR in patients with constrictive pericarditis. As a consequence of limited ventricular diastolic filling, bradycardia is poorly tolerated and reflects a decrease in SV that can lead to hypotension. Using anesthetic medications that preserve HR and myocardial contractility, such as pancuronium or ketamine, is hemodynamically advantageous. Inhalation agents that cause myocardial depression should be used with caution. Administration of opioids and etomidate and benzodiazepines for the induction and maintenance of anesthesia is suitable in this setting. The clinician should be aware that vigorous positive-pressure ventilation may cause a decrease in venous return to the heart and result in a further decrease in CO.[43]

Immediate hemodynamic improvement may not occur after removal of the constricting tissue. Consistently low CO after pericardiectomy may be secondary to diffuse atrophy of myocardial muscle fibers or myocardial damage from the underlying disease. Intensive postoperative care with inotropic support and awareness of the potential for dysrhythmia or bleeding are integral components of the anesthetic management plan.

Cardiac Tamponade

Cardiac tamponade is a syndrome caused by the impairment of diastolic filling of the heart because of continual increases in intrapericardial pressure.[44] Slow accumulation of fluid in the pericardial space can cause minute increases in intrapericardial pressure. This occurs as a result of the pericardium's ability to stretch to accommodate this increase in volume. If the pericardial fluid accumulates rapidly, the presence of a few hundred milliliters may cause a significant increase in intrapericardial pressure that may result in cardiovascular collapse. Cardiac tamponade is the cause of cardiac compressive shock that can result in inadequate peripheral perfusion, acidosis, and death (Figure 23-36).

Classification of the causes of cardiac tamponade includes: (1) trauma, including sharp or blunt trauma to the chest and dissecting aortic aneurysms; (2) causes associated with cardiac surgery; (3) malignancy within the mediastinum; and (4) expansion of pericardial effusions after any form of pericarditis.[45]

Pathophysiology. Normal intrapericardial pressure is subatmospheric. Accumulation of pericardial fluid leads to an increase in intrapericardial pressure. As a result, diastolic expansion of the ventricles decreases. As in constrictive pericarditis, poor ventricular filling develops and leads to peripheral congestion and a decrease in SV and CO. The decrease in SV decreases peripheral perfusion causing catecholamine release manifested as tachycardia, vasoconstriction, and increased venous pressure, which helps maintain CO. If these mechanisms fail, cardiac collapse can occur.[46] The left ventricular pressure-volume loop associated with cardiac tamponade represents decreased LV volume and decreased SV due to compression (Figure 23-37).

Clinical Presentation. In addition to obvious indications of cardiac distress, specific signs of cardiac tamponade include Beck's triad: hypotension, jugular venous distention, and distant muffled heart sounds.[47] Another common finding is pulsus paradoxus, an exaggerated (i.e., greater than 10 mmHg) decrease in systolic blood pressure that normally occurs with inspiration. Other conditions that may result in pulsus paradoxus are chronic obstructive

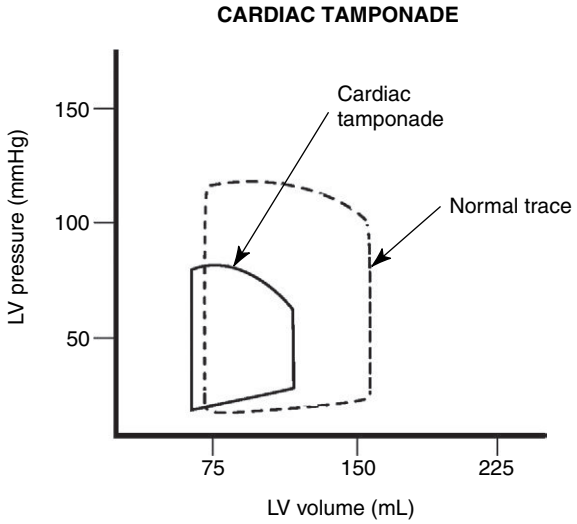

FIGURE **23-37** Left ventricular pressure-volume loop associated with cardiac tamponade.

pulmonary disease, obesity, and congestive heart failure. Jugular venous distention that occurs because of decreased forward blood flow through the heart may also be present.

In cardiac tamponade, chest radiography may show an enlarged cardiac silhouette. The electrocardiogram usually demonstrates a decrease in voltage across all leads or electrical alterations of either the P wave or the QRS complex.[48] Echocardiography is the most sensitive, noninvasive method for detection of pericardial effusion and exclusion of tamponade. Use of a pulmonary artery catheter may reveal equilibration of right and left atrial pressures and right ventricular end-diastolic filling pressures at approximately 20 mmHg.[49]

The definitive treatment for cardiac tamponade is pericardiocentesis, performed either percutaneously by needle decompression, through a subxiphoid incision, or via thoracotomy or video-assisted thoracoscopic surgery to create a pericardial window. In contrast to patients with constrictive pericarditis, in patients with cardiac tamponade, immediate hemodynamic improvement occurs once the pericardium is opened. However, despite this fact, pulmonary edema, acute right and left ventricular dysfunction, and circulatory collapse can occur.[42]

Anesthetic Management. Preoperatively the patient's clinical status should be optimized. This includes expansion of intravascular fluid volume, use of positive inotropic agents, and correction of acidosis. The degree to which these measures are instituted depends on the hemodynamic state of the patient. Severely compromised patients require immediate medical therapy, and therefore emergency pericardiocentesis is indicated. Invasive hemodynamic monitoring should be established before the procedure. Intraarterial and central venous pressure catheters are required for frequent sampling of blood, continuous blood pressure monitoring, and assessment of intravascular fluid status.

Local infiltration anesthesia is the technique of choice for operative correction of cardiac tamponade.[50] Severe hypotension and cardiac arrest after induction of general anesthesia in patients with tamponade can occur.[51,52] The potential for decompensation associated with the use of general anesthetics is attributed to direct myocardial depression and vasodilation in patients with established impairment of cardiac filling. The use of positive-pressure ventilation in such patients may result in a decrease of venous return to the heart and can further decrease CO.[53] After percutaneous pericardiocentesis and the improvement of hemodynamic status, induction of general anesthesia and initiation of positive-pressure ventilation are sufficient for further surgical exploration.

When it is not possible to relieve intrapericardial pressure that causes cardiac tamponade before the induction of anesthesia, the same anesthetic principles that are applied to the anesthetic management of patients with constrictive pericarditis should be used, including the use of anesthetic agents that preserve myocardial contractility, HR, preload, and afterload. Because of the sympathomimetic effects of ketamine, this drug has been advocated for the induction and maintenance of anesthesia.[4,50] However, many combinations of anesthetic agents that preserve the previously mentioned determinants of CO have been used safely.[43,50,52]

Continuous postoperative monitoring of blood pressure, central venous pressure, and chest-tube drainage is necessary. Possible complications after pericardiocentesis include the reaccumulation of pericardial fluid, coronary laceration, cardiac puncture, and pneumothorax. Table 23-8 lists hemodynamic goals for patients with cardiac tamponade.

TABLE 23-8 Hemodynamic Goals for Management of Cardiac Tamponade

Parameter	Goal
Preload	Maintain or increase
Afterload	Maintain
Contractility	Maintain or increase
Heart rate	Maintain
Heart rhythm	Normal sinus rhythm
Treatment	Pericardiocentesis, pericardial window

Acquired Valvular Heart Disease

The cardiac valves are membranous leaflets that separate the chambers of the heart. When open, they allow blood flow between the chambers and great vessels, and when closed, they prevent regurgitant blood flow between the chambers or backflow from the great vessels. A valve orifice of normal size presents a small degree of flow obstruction and thereby creates a hemodynamically insignificant gradient. Primary dysfunction of the mitral and aortic valves represents the most common and most severe hemodynamic derangement. Acquired primary dysfunction of the tricuspid or pulmonic valves is rare and therefore is not addressed in this chapter.

Valvular disease is classified according to the type of lesion that exists—stenosis, insufficiency, or mixed lesions. Valvular stenosis is a narrowing of the valvular orifice, which restricts flow through the orifice when the valve is open. This situation creates an increase in flow resistance and increases turbulent blood flow. Valvular insufficiency results in regurgitation secondary to incomplete or partial valve closure, which allows blood to flow back through the valve into the previous chamber. In patients with mixed lesions (stenosis with insufficiency or insufficiency with stenosis), one type of dysfunction is considered dominant over the other on the basis of the severity of clinical symptoms.

Valvular dysfunction is classified as either primary or secondary. In primary valvular dysfunction, the valve leaflets or the anchoring and supporting structures are damaged or do not function properly. In secondary valvular dysfunction, the valve is not directly damaged. However, normal valve function is altered secondary to another pathophysiologic entity. Causes of this type of

manifestation include ventricular dilation, which produces mitral insufficiency; retrograde aortic dissection, which creates aortic insufficiency (AI); and papillary muscle infarction, which causes mitral insufficiency.[54,55]

Cardiac Output. The primary components of CO are preload, afterload, contractility, LV compliance, and HR.[55-57] Blood flow may increase due to an increase in HR or an increase in SV. Because blood viscosity decreases with decreasing hematocrit and increasing flow rate, normovolemic anemia reduces cardiac afterload, thereby facilitating the augmentation of CO. This sequence of events occurs so long as intravascular volume is maintained and cardiac reserve is ample. The amount of afterload present determines the degree of tension cardiac fibers must develop before systolic ejection can occur.[58]

Evaluation of the Patient. Evaluation of the patient with valvular heart disease should focus on the pathophysiologic derangements and their effects on cardiac function. The systematic evaluation of primary valvular dysfunction should include the following:

1. *Category of valvular dysfunction*
   - Stenosis (progressive narrowing of the valve orifice)
   - Insufficiency (incomplete valve closure that causes backflow through the valve)
   - Mixed (regurgitant and stenotic dysfunction)
2. *Status of left ventricular loading*
   - Left ventricle (LV) overload from mitral or aortic regurgitation (AR)
   - Pressure overloading from aortic stenosis
   - Volume underloading from mitral stenosis
3. *Acute versus chronic evolution of the dysfunction*
   - Acute lesions have severe and precipitous hemodynamic consequences.
4. *Cardiac rhythm and its effects on ventricular diastolic filling time*
5. *Left ventricular function*
   - Poor left ventricular function places the patient at higher risk for perioperative cardiac morbidity.
6. *Secondary effects on the pulmonary vasculature and right ventricular function*
   - Secondary pulmonary hypertension from valvular lesions can significantly affect right ventricular function.
7. *Heart rate*
   - Changes in HR (either bradycardia or tachycardia) can significantly alter the hemodynamic manifestations of a specific valvular lesion.
   - Bradycardia occurring with regurgitant lesions can result in a significant increase in the regurgitant fraction.
   - Tachycardia is detrimental in patients with stenotic lesions because it shortens the time of ejection and increases myocardial oxygen demand.[27-30,33,34]
8. *Perioperative anticoagulation as discussed in Chapter 34*

Clinical Symptoms. The most frequent clinical signs and symptoms associated with valvular dysfunction are congestive heart failure, dysrhythmias, syncope, and angina pectoris. Symptoms commonly associated with congestive heart failure include dyspnea, orthopnea, and fatigue. The severity of left ventricular dysfunction can be related to the patient's activity level before the onset of cardiac symptoms.[35]

Patient Evaluation: Compensatory Mechanisms. To maintain cardiac function despite progressive valvular dysfunction, sympathetic activity increases to compensate for decreased peripheral perfusion. A decrease in sympathetic tone that occurs during anesthesia can cause severe myocardial dysfunction. Evaluation of the patient should include recognition of sympathetic compensatory mechanisms and strategies to maintain hemodynamic stability. Despite maximum medical therapy, patients with severe valvular dysfunction may remain in congestive heart failure.

The evaluation should also focus on associated organ dysfunction. Cardiac output that is decreased by chronic myocardial failure can cause significant major organ dysfunction, including renal and hepatic insufficiency, as well as poor cerebral perfusion, which can produce an altered level of consciousness, restlessness, agitation, and lethargy.

Diagnostic Modalities. The most valuable diagnostic modalities used to evaluate valvular heart disease include electrocardiography, chest radiography, color flow Doppler imaging, echocardiography, and cardiac catheterization of both the right and left chambers of the heart. Electrocardiography can be used for evaluation of ventricular hypertrophy, atrial enlargement, axis deviation and—most important—determining cardiac rhythm. Chest radiography demonstrates the size of the cardiac silhouette and signs of pulmonary vascular congestion. Color flow Doppler imaging can be used to determine the valvular area, transvalvular gradients, degree of regurgitation, and flow velocity and direction and can measure cardiac function. Cardiac catheterization can be used directly to measure transvalvular gradients, estimate the degree of regurgitation, visualize the coronary arteries, and determine intracardiac pressures.[59-63]

MITRAL STENOSIS

Pathophysiology

In mitral stenosis, the mitral valve orifice becomes progressively narrowed. The normal mitral valve area is 4 to 6 cm^2. This narrowing reduces flow from the LA into the LV during diastole. The narrowing of the mitral valve orifice has two significant hemodynamic consequences. First, a gradient develops across the valve orifice. This change represents a compensatory response directed at maintaining adequate flow. Second, as the cross-sectional area of the orifice decreases and the gradient increases, flow is restricted and left ventricular volume is decreased. The clinical symptomatology of severe mitral stenosis results in pulmonary congestion, decreased CO, and potentially RV overload/failure. Pulmonary congestion occurs as a result of increases in left atrial pressure. Decreased SV is caused by decreased left ventricular volume. Left ventricular filling is dependent on the length of diastole, the gradient between the LA and LV, and the surface area of the mitral valve. As the valve area narrows to 1.5 to 2.5 cm^2, patients frequently develop increased heart rate and cardiac output.[64] At a mitral valve area of less than 1 cm^2, the prolonged diastolic filling time and elevated mean left atrial pressure are incapable of maintaining normal LVEDV, and decreases in left ventricular volume occur, resulting in symptoms that occur at rest.[55] Atrial systole accounts for 20% to 30% of LVEDV. Because mitral stenosis presents a fixed resistance to ventricular inflow, most of the pressure generated during atrial systole is used to overcome the resistance caused by the stenotic valve rather than used for producing forward flow. As the HR increases to greater than 90 beats per minute and diastolic time intervals are shortened, LVEDV is decreased. This is demonstrated by the Gorlin equation, where mitral valve flow (MVF) is estimated using the following equation:

$$\text{MVF} = \frac{\text{Cardiac output}}{\text{Diastolic filling time} \times \text{heart rate}}$$

Any subsequent increase in flow rate or decrease in diastolic filling time reflects an increase in the pressure gradient between the LA and the LV. As the diastolic time interval shortens, the pressure gradient increases by the square of the increase in flow rate. Therefore any marked increase in HR can result in an increase in

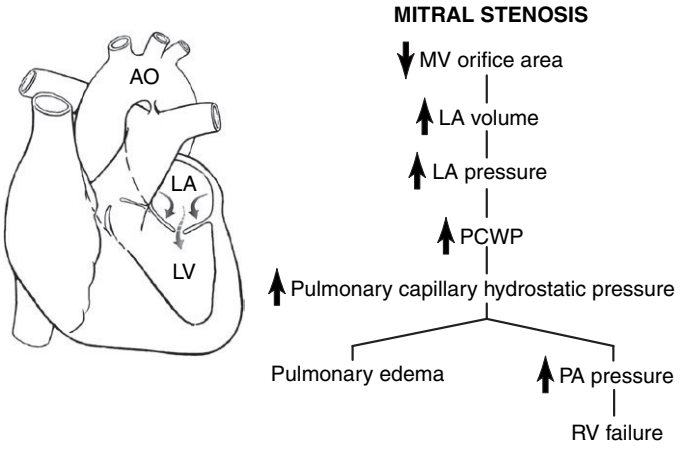

FIGURE **23-38** Pathophysiology associated with mitral stenosis.

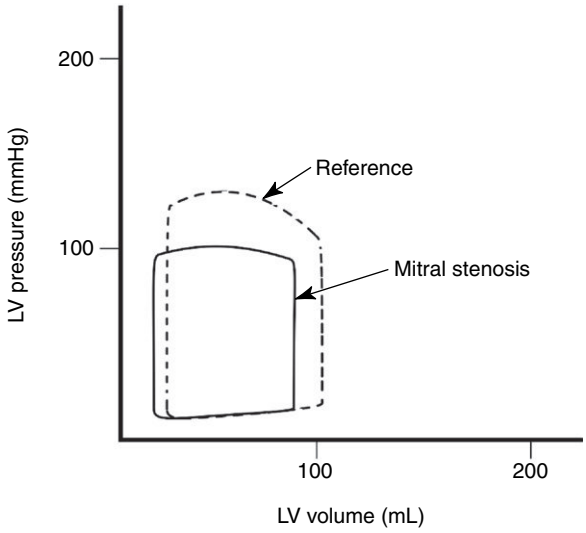

FIGURE **23-39** Left ventricular pressure-volume loop associated with mitral stenosis.

left atrial pressure, which can precipitate a rise in pulmonary artery pressures and ultimately leads to pulmonary edema.[65]

Left atrial hypertrophy and distention are consequences of elevated left atrial pressures. As a result of the increased left atrial pressure caused by mitral stenosis, the pulmonary capillary wedge pressure is artificially high, that is, overestimates the actual left ventricular end-diastolic pressure and left ventricular end-diastolic volume. This distention of the LA can lead to atrial dysrhythmias, most commonly atrial fibrillation. The atrial systolic "kick" is lost during atrial fibrillation; this implies that diastolic filling can be maintained only by a further increase in left atrial pressure. Mean left atrial pressure is limited by the development of pulmonary congestion at pressures greater than 25 mmHg. Elevation of left atrial pressures to greater than 25 mmHg leads to pulmonary congestion and eventually pulmonary edema. In patients with chronic mitral stenosis, pulmonary hypertension develops because of continuous elevations in left atrial pressure (Figure 23-38).

Pulmonary Vascular Changes in Right Ventricular Function

The pulmonary vasculature and eventually the RV are adversely affected by the chronic elevation of left atrial pressure that occurs with mitral stenosis. As mitral stenosis progresses, chronic elevation of left atrial pressure causes increased blood volume in the pulmonary vascular circuit. This can cause perivascular edema, and changes in pulmonary vascular resistance may ensue. These changes in pulmonary vascular resistance result in an increase in RV afterload. As a compensatory response, right ventricular hypertrophy occurs; however, because the RV is not capable of generating high pressures, it eventually begins to fail.[55-57] As the disease progresses, overt signs of biventricular failure such as low CO with poor systemic perfusion become evident. Peripheral edema, hepatic congestion, and marked venous distention are signs of right ventricular failure. The deterioration of right ventricular function decreases adequate left ventricular filling and therefore causes further deterioration in CO (Figure 23-39).

Anesthetic Considerations

Any anesthetic technique should be based on a thorough understanding of the pathophysiology of mitral stenosis, as well as the cardiovascular effects of the anesthetic agents employed. The following goals should be achieved in the anesthetic management of the patient with mitral stenosis:

- Maintenance of sinus rhythm at low normal heart rate.
- LVEDV adequate to maintain adequate CO without increasing pulmonary congestion.
- Avoid extreme decreases in myocardial contractility.
- Reduction in both right ventricular and left ventricular afterload may improve hemodynamics; this must be done in a controlled manner and with careful monitoring. The extent of the surgical procedure and the degree and severity of mitral stenosis determine the level of monitoring necessary.
- Cardioversion as treatment for atrial tachyarrhythmias that cause hemodynamic instability.
- Hypotension treated with small doses of phenylephrine.

The LVEDV is normal in approximately 85% of patients with mitral stenosis. An increased LVEDV in patients with mitral stenosis should alert the anesthesia provider to the presence of mitral or aortic insufficiency or primary coronary artery disease. Most patients with moderate mitral stenosis also have low to normal SV and therefore may have a normal EF. Approximately 33% of patients with mitral stenosis have an EF below normal (normal, 0.67 ± 0.08).[56] When the mitral valve is narrowed to less than 1 cm^2 (severe mitral stenosis), a mean left atrial pressure of 25 mmHg is necessary for maintaining even an adequate resting CO. Owing to the abnormal transvalvular gradient, the pulmonary capillary wedge pressure (PCWP) overestimates LVEDP. On the PCWP, a prominent *a wave* and a decreased *y descent* are present in patients with mitral stenosis.

MITRAL REGURGITATION AND INSUFFICIENCY

Pathophysiology

During ventricular systole, the mitral valve is closed, preventing blood flow from the LV back into the LA. However, if for any reason the two leaflets of the mitral valve are not in opposition to each other, a portion of systolic ventricular flow regurgitates back through this incompetent (insufficient) valve. Therefore the LV has a double outlet for systolic ejection. Ejection into the aorta is a high-impedance outlet, and regurgitation through the mitral valve back into the LA is a low-impedance outlet. This condition is termed *mitral regurgitation* (MR) or *mitral insufficiency*. The degree of regurgitation (quantitatively), called the *regurgitant fraction*, is determined by four factors:

1. Size of the regurgitant valve orifice (surface area measured in square centimeters)

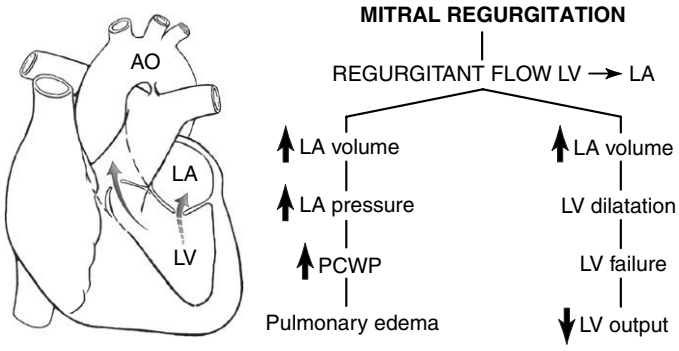

FIGURE **23-40** Pathophysiology associated with mitral regurgitation. *LA,* left atrium; *LV,* left ventricle; *PCWP,* pulmonary capillary wedge pressure.

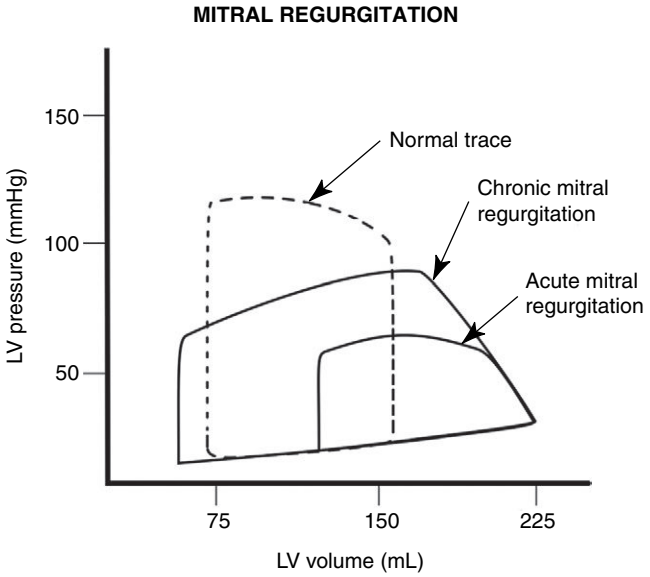

FIGURE **23-41** Left ventricular (LV) pressure-volume loop associated with mitral regurgitation. The large volume and stroke volume associated with chronic mitral regurgitation occur because of LV hypertrophy. Notice that during the isovolumetric contraction phase, LV volume decreases as a result of the incompetent mitral valve.

2. The pressure gradient between the LA and the LV
   - Inotropic state of the LV (peak systolic pressure)
   - Compliance of the LA and pulmonary veins
3. Time available for regurgitation (systole); systolic interval determines length of time during which regurgitation can occur; length of systolic time interval is inversely proportional to HR
4. Aortic outflow impedance SVR; regurgitant fraction can be significantly influenced by changes in impedance to aortic blood flow

The major pathophysiologic derangement associated with MR is volume overload of the LV. This occurs because the regurgitant fraction (retrograde blood flow ejected into the LA during ventricular systole) delivers an increased diastolic volume to the LV. This increase in LVEDV results in ventricular dilation.[44,55,65] Acute MR and chronic MR have substantially different pathophysiologic manifestations. The primary determinant of these pathophysiologic adaptations is left atrial compliance. If acute MR is caused by papillary muscle rupture, the mortality rate approaches 75% within 24 hours and 95% within 48 hours.[66] Chronic MR produces a dilated, compliant LA, whereas the longstanding and gradual elevation of left atrial pressure results in left atrial dilation. This consequently facilitates containment of relatively large end-diastolic volumes while reflecting relatively low increases in LA pressures (Figure 23-40). With chronic MR, compensatory hypertrophic changes occur in response to a continual increased left ventricular volume by increasing the left ventricular chamber size. This type of hypertrophic change is called *eccentric hypertrophy*.

In contrast, in acute MR the LA is small and noncompliant, but over time eccentric hypertrophic changes occur to compensate for progressive increases in volume (Figure 23-41). In this situation, a small regurgitant volume bolus can generate deflections or *v* waves that appear in the PCWP tracing. This *v* wave appears as a result of a systolic jet (ejection) back through the incompetent mitral valve. The pressure wave produced by this jet is transmitted upstream into the pulmonary artery and designated as a *pathologic v wave*. The time delay for this pressure wave to be transmitted results in its appearance at the time interval in which the normal *v* wave (passive atrial filling) occurs.[55] The height of the *v* wave in MR does not represent a measurement of regurgitant volume but rather of left atrial compliance in relationship to the regurgitated volume. The hypertrophic LA accommodates a larger regurgitant volume, which results in small increases in pressure. The dilated and compliant LA allows the pulmonary vascular circuit to be buffered from the excessive left atrial volume. However, chronic MR causes pulmonary venous congestion, which creates pulmonary vascular reactive changes that eventually result in pulmonary artery hypertension. Distention of the LA may lead to atrial fibrillation, a common arrhythmia associated with MR.

Pulmonary Vasculature and Right Ventricular Function

In acute MR, the pulmonary circuit is exposed to immediate and marked elevation of left atrial pressure because of a small and noncompliant LA. Pulmonary vascular congestion is precipitous and results in almost immediate development of pulmonary edema. An acute rise in left atrial pressure and congestion of the pulmonary circuit creates an increased right ventricular workload. This immediate increase in right ventricular afterload results in ventricular dilation and consequently may lead to right ventricular failure. In chronic MR, elevation of baseline pulmonary pressures is much more gradual, occurring over a prolonged period. This allows secondary pulmonary artery hypertension via intimal fibroelastosis generated by chronic perivascular edema. If the patient has coexisting mitral stenosis, pulmonary vascular resistance and right ventricular pressures may be excessively elevated.[44,55,65]

Effects of Afterload Reductions

The path of least resistance for blood flow during left ventricular systole is retrograde into the LA. Reduction of SVR via arterial vasodilation reduces impedance to systolic outflow into the aorta and increases forward flow. Conversely, increases in SVR have marked effects on the reduction in forward flow and the increase in the regurgitant fraction. A 20% increase in MAP raises LA pressure by 50% and reflects a 120% increase in regurgitant flow concurrent with a 16% decrease in forward flow.[55]

Anesthetic Considerations

An otherwise healthy patient with stable and controlled MR undergoing an ambulatory or uncomplicated surgical procedure has a minimal increase in risk of adverse hemodynamic fluctuations. Patients with cardiovascular disease who undergo major vascular, intrathoracic, intraabdominal, neurosurgical, orthopedic, or emergency procedures may have a 25% to 50% higher mortality risk than patients without the disease process. Controversy exists

regarding whether the duration of surgery correlates with perioperative cardiac morbidity.[35,54,55]

Preoperative assessment is essential for evaluating the degree of cardiac compensation (Table 23-9). Anesthetic management of the patient with MR should focus on these hemodynamic goals: decreasing regurgitant blood flow to enhance CO by decreasing afterload, maintaining or increasing preload, and maintaining cardiac contractility. Bradycardia or dysrhythmias that cause a loss of atrial kick can result in pulmonary congestion, left atrial and left ventricular overload, and a significant decrease in CO.[54-56]

Another anesthetic consideration of MR includes decreasing SVR or afterload. Cautiously lowering SVR via an arterial vasodilator such as sodium nitroprusside improves forward flow. However, extreme reductions in blood pressure, and especially diastolic pressure, can lead to decreased coronary artery blood flow and decreased CO.

Selection of the anesthetic technique should take into consideration the adverse effects associated with changes in HR and SVR. General anesthesia is the technique of choice in patients with MR. Regional anesthesia (spinal or epidural) is not contraindicated; however, the potential for profound and precipitous decreases in blood pressure via sympathetic blockade should be considered. Induction of general anesthesia can be safely achieved with any of the presently available agents. Hemodynamic goals include avoiding bradycardia and significant increases in afterload. The use of muscle relaxants does not present a significant risk as long as the resulting changes in HR do not cause severe bradycardia. The vagolytic properties of pancuronium may help to maintain HR. Maintenance of anesthesia can be accomplished with narcotics and a volatile agent. There is no definitive evidence to support that a particular volatile agent yields superior outcomes for patients with MR. Isoflurane may be an ideal choice because of its significant vasodilatory effects, causing an increased HR. Because all volatile agents cause a dose-dependent decrease in myocardial contractility, their use may be detrimental in patients with severe ventricular dysfunction. In this instance, the use of a high-dose opioid technique may provide for a more effective hemodynamic profile. Anesthetic management should focus on avoiding bradycardia or increases in SVR.[55] See Table 23-9 for anesthetic goals for management of mitral lesions.

TABLE 23-9 Hemodynamic Goals for Management of Mitral Valve Lesions

Parameter	Mitral Regurgitation (Insufficiency) Goal	Mitral Stenosis Goal
Heart rate	Increase	Decrease to normal
Rhythm	Maintain normal sinus rhythm	Maintain normal sinus rhythm
Afterload	Decrease	Maintain normal
Pulmonary vascular resistance	Avoid increases	Avoid increases
Preload	Normal to increased	Normal to increased

AORTIC STENOSIS

Etiology and Pathophysiology

The most common causes of aortic stenosis include a congenital defect resulting in a bicuspid aortic valve (especially in males) and the sequelae of rheumatic valvular heart disease. Isolated aortic valvular dysfunction in patients with rheumatic heart disease is rare. Commonly, rheumatic valvular disease is associated with mitral valve involvement. Whatever the cause, the pathophysiology remains the same and results in the need for increased left ventricular systolic pressure to overcome the left ventricular outflow tract obstruction caused by a narrowed aortic valve orifice (Figure 23-42). During auscultation, a low-frequency, systolic ejection murmur is characteristic of aortic stenosis.[67]

An understanding of the flow rates through a normal aortic valve orifice is needed for gaining an appreciation of ventricular pressure overload. A normal aortic valve area of 2.5 to 3.5 cm^2 and SV of approximately 80 mL result in a flow rate of 250 mL/min during the interval of ventricular systole (80 mL/sec × 0.32 sec − systolic time interval). The flow rate through a normal orifice results in a minimal gradient (2 to 4 mmHg). The normal left ventricular systolic pressure of 100 to 130 mmHg is sufficient to generate flow rates of 250 to 300 mL/sec. To ensure normal flow rates and therefore CO through the narrowed orifice, the velocity of systolic ejection must increase. For systolic ejection to be increased, ventricular systolic pressure increases dramatically, depending on the degree of valvular pathology. The LV must compensate for gradually increasing mechanical impedance to ejection. This results in LVH, which allows the heart to generate high ventricular systolic pressure and overcome impedance to ejection. The elevation of systolic ejection pressure produces a gradient between the left ventricular cavity and the aorta. The valve area must be constricted by at least 50% before the gradient becomes

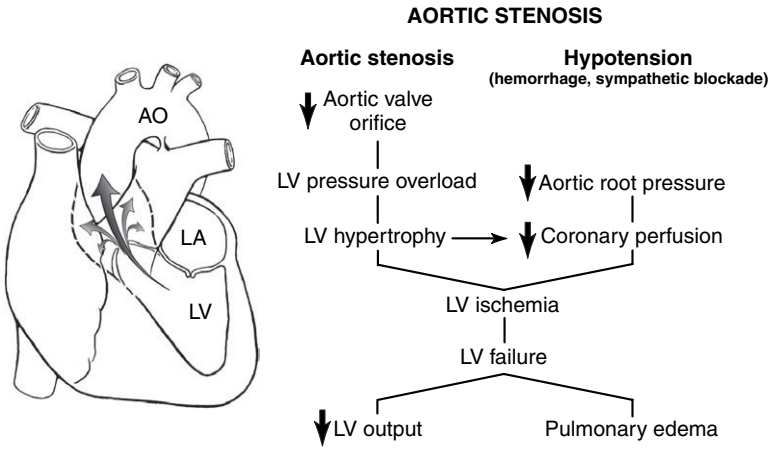

FIGURE 23-42 Pathophysiology associated with aortic stenosis. *LA*, left atrium; *LV*, left ventricle; *AO*, aorta.

significant to the point that symptoms occur at rest. An aortic valve area of less than 1 cm^2 produces a clinical triad of symptoms that include angina (even in the absence of significant coronary artery disease), syncope, and congestive heart failure.[65] An aortic valve area of less than 1 cm^2 represents severe aortic stenosis and should be a cause of concern in planning anesthetic management because of the associated increase in perioperative cardiac morbidity.[35] An aortic valve area less than 0.7 cm^2 is associated with sudden death.[68] For adequate assessment of the degree of valvular stenosis, both the flow rate across the valve and the pressure gradient should be evaluated, either by cardiac catheterization or echocardiography.[62,63]

Left Ventricular Function

Left ventricular concentric hypertrophy is the compensatory change associated with aortic stenosis. It results in several hemodynamic adaptations that are unique to aortic stenosis and present a challenge and a dilemma with regard to anesthesia management. The consequence of LVH in aortic stenosis is a decrease in ventricular compliance, hypertrophic remodeling, and an eventual decrease in the intrinsic contractility of the myocardium.[69] The reduction in ventricular compliance affects normal hemodynamics as follows:

I. Higher filling pressures are needed to produce the same amount of ventricular work.
II. To achieve adequate left ventricular filling, normal sinus rhythm must be maintained to ensure adequate LVEDV from the atrial kick.
III. Concentric ventricular hypertrophy causes alterations in myocardial oxygen balance.
   A. Myocardial oxygen consumption is increased.
      1. Myocardial mass is increased.
      2. Pressure generation (isovolumetric contraction) uses more energy than left ventricular ejection; a high intracavitary pressure must be generated to maintain CO.
      3. The ejection phase is prolonged.
   B. Myocardial oxygen supply is decreased.
      1. CPP is decreased as a result of an increase in LVEDP.
      2. Systolic coronary flow is absent because left ventricular systolic pressure exceeds aortic systolic pressure.
      3. Prolonged systolic ejection reduces the coronary perfusion interval.
      4. Subendocardial capillaries are compressed by hypertrophic myocardium.[44,54,55]

Pulmonary Circuit and Right Ventricular Responses

To maintain CO in the presence of a noncompliant and hypertrophic LV, left atrial pressures increase to accommodate left ventricular filling (Figure 23-43). Left atrial pressures of greater than 18 mmHg can cause an increase in pulmonary artery pressure, resulting in passive pulmonary venous congestion. Eventually, pulmonary fibroelastosis occurs, causing pulmonary artery hypertension. If the ventricular EF is decreased to less than 40% in association with aortic stenosis, CO can be maintained only with increases in left atrial pressures. These pressures increase to 25 to 30 mmHg, which results in increased mean pulmonary artery pressure. Elevated mean pulmonary artery pressure increases pulmonary vascular resistance, which can cause right ventricular failure. Decreasing left ventricular preload in association with significant aortic stenosis can result in decreases in CO.

Anesthetic Considerations

The goals of anesthesia management include maintaining hemodynamic stability without causing significant alterations in compensatory mechanisms. Anesthetic management of patients with aortic stenosis should focus on the following hemodynamic factors:

- Maintain normal sinus rhythm and HR 70 to 80 beats per minute
- Ensure sufficient preload (LVEDV) to maintain CO
- Ensure adequate coronary perfusion by maintaining diastolic blood pressure levels
- Avoid myocardial depression, especially with poor LV function
- Maintain or allow slight increase in afterload

General anesthesia is the preferred technique for major surgical procedures involving patients with aortic stenosis because of the ability to manipulate hemodynamic parameters, especially diastolic blood pressure. Central neural blockade (spinal or epidural) must be used with extreme caution, because precipitous reductions in blood pressure associated with a sympathectomy decrease SVR.[67] Epidural anesthesia offers the advantage of a slower onset of vasodilation. Depending on the degree of compromise, the heart may not be able to compensate for moderate to severe systemic vasodilation. Therefore lower dermatome level blocks decrease the degree of systemic vasodilation and maintain afterload. Successful cardiopulmonary resuscitation is virtually impossible because of the mechanical left ventricular outflow obstruction associated with this type of valvular pathology. The pressure necessary to overcome outflow obstruction and produce adequate coronary artery perfusion and CO cannot be generated with closed-chest compressions. Furthermore, short periods of hypotension may lead to a decrease in coronary perfusion and should be treated with volume and phenylephrine.[70] Because of the increased oxygen demands of the LV, irreversible myocardial ischemia and cardiovascular collapse can occur if hypotension is not promptly and aggressively treated.

Intraoperative control of HR and rhythm is a major goal of the anesthetic management of patients with aortic stenosis. Tachycardia can be detrimental because it decreases diastolic filling time, resulting in a reduction of left ventricular preload. The reduced time interval for coronary artery perfusion reduces oxygen supply to the myocardium. In patients with HRs of greater than 110 beats per minute, systolic ejection time and CO are decreased.[55,56] Bradycardia (fewer than 60 beats per minute) is detrimental in aortic stenosis. Prolonged diastolic filling time, which occurs as a result

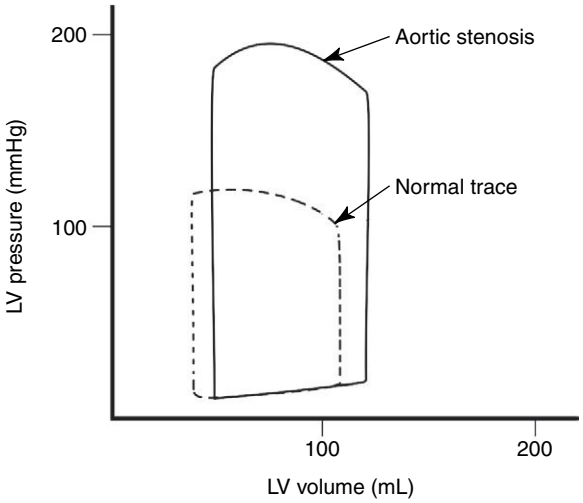

FIGURE **23-43** Left ventricular pressure-volume loop associated with aortic stenosis.

of bradycardia, causes ventricular distention, which can further decrease CPP, especially to the subendocardium.[44,54,55]

Monitoring and Premedication

It is prudent to titrate preoperative sedatives while vital signs can be continuously monitored. In addition to standard intraoperative monitoring, complete invasive monitoring may be required for patients with aortic stenosis, even for routine procedures. Any significant change in basic hemodynamic variables (i.e., HR, heart rhythm, LVEDV, CPP) can rapidly cause irreversible myocardial deterioration. It is imperative that these variables be monitored closely and appropriate interventions be performed to prevent adverse hemodynamic consequences. The complexity of hemodynamic monitoring modalities is dependent on the physical status of the patient, the severity of aortic stenosis, the extent of the surgical procedure, and the ability of the anesthesia provider to use and interpret hemodynamic values.

The use of intraarterial monitoring for direct beat-to-beat blood pressure assessment allows the anesthesia provider to rapidly treat undesirable hemodynamic changes. Pulmonary artery catheterization provides the ability to monitor all the hemodynamic parameters necessary for diagnosing and treating adverse hemodynamic events. Absolute criteria for intraoperative invasive monitoring for patients with aortic stenosis are controversial. However, clinical judgment, experience, and the ability to appropriately use the pulmonary artery catheter should be considered before implementation.[68,71]

Maintenance of Anesthesia

Commonly used induction agents can be given so long as caution to avoid profound hypotension is exercised. Tracheal intubation can be performed with any of the available muscle relaxants, but caution must be exercised to avoid histamine release, which can dramatically increase HR. Anesthetic maintenance can be accomplished with the use of a volatile agent in conjunction with nitrous oxide, opiates, or both. The adverse cardiovascular effects of the volatile agents must be considered before these drugs are used. Higher concentrations of inhaled agent result in greater degrees of myocardial depression and vasodilation. Volatile agents must be used with caution, because the myocardial depressant effect can be deleterious in patients with impaired ventricular function. The use of higher-dose opioid-based techniques is an alternative anesthetic approach that may help achieve cardiovascular stability without causing a significant amount of myocardial depression. Finally, a combination of inhaled agents and narcotics has been used safely to provide anesthesia for patients with aortic stenosis. Whatever the anesthetic technique chosen for patients with aortic stenosis, immediate and aggressive treatment of adverse changes that occur in HR and rhythm, SVR, blood pressure, and LVEDV is paramount if successful anesthetic outcomes are to be achieved.[68,71]

AORTIC INSUFFICIENCY

AI, also known as *aortic regurgitation*, can be classified as acute or chronic and as primary or secondary, depending on the cause. Primary *chronic* AI is caused by rheumatic valvular disease and almost always involves the mitral valve to some degree. Primary *acute* AI usually is caused by infective endocarditis, which is caused by direct damage to the valve cusps. Acute secondary (functional) AI results from aortic root dissection caused either by trauma or aneurysm and results in a mechanical and functional impairment of functional aortic valve closure.

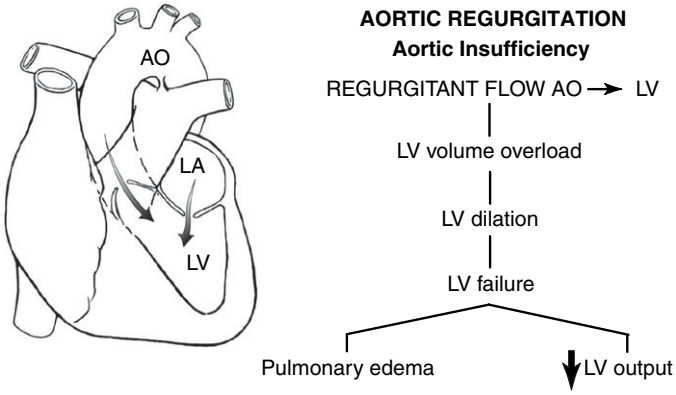

FIGURE **23-44** Pathophysiology associated with aortic regurgitation. *AO*, Aorta; *LA*, left atrium; *LV*, left ventricle.

Pathophysiology

The major hemodynamic aberration related to AI occurs during diastole. A portion of the blood volume ejected from the LV into the aorta regurgitates back into the ventricle because of incomplete closure of the aortic valve. Aortic insufficiency causes volume overload of the LV. Chronic ventricular overload causes eccentric ventricular hypertrophy and chamber dilation (Figure 23-44). The degree of regurgitation depends on three factors: the diastolic time available for regurgitation to occur, the diastolic pressure gradient between the aorta and the LV, and the degree of incompetence of the aortic valve.[65,68]

Diastolic time and diastolic pressure can be manipulated during the course of anesthesia so that the amount of regurgitant flow is decreased and the amount of forward flow is increased. An HR of 90 to 110 beats per minute and decreases in diastolic time interval occur and thereby reduce the time available for regurgitation. Reducing SVR reduces aortic diastolic pressure and decreases the gradient between the aorta and the LV. Unique pathophysiologic adaptations differentiate chronic AI from the acute form. In chronic AI, the LV has had time to compensate for the increased volume. In time, LV hypertrophy allows the LV to tolerate significant increases in volume without dramatic decreases in EF.[44,55] In situations in which the onset of AI is acute, the LV has inadequate time to adapt to volume overload, which renders compensatory mechanisms ineffective (Figure 23-45). Frequently, left ventricular failure, pulmonary edema, and cardiovascular collapse occur. Left ventricular end-diastolic pressure rises precipitously in acute AI because of the inability of the LV to alter its compliance.

Patients with chronic AI can remain asymptomatic for long periods. Except during times of stress, the clinical symptoms associated with chronic AI are usually not incapacitating. End-stage AI is characterized by myocardial failure with decreased CO and precipitous elevation of LVEDV with evidence of pulmonary congestion. As long as ventricular hypertrophy and dilation do not affect the mitral valve, the pulmonary circulation is not affected by the pathophysiologic changes associated with AI. Increased myocardial oxygen consumption occurs because of the development of eccentric hypertrophy. The decrease in aortic diastolic pressure that results from AI reduces coronary flow and can cause subendocardial ischemia. In acute AI, a precipitous increase in LVEDP with a decrease in aortic diastolic pressure can severely compromise coronary blood flow and result in acute myocardial ischemia. The RV and pulmonary vascular circuit usually are spared in chronic AI until secondary (functional) MR occurs. This results in dilation of the mitral valve annulus. A gradual increase in LA pressure and pulmonary artery pressure caused by functional MR eventually causes pulmonary hypertension; right ventricular failure can occur

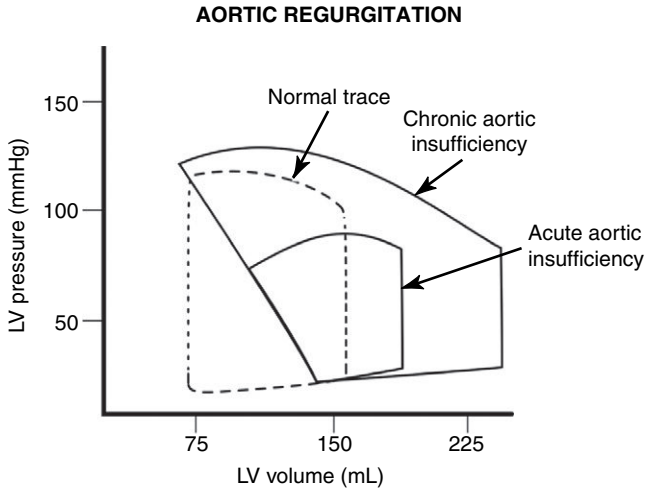

FIGURE **23-45** Left ventricular (LV) pressure-volume loop associated with aortic insufficiency. Increased LV pressure, volume, and stroke volume are associated with chronic aortic insufficiency and are reflective of LV hypertrophy. Notice that during the relaxation phase, as isovolumetric relaxation occurs, LV volume increases as a result of the incompetent aortic valve.

if pulmonary hypertension becomes severe. In acute AI, functional MR is poorly tolerated, owing to a noncompliant LA. This situation leads to immediate pulmonary vascular congestion and pulmonary edema. Patients with asymptomatic AI have a 0.2% annual mortality rate as compared with symptomatic patients, who have a greater than 10% mortality rate per year.[72] Therefore when evidence suggests that increases in left ventricular volume result in left ventricular dysfunction, aortic valve replacement is recommended.

Anesthesia Management

The goals for anesthesia management are to increase forward flow and decrease the degree of regurgitation and therefore should focus on the following hemodynamic factors:

- Heart rate should be maintained slightly higher than normal (80 to 110 beats per minute).
- Afterload (especially diastolic pressure) should be decreased.
- Avoid myocardial depression.
- Maintain normal sinus rhythm (NSR).
- Maintain/increase preload.

Central neural blockade is an appropriate anesthetic choice, depending on the invasiveness of the surgical procedure. Reduction in SVR resulting from sympathetic blockade may reduce the degree of regurgitation. The potential for immediate and uncontrolled hypotension during spinal anesthesia is a concern. However, spinal and epidural anesthesia has been used successfully for patients with AI. Induction of general anesthesia can be accomplished with any of the available intravenous agents. Tracheal intubation can be achieved with the use of available nondepolarizing muscle relaxants. As mentioned in the anesthetic management for patients with mitral regurgitation, the vagolytic properties associated with pancuronium are desirable and may offset the vagotonic effects of narcotics. Succinylcholine may be used, but its potential to cause bradycardia (although rarely) must be considered. Maintenance of anesthesia can be achieved with nitrous oxide and a volatile agent. Isoflurane, with its ability to increase HR and decrease SVR, produces little myocardial depression in lower doses, and therefore its use is preferred over use of other volatile agents. If significant ventricular dysfunction exists, an opioid-based anesthetic technique may be preferable.[52,55,56]

TABLE 23-10 Hemodynamic Goals for Management of Aortic Lesions

Parameter	Aortic Regurgitation (Insufficiency) Goal	Aortic Stenosis Goal
Heart rate	Moderate increase	Normal to slow
Heart rhythm	Normal sinus rhythm	Normal sinus rhythm
Afterload	Decrease	Maintain to slight increase
Pulmonary vascular resistance	Maintain	Maintain
Preload	Normal to increased	Increased

Monitoring and Premedication

Unless end-stage AR or significant preoperative ventricular dysfunction exists, aggressive invasive monitoring is not warranted. However, if the surgical procedure is extensive or if vasodilators or inotropes are being used, then an arterial line and a pulmonary artery catheter should be used for assessing the results and efficacy of these therapeutic agents. Premedication should be tailored to the patient's clinical condition. In elderly or debilitated patients, a conservative amount of premedication in a monitored environment should be titrated until effective.

Appropriate anesthetic management of the patient with valvular heart disease requires a basic knowledge of cardiac physiology and the pathophysiologic changes that occur with valvular dysfunction. The cardiovascular effects of all the agents, techniques, and adjunct pharmacologic agents used during anesthesia must be integrated into the anesthetic plan. A thorough understanding of the use of invasive monitoring along with other sophisticated diagnostic modalities enables the clinician to continuously monitor hemodynamic parameters. Contemporary anesthesia practice has allowed patients with severe valvular dysfunction to undergo surgical procedures that would not have been performed a decade ago.[68] Table 23-10 lists anesthetic goals for management of aortic lesions.

MITRAL VALVE PROLAPSE

Description and Etiology

The incidence of mitral valve prolapse, which was thought to be present in 5% to 15% of the U.S. population, is presently estimated at 1.6% to 2.4% of adults.[72] A familial predisposition exists, and women are three times more likely than men to develop mitral valve prolapse. Other conditions frequently associated with mitral valve prolapse include pectus excavatum and kyphoscoliosis. Symptoms are general and include weakness, dizziness, syncope, atypical chest pain, and palpitations. Atrial and ventricular dysrhythmias are common findings in asymptomatic patients. A diagnosis of mitral valve prolapse is confirmed through echocardiography. Most patients with this condition remain undiagnosed. Despite its benign nature, mitral valve prolapse can produce potentially life-threatening complications. Premature ventricular contractions are the most common dysrhythmia associated with mitral valve prolapse. Prolonged periods of ventricular tachycardia occur in approximately 21% of patients with mitral valve prolapse. Mitral valve prolapse is also the most common cause of isolated MR. Supraventricular tachyarrhythmias and bradycardia associated with AV block may occur. Medical therapy for mitral valve prolapse consists primarily of the use of β-blocking drugs, which are thought to inhibit an autonomic imbalance that exists in women with mitral valve prolapse. Additionally, β-blocking

TABLE 23-11 Hemodynamic Goals for Management of Mitral Valve Prolapse

Parameter	Goal
Preload	Maintain or increase
Afterload	Maintain
Contractility	Maintain
Heart rate	Maintain
Heart rhythm	Normal sinus rhythm

drugs may increase end-diastolic volume and thereby decrease the degree of prolapse. The majority of patients with mitral valve prolapse do not require medical or pharmacologic management, which reflects the asymptomatic nature of this relatively common valvular abnormality (Table 23-11).[33,71]

Pathophysiology and Unique Problems

The pathophysiologic changes that occur in mitral valve prolapse primarily affect the cusps and the chordae tendineae. Involved is a myxomatous degeneration of the valve cusps that replaces normal fibrous tissue. Also, this myxomatous degeneration affects the chordae tendineae and causes them to become pliable and elongated. The valve leaflets become supple and redundant, as the valve everts into the LA during systole.[73]

Mitral valve prolapse is undiagnosed in the majority of patients. A manifestation that commonly occurs in healthy patients who are receiving anesthesia is an unexpected dysrhythmia (e.g., premature ventricular contractions), many of which resolve spontaneously. Lidocaine does not always terminate the premature ventricular contractions for patients with mitral valve prolapse. β-Blockers are the best choice for control of dysrhythmias in patients with mitral valve prolapse. Hemodynamic events and certain positions tend to exacerbate the degree of mitral valve prolapse and dysrhythmias. Hemodynamic changes that cause a decrease in ventricular preload and increase the incidence of eversion of the mitral valve are caused by increased myocardial contractility, decreased SVR, head-up or sitting positions, use of drugs that decrease ventricular preload (e.g., nitroglycerin and sodium nitroprusside), and hypovolemia.

Pharmacology

Preoperative anxiety stimulates the sympathetic nervous system and can increase the degree of mitral valve prolapse and concomitant dysrhythmias. Decreasing anxiety can reduce the sympathetically mediated responses and improve the hemodynamic profile characteristic of mitral valve prolapse. Anticholinergics can cause tachycardia and should therefore be omitted from the preoperative regimen.

Anesthetic Management

Regional anesthesia is an acceptable anesthetic technique for patients with mitral valve prolapse. SVR should be maintained slightly above normal, even in the presence of sympathetic blockade. General anesthesia is an appropriate choice and may be preferred in many instances. Whichever technique is chosen, it is important that preload be maintained. Induction of anesthesia can be accomplished with any of the available intravenous agents. Ketamine, with its ability to stimulate the sympathetic nervous system, should not be used in patients with mitral valve prolapse. Use of a volatile agent alone or in combination with opioids is appropriate for maintenance of anesthesia. Muscle relaxants that have a stable cardiovascular profile can be used. Because of the vagolytic effects of pancuronium, tachycardia and stimulation of the sympathetic nervous system can occur. These cardiovascular effects can be minimized if the drug is administered slowly.[73] Antibiotic prophylaxis is recommended for patients with mitral valve prolapse because of the potential for endocarditis. Currently the American Heart Association has guidelines for antibiotic prophylaxis in surgical patients with valvular disease. All patients who have valvular dysfunction or prosthetic valves are candidates for antibiotic prophylaxis.[74]

CARDIOMYOPATHY

Cardiomyopathy is a general term used to describe specific but distinct cardiac pathology that can ultimately result in fatal dysrhythmias, severely decreased stroke volume, progressive cardiac disability, and sudden cardiac death. All forms of cardiomyopathy can result in congestive heart failure and death. Cardiomyopathy means heart muscle disease and can be categorically differentiated by a general pathologic cause as either extrinsic or intrinsic. Intrinsic cardiomyopathy is described as decreased contractile state of the heart muscle that cannot be attributed to a specific external causative factor. In contrast, the cause of extrinsic cardiomyopathy can be directly attributed to a disease process or toxin that adversely damages cardiac muscle. Factors that can cause extrinsic cardiomyopathy include but are not limited to ischemia, chronic inflammation, congenital heart disease, metabolic diseases (e.g., hemochromatosis), and toxins (e.g., chronic alcohol intake, chemotherapeutic agents). Frequently, histologic findings consistent with cardiomyopathies include myocyte hypertrophy, degradation of the cardiac cytoskeleton, and cellular fibrosis. The four major types of cardiomyopathy include dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), restrictive cardiomyopathy (RCM), and arrhythmogenic right ventricular cardiomyopathy (ARVC). Frequently the discovery of significant cardiomyopathy is accomplished post mortem because sudden cardiac death commonly occurs in those with cardiomyopathy. A discussion of various types of cardiomyopathies, signs and symptoms, and anesthetic implications are included below.

Frequently patients with severe cardiomyopathy have surgery for cardiac procedures such as pacemaker implantation or heart transplantation. A thorough preoperative evaluation is essential to create a comprehensive anesthetic plan that is individualized. In addition to physical examination, a determination of the patient's preoperative medication regimen and assessing the degree of compliance with his or her medications is a component part of medical optimization. A detailed analysis of the invasive and noninvasive cardiac studies including TEE and the cardiologist's impression of the patient's cardiac status is vital. An understanding of the specific cardiomyopathologic differences is necessary for prudent management.

Hypertrophic Cardiomyopathy

Cardiomyopathy is a compensatory enlargement of the heart. Hypertrophic cardiomyopathy, a genetically transmitted disorder, is a form of myocardial dysfunction that can cause coronary artery disease, valvular dysfunction, ventricular remodeling, and hypertension. The incidence in the adult population is approximately 1 in 500 persons.[75] Obstructive HCM has previously been referred to as *idiopathic hypertrophic subaortic stenosis*. Currently the preferred term used to describe this pathologic state is *HCM with or without left ventricular outflow obstruction*.[76]

A summary of the pathophysiology, signs and symptoms, and anesthetic considerations is listed in Table 23-12.

TABLE 23-12 Pathology and Anesthetic Considerations for Various Cardiomyopathies

Cardiomyopathy	Distinctive Features	Signs and Symptoms	Anesthetic Considerations
Dilated	Eccentric left and right ventricular hypertrophy causing systolic and diastolic dysfunction	Chest pain Jugular venous distention Weakness Exercise intolerance Rales Tachycardia Pulsus alternans Atrial fibrillation Atrial and ventricular dysrhythmias Atrioventricular valve regurgitation X-ray–pulmonary venous congestion/spherical appearance of LV/cardiomegaly	Promote afterload reduction Avoid large fluid bolus Choose anesthetic techniques, agents that minimize myocardial depression
Restrictive	Stiff and noncompliant ventricles decrease ventricular end-diastolic volume despite near-normal systolic function	Dyspnea Fatigue Cardiomegaly Atrioventricular valve regurgitation JVD Pulmonary hypertension Rales	TEE and invasive hemodynamic monitoring IV inotropic support may be necessary Choose anesthetic techniques, agents that minimize myocardial depression
Hypertrophic	Left ventricular hypertrophy resulting in decreased LV chamber size and LV outflow tract obstruction	Chest pain Shortness of breath Palpitations Rales Systolic murmur (S_3 and S_4) Ventricular dysrhythmias Syncope	Ensure adequate preload Myocardial depression is desirable Maintenance of normal sinus rhythm Avoid tachycardia Ensure adequate depth of anesthesia
Arrhythmogenic right ventricular	Fatty tissue infiltrates; dilation and outflow tract obstruction of the right ventricle	Tachycardia Ventricular dysrhythmias (ventricular tachycardia, ventricular fibrillation) T wave inversion (leads V_1 and V_3) Bundle branch block Hypokinetic right ventricle Decreased right ventricular ejection Jugular venous distention Syncope Peripheral edema	Treat events that cause moderate to severe sympathetic nervous system predominance Monitor and treat hemodynamically compromising ventricular dysrhythmias with amiodarone

JVD, Jugular venous distention; *LV,* left ventricle; *TEE,* transesophageal echocardiography.

Pathophysiology

Hypertrophic cardiomyopathy is the most common cause of sudden death in the pediatric and young adult populations.[77] The major cardiac changes associated with HCM include: (1) ventricular hypertrophy, (2) decreased ventricular chamber size, (3) increased ventricular wall thickness, and (4) impaired ventricular relaxation. The myocardial defect associated with HCM is related to the contractile mechanism. An increase in the density of calcium channels is one abnormality that appears to lead to myocardial hypertrophy. Asymmetric hypertrophy of the interventricular septum of the LV occurs. It has been determined that there is a genetic predisposition to developing HCM. Patients with HCM and sarcomere myofilament mutations have a greater degree of microvascular impairment, an increased incidence of myocardial fibrosis, and impaired myocardial remodeling.[78] The asymmetric hypertrophy of the intraventricular septum causes a left outflow tract obstruction, and the hemodynamic consequences are similar to those that are characteristic of aortic stenosis. Coronary arterial walls are narrowed because of the presence of collagen. If the entire myocardium is involved, a disproportionate hypertrophy of the intraventricular septum exists. The contraction of the hypertrophic septum bulging into the subaortic area of the left ventricular outflow tract creates a dynamic gradient. The left ventricular outflow tract is bounded anteriorly by the intraventricular septum and posteriorly by the anterior leaflet of the mitral valve. The rapid acceleration of blood traveling through the narrowed outflow tract creates a Venturi effect, which pulls the anterior mitral valve leaflet into the outflow tract. A LV outflow tract obstruction is present in approximately two thirds of patients with hypertrophic cardiomyopathy.[79] The systolic anterior motion of the anterior mitral valve leaflet further obstructs left ventricular outflow. The valve leaflet may even contact the septum and further compromise left ventricular outflow.[67]

The pathophysiologic abnormalities related to HCM include the presence of systolic and diastolic dysfunction. A loss of diastolic compliance results in an abnormally elevated LVEDP in the presence of low-normal end-diastolic volume. Loss of left ventricular diastolic compliance requires a greater contribution of volume from atrial contraction. As a result, congestive heart failure may ensue as left atrial pressures continue to increase.[68] Because as much as 75% of left ventricular preload comes from the LA, maintenance of normal sinus rhythm is critical for adequate SV. The increase in LVEDP, which results from a noncompliant LV, decreases CPP to the hypertrophic LV. Altered coronary perfusion

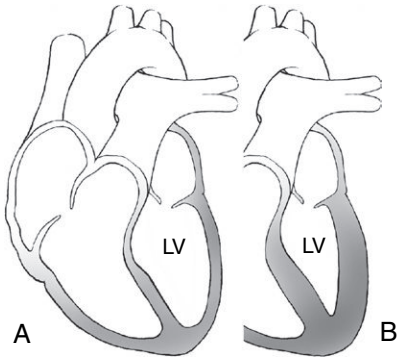

FIGURE **23-46** **A,** Normal left ventricular outflow tract. **B,** Hypertrophic cardiomyopathy with an enlarged interventricular septum and decreased left ventricular chamber size. A further decrease of left ventricular outflow is caused by migration of the anterior mitral leaflet toward the septum.

decreases myocardial blood supply, and the presence of left ventricular hypertrophy increases myocardial oxygen demand. Thickening of the internal lumen of the coronary arteries decreases myocardial perfusion, leading to ischemia.[79]

Hypertrophic cardiomyopathy with obstruction is characterized by its dynamic nature. Three basic hemodynamic parameters can affect the degree of left ventricular outflow tract obstruction. Manipulation of these parameters can exacerbate or ameliorate the hemodynamic consequences of outflow obstruction. These three parameters include preload, afterload, and contractility.[33] Increasing myocardial contractility in patients with HCM exacerbates the obstruction by increasing septal wall contraction and decreasing CO. Increased blood flow velocity causes a greater degree of systolic anterior motion of the mitral valve's anterior leaflet, creating further obstruction. Decreased preload changes left ventricular geometry and thereby brings the anterior leaflet of the mitral valve into closer proximity to the hypertrophic septum. Increases in left ventricular contractility cause the LV to empty more completely and increase the degree of septal contractility, which results in a greater degree of obstruction.[76] A summary of the signs and symptoms is included in Table 23-12.

In HCM with outflow tract obstruction, conditions that impair ventricular function under normal physiologic conditions improve cardiac function. This implies that factors that normally impair contractility (e.g., myocardial depression, increased end-diastolic volume, and increased SVR) improve forward flow and diminish the degree of obstruction. Figure 23-46 illustrates the pathology related to HCM.

Anesthetic Considerations

Anesthetic management should focus on strategies that alleviate and do not increase left ventricular outflow obstruction. It is imperative that adequate or slightly elevated left ventricular volume be maintained. Measures that decrease venous return and interfere with adequate ventricular preload should be avoided. Factors that increase myocardial contractility should be avoided. Inadequate depth of anesthesia that causes sympathetic nervous system stimulation may be detrimental. In the event that hypotension occurs, adequate perfusion pressure should be maintained by increasing preload with fluid administration and increasing SVR with phenylephrine.

Pharmacologic therapy used to treat HCM (including β-blockers and calcium channel blockers) should be continued until the time of surgery.[15] β-Blockers may be administered intraoperatively to reduce HR and contractility. Dysrhythmias must be avoided and immediately treated if they occur; the atrial contribution to left ventricular volume is necessary to maintain CO.[71,76] Table 23-13 lists hemodynamic goals for patients with HCM.

TABLE 23-13 Hemodynamic Goals for Management of Hypertrophic Cardiomyopathy

Parameter	Goal
Preload	Increase
Afterload	Increase
Contractility	Decrease
Heart rate	Maintain
Heart rhythm	Normal sinus rhythm

Anesthetic management must focus on increasing left ventricular preload, decreasing myocardial contractility, controlling HR, and maintaining or increasing afterload. Regional anesthesia is not contraindicated in patients with dilated cardiomyopathy. Decreases in blood pressure must be treated immediately. Hypovolemia must be avoided and expeditiously treated if it occurs. Deep general anesthesia with a volatile agent is preferred in patients with HCM and obstruction.

The potential for hemodynamic deterioration because of increasing subaortic obstruction along with secondary MR necessitates aggressive hemodynamic monitoring. Invasive monitoring via a pulmonary artery catheter allows for maintenance of adequate LVEDV. Because of reduced diastolic compliance associated with HCM, PCWP does not accurately correlate directly with LVEDV. The PCWP should be maintained at approximately 18 to 25 mmHg. If the hemodynamic status deteriorates and exacerbation of outflow obstruction is suspected, β-blocking drugs (propranolol, metoprolol or esmolol) should be administered. In addition, vasoconstrictors such as phenylephrine should be used to increase SVR.[33]

Dilated Cardiomyopathy

Dilated cardiomyopathy (DCM) is the most common form of cardiomyopathy, and it most often occurs in adults.[80] As with HCM, there is believed to be a genetic link for those people who develop this cardiac pathology. Between 20% and 30% of DCM cases are caused by an autosomal dominant mutation resulting in abnormal cardiac cytoskeleton protein generation.[78] DCM can also occur in patients as a result of autosomal recessive traits, such as in patients with Duchenne muscular dystrophy. When genetic predisposition is not the cause, the specific etiology has not been definitively determined but is not limited to a viral illness, increased inflammation from metabolic abnormalities, autoimmune mechanism, or toxins. It occurs more often in men than in women and is attributed to being a significant risk factor for developing congestive heart failure. For women who develop congestive heart failure during pregnancy, peripartum cardiomyopathy is associated with higher maternal and neonatal mortality.[81] A summary of the pathophysiology, signs and symptoms, and anesthetic considerations is listed in Table 23-12.

Pathophysiology

In DCM, eccentric hypertrophy affects both left and right ventricles. As cardiac cytoskeleton uncoupling occurs, caused by interstitial fibrosis and myocardial cell death, the ventricular chambers increase in size without an associated increase in the diameter of the ventricular walls or interventricular septum. The law of Laplace, as

shown in the following equation, helps us describe why the heart becomes an inefficient pump for patients with DCM. Tension on the ventricular walls is increased due to the decreased size and increased diameter of the ventricular walls. After a period when increased ventricular volumes induce compensatory eccentric hypertrophic changes, impaired systolic function (decreased stroke volume) occurs because of the loss of myocardium causing decreased contractility. Myocardial oxygen consumption is increased as ventricular end-diastolic volume and pressure are increased.

$$T = (P \times R) / M$$

$$T = \text{tension},\ P = \text{pressure},\ R = \text{radius},\ M = \text{wall thickness}$$

This pathologic process does not cause direct damage to the atrioventricular valves. However, as ventricular dilation occurs, changes in ventricular dimensions can cause mitral valve and/or tricuspid valve regurgitation potentially intensifying volume overload, decreased stroke volume, and increased pulmonary congestion.

As the ejection fraction decreases, decreased peripheral perfusion causes increased circulating catecholamines, cortisol excretion, and activation of the renin-angiotensin-aldosterone system, which causes vasoconstriction and increased renal absorption of fluid. Left-sided heart failure resulting in pulmonary venous congestion or biventricular failure leads to fulminant congestive heart failure. These patients are at increased risk of thromboembolism as a result of stasis of blood from inadequate ventricular emptying.

Anesthetic Considerations

Pharmacologic medical treatment for patients with DCM include diuretics, ACE inhibitors, and digoxin. Other interventions for moderate to severe DCM include dual chamber pacing, cardiomyoplasty, or use of a left ventricular assist device. Because of the potential for severely compromised ventricular performance, minimizing myocardial depression is essential. Afterload reduction is important to promote forward blood flow through the heart. As a result, neuraxial anesthesia is an acceptable anesthetic technique for patients with DCM.[82] Narcotics are a common choice for patients with cardiomyopathy because they do not have a direct effect on myocardial contractility. However, patients with DCM who have a severely compromised ejection fraction depend on sympathetic nervous system innervation to augment their cardiac output. Therefore incremental titration of narcotics is warranted. Etomidate is an appropriate choice of induction agent because of the lesser amount of myocardial depression as compared to propofol. Because all inhalation agents cause myocardial depression in a dose-dependent fashion, titration of inhalation agents and adjusting concentrations based on blood pressure, central venous pressure, and pulmonary capillary wedge pressure is indicated.[78]

Restrictive Cardiomyopathy

The term *restrictive cardiomyopath*y (RCM) represents several types of pathologic conditions depending on whether the myocardium or endomyocardial muscle layer is affected. Causes of myocardial RCM include genetic predisposition (e.g., familial cardiomyopathy), infiltrative disease (e.g., sarcoidosis), storage diseases (e.g., hemachromotosis), and endomyocardial dysfunction (e.g., endomyocardial fibrosis). RCM can occur in the pediatric population; however, it is one of the rarest forms of cardiomyopathy that occurs in children. It is associated with a high mortality rate once symptoms begin to develop.[83] A summary of the pathophysiology, signs and symptoms, and anesthetic considerations is listed in Table 23-12.

Pathophysiology

Infiltration of fibrous tissue and deposition into the myocardium and or endomyocardium is the pathologic mechanism by which RCM develops. As a result, one or both ventricles become stiff and noncompliant, which inhibits normal diastolic filling. As a result of reduced end-diastolic volume (reduce ventricular preload) caused by restricted ventricular filling, stroke volume is decreased. An increase in the sensitivity of the troponin and tropomyosin complex of calcium-mediated myofilament is thought to be the cause of genetically derived RCM.[84] Systolic ejection remains relatively normal. The atria become dilated as a compensatory response to volume overload, and left- and/or right-sided heart failure can occur. Significantly elevated RA pressures (15 to 20 mmHg) and pulmonary artery systolic pressure (as high as 50 mmHg) can occur as the disease progresses.[80]

Anesthetic Considerations

Medical management for RCM is similar to DCM and includes use of diuretics, sodium and water restriction, anticoagulation agents, and treatment of dysrhythmias. Maintenance of normal sinus rhythm, adequate preload, and minimal myocardial depression is essential to anesthetic management. As with DCM, an anesthetic technique that minimizes myocardial depression, which is accomplished using higher doses of narcotic as compared to inhalation agents, may be prudent. Results from studies are often conflicting regarding the degree of myocardial depressant effects of modern inhalation agents (isoflurane, sevoflurane, desflurane) in relation to cardiomyopathy and impaired systolic ejection and diastolic relaxation.[85,86] Patients with moderate to severe cardiomyopathy depend on sympathetic nervous system activity to augment myocardial performance. Despite the minimal direct myocardial depressant effects of narcotics, their inhibition of the sympathetic nervous system has an indirect depressant effect on the heart. Thus titration of narcotics and assessment of the patient's hemodynamic status is important.

Arrhythmogenic Right Ventricular Cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy (ARVC), also known as *arrhythmogenic right ventricular dysplasia*, is an autosomal dominant genetically inherited disorder. Diagnosis is often made post mortem in patients with ARVC because sudden cardiac death is a common occurrence with this cardiomyopathy. Signs and symptoms can occur during childhood, but more often manifest during adolescence. During sports-related exercise, severe intolerance caused by increasing myocardial oxygen demand can result in lightheadedness, syncope, and or sudden death. A summary of the pathophysiology, signs and symptoms, and anesthetic considerations is listed in Table 23-12.

Pathophysiology

Fibrous fatty infiltrates invade the right ventricular myocardium and cause myocyte dysfunction and death. As a result, right ventricular cardiac output is decreased. The left ventricle undergoes this type of pathologic change in approximately half of patients with ARVC, and congestive heart failure is a sign of disease progression. Ventricular dysrhythmias are common and range from premature ventricular contractions to ventricular fibrillation. Patients with ARVC may be exquisitely sensitive to increased catecholamine levels, which may further provoke these dysrhythmias.

Anesthetic Considerations

Anesthetic management for patients with ARVC should focus on identification and treatment of fatal dysrhythmias. Many events increase sympathetic nervous system predominance—examples include hypoxia, hypotension, hypercarbia, and surgical stimulation. Excessive catecholamine release can induce fatal dysrhythmias. Amiodarone has been used successfully to treat dysrhythmias in these patients. Prophylactic preoperative administration of antiarrhythmic agents has not been shown to be effective at suppressing ventricular dysrhythmias intraoperatively.[80]

SUMMARY

As the population continues to age and the incidence of obesity rises, the prevalence of cardiovascular disease will increase to reflect the progressive nature of its pathology. Anesthesia providers are nonetheless able to safely manage these extremely critical patients with respect to the full spectrum of surgical needs. A thorough knowledge of cardiac physiology and function is imperative to maintaining administration of high-quality anesthesia care. Improved patient outcomes are consistently being achieved as better assessment, monitoring, and anesthesia management techniques are developed.

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24 CHAPTER Anesthesia for Cardiac Surgery

◆ *Margaret A. Contrera, Melissa Patterson, and Mary Cushing*

Despite advances in prevention and treatment, cardiovascular disease (CVD) remains the leading cause of death globally, accounting for 30% of mortality. The World Health Organization estimates that CVD will remain the predominant cause of mortality, resulting in 23.6 million deaths by 2030, mostly from coronary artery disease (CAD).[1] In the United States, CVD causes 1 of every 2.9 deaths, half of them due to CAD.[2] Because of the aging population, degenerative valvular heart disease (VHD) is on the rise. There are currently over 290,000 heart valve operations performed annually worldwide, and that number is expected to triple by 2050, reaching 850,000.[3] Both CAD and VHD lead to heart failure, which impacts more than 5 million Americans. The mortality rate for symptomatic patients is a staggering 45%, worse than that of most cancers.[4] The Centers for Disease Control and Prevention estimates that $444 billion, or $1 out of every $6, in health care costs is spent on cardiovascular disease treatment.[5]

Clearly CVD presents an enormous public health burden. Scientific and medical communities, together with governmental agencies, have worked tirelessly to improve this situation. Consequently, new knowledge about these diseases is accumulating exponentially and technologic advancements have led to the development of cardiac procedures that were once inconceivable. Percutaneous techniques, hybrid operating rooms, mechanical assist devices, robotics, and minimally invasive technology now play significant roles in the practice of cardiothoracic anesthesia. The field has become more diverse, exciting, challenging, and rewarding than ever before.

Care of these high-risk patients in regard to the complex, ever-evolving surgical procedures may at first seem intimidating. But as Richard Morris, a pioneer in the field of cardiothoracic nurse anesthesia advised, "It's simple really; just manage the pump, pipes and volume." Accordingly, the first half of the chapter is about general cardiac surgery. It begins with a brief overview of the key physiologic principles that form the foundation of the evidence-based anesthetic management strategies for cardiac surgery. Next, cardiopulmonary bypass (CPB) is discussed, including a description of the circuit components and the physiologic implications of bypass. Then each phase of the perioperative period is examined and the anesthetic implications detailed. The second half of the chapter covers anesthetic considerations for specific cardiovascular diseases and procedures. The pathophysiology of CAD and VHD is briefly reviewed, and anesthetic management of traditional myocardial revascularization and valvular surgery is detailed. New technologic advancements have changed the landscape of cardiac anesthesia. Consequently, the next sections are devoted to management of first, the innovative, minimally invasive approaches that are now used for both valvular surgery and myocardial revascularization. This is followed by a discussion of the devices and procedures that are bringing new hope to the management of end-stage heart failure. The chapter concludes with the anesthetic management of procedures on the ascending aorta and arch that require CPB, including the considerations for deep hypothermic circulatory arrest.

ANESTHETIC MANAGEMENT OF GENERAL CARDIAC SURGERY

Key Physiologic Principles

Appropriate management of the cardiac surgical patient begins with a comprehensive understanding of normal cardiac anatomy, physiology, pharmacology, and monitoring, as well as the pathophysiologic response to disease. The reader is advised to review the excellent discussions of these topics found in Chapters 13, 16, and 23 as background for the information presented in this chapter. Nevertheless, there are certain key principles that apply to most cardiac surgical patients. An imbalance in myocardial oxygen supply and demand, often as a result of CAD, leads to ischemia or infarction. As a result of the imbalance, the left ventricle hypertrophies by thickening or dilating. The abnormal pressure and volume loads caused by stenotic and regurgitant valves likewise causes the ventricle to compensate by altering its structure, function, and neurohormonal balance. Although each disease starts with a different etiology and pathophysiologic process, with progression of the disease, the limits of compensation are reached and severe decompensated heart failure then ensues.

Myocardial Oxygen Supply and Demand

Myocardial injury and/or infarction are the single most frequent complications after cardiac surgery; they are also the primary cause of complications and death that occur in the hospital setting.[6] Clearly, optimizing the balance between myocardial oxygen supply and demand is of paramount importance (Figure 24-1). Coronary perfusion pressure (CPP) is equal to the aortic diastolic blood pressure minus the left ventricular end-diastolic pressure (LVEDP).

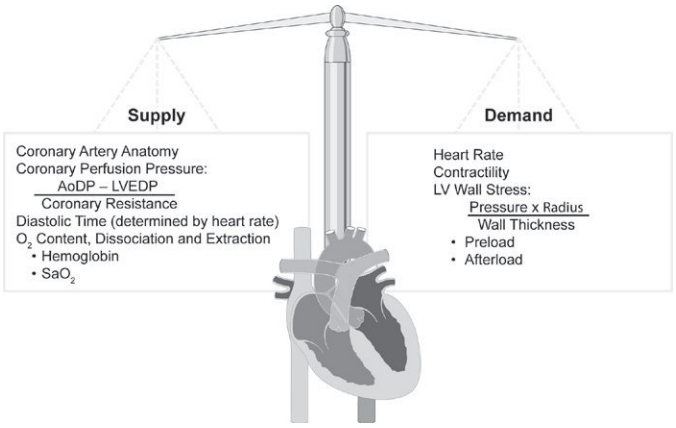


FIGURE **24-1** Myocardial oxygen supply and demand balance. Heart rate and left ventricular pressure affect both supply and demand. *AoDP*, Arterial diastolic pressure; *LVEDP*, left ventricular end-diastolic pressure; SaO_2, arterial oxygen saturation. (Reprinted with permission from Cleveland Clinic Center for Medical Art & Photography © 2006-2012. All rights reserved.)

The subendocardium or inner third of the heart muscle is at greatest risk for ischemia because it is exposed to the highest pressure, especially at the peak of systole. Normally CPP is autoregulated between a mean arterial pressure (MAP) of 60 to 140 mmHg. Consequently, MAP is the most useful measure of coronary perfusion in the clinical setting.[7] However, in patients with CAD, flow is no longer autoregulated after it passes the partial obstruction. Instead, perfusion becomes pressure dependent; especially when the MAP drops below 70 mmHg[8,9] (Figure 24-2). Total coronary blood flow is determined by the perfusion pressure gradient, the time allotted for flow, coronary anatomy, and the resistance. Eighty percent of blood flow to the left ventricle occurs during diastole when the pressure is low (Figure 24-3). Diastolic time progressively shortens as the heart rate increases, resulting in decreased time for coronary perfusion at higher heart rates. Note that elevations in LVEDP and heart rate not only decrease myocardial blood supply but also increase myocardial oxygen demand. An increase in heart rate proportionally increases myocardial oxygen demand and decreases diastolic time.[7] Large epidemiologic studies show that heart rate is an independent predictor for cardiac and all-cause morbidity and mortality in men and women with and without CVD.[8] Heart rate is also the most significant cause of perioperative ischemia.[9] Therefore maintaining an adequate aortic mean pressure and a low heart rate is critical, particularly in patients who have CAD or an elevated LVEDP. The ideal heart rate must be determined on an individual basis, but less than 70 beats per minute (bpm) is a reasonable guide.[10] Patients with concentric left ventricular hypertrophy (LVH) have an elevated LVEDP, so they too are best managed with a higher MAP and lower heart rate. Table 24-1 outlines some of the causes and treatments of alterations in myocardial oxygen supply and demand.

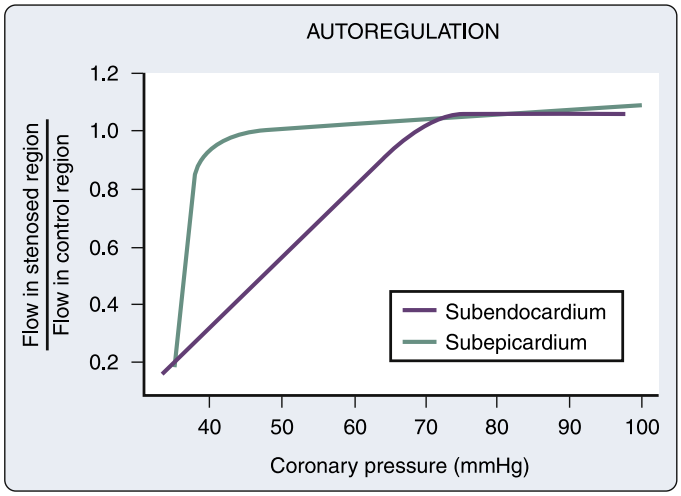


FIGURE **24-2** Pressure-flow relations of the subepicardial and subendocardial thirds of the left ventricle in anesthetized dogs. In the subendocardium, autoregulation is exhausted and flow becomes pressure dependent when pressure distal to a stenosis declines to less than 70 mmHg. In the subepicardium, autoregulation persists until perfusion pressure declines to less than 40 mmHg. Autoregulatory coronary reserve is less in the subendocardium. (Redrawn from Guyton RA, et al. Significance of subendocardial ST segment elevation caused by coronary stenosis in the dog. *Am J Cardiol.* 1977;40:373.)

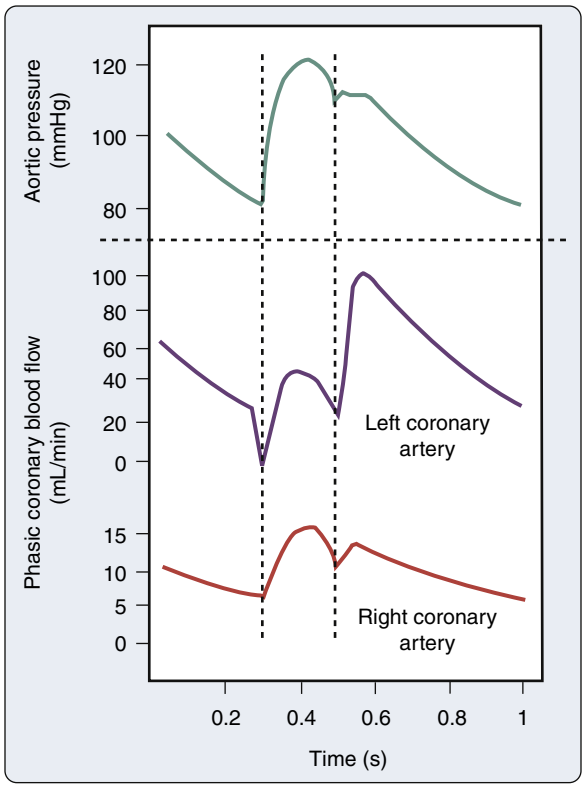


FIGURE **24-3** Blood flow in the left and right coronary arteries. The right ventricle is perfused throughout the cardiac cycle. Flow to the left ventricle is largely confined to diastole. (From Berne RM, Levy MN. Special circulations. In: Berne RM, Levy MN, eds. *Physiology*. St. Louis: Mosby; 2003.)

TABLE 24-1 Perioperative Management of Alterations in Myocardial O_2 Balance

Causes of Decreased O_2 Supply	Perioperative Management Strategy
Tachycardia (↓ diastolic time)	Keep heart rate relatively low (less than 70 bpm) Deepen anesthesia during stimulating periods
Hypotension	Maintain high normal MAP; consider phenylephrine ↓ anesthetic depth during less stimulating periods and surgical manipulation that causes ↓ MAP
↑ PaEDP	Consider nitroglycerin Evaluate LV volume with TEE (PaEDP can be falsely elevated in patients with concentric LVH)
↓ O_2 Content	Maintain Sa_{O_2} at greater than 95%
Anemia	Maintain adequate hemoglobin
Causes of Increased O_2 Demand	**Perioperative Management Strategy**
SNS stimulation	Maintain adequate depth of anesthesia Anticipate stimulating events and treat preemptively.
Tachycardia	Keep heart rate relatively low (less than 70 bpm) Consider β-blockers
↑ Preload	Consider nitroglycerin or diuretic to decrease
↑ Contractility	Consider agents that depress contractility (β-blockers/volatile anesthetics)
↑ Afterload	Avoid hypertension; consider vasodilator

↓, Decreased; ↑, increased; *bpm*, beats per minute; *LVH*, left ventricular hypertrophy; *MAP*, mean arterial pressure; *PaEDP*, pulmonary artery end-diastolic pressure; Sa_{O_2}, saturation of arterial oxygen; *TEE*, transesophageal echocardiography.

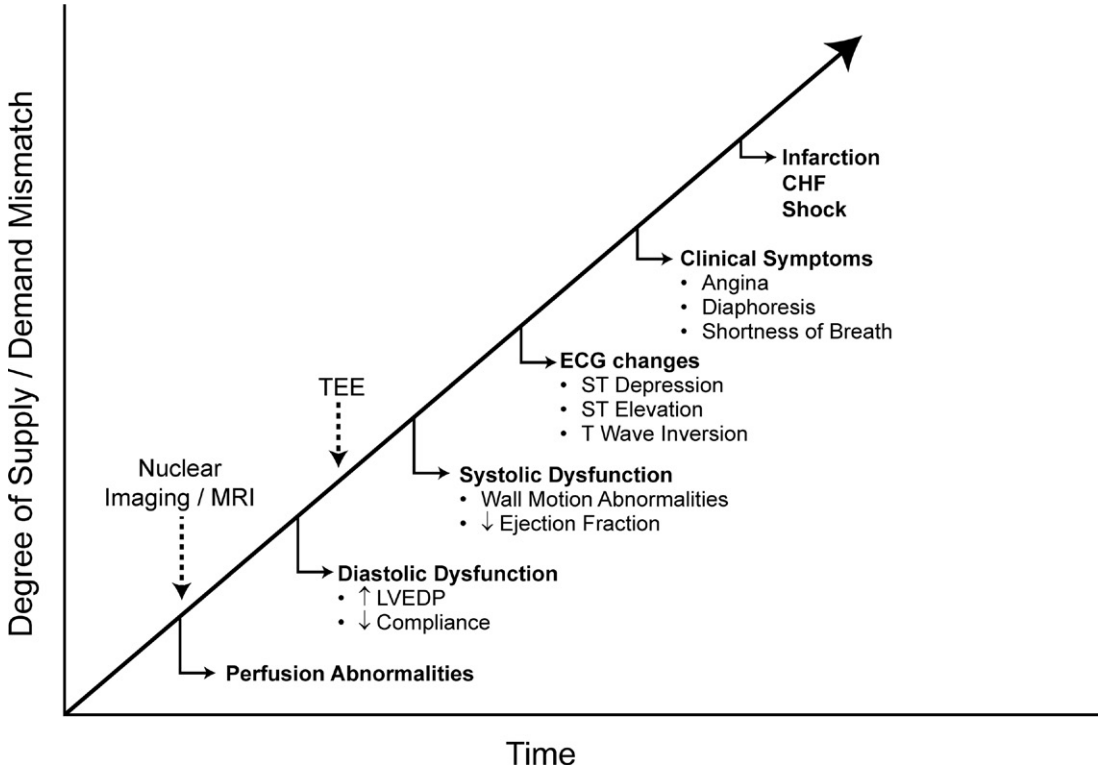


FIGURE **24-4** The ischemic cascade. Pathophysiologic sequence of developing myocardial ischemia correlated with timing of detection using various cardiovascular examinations. (Reprinted with permission from Cleveland Clinic Center for Medical Art & Photography © 2006-2012. All rights reserved.)

Ischemia Cascade

Myocardial ischemia leads to a cascade of events as shown in Figure 24-4.[11] It is important to emphasize that diastolic dysfunction precedes systolic dysfunction, and that regional wall motion abnormalities occur on echocardiography before changes on the electrocardiogram (ECG). An imbalance between myocardial oxygen supply and demand will initially induce diastolic dysfunction, making the ventricle stiff and less compliant. These abnormalities will manifest as an increase in the pulmonary artery end-diastolic pressure (PAEDP); however, multiple studies show that the PAEDP is not specific for ischemia.[12] Systolic dysfunction causes regional wall motion abnormalities that can be readily detected on transesophageal echocardiography (TEE). Consequently, TEE is the most sensitive intraoperative monitor for detecting myocardial ischemia.[13] The single best ECG lead for detecting myocardial ischemia is V_5, which detects 75% of events, so it is important to ensure that the V (brown lead) of the ECG is correctly placed at the fifth intercostal space anterior axillary line. Combining V_4 or V_5 with lead II and using automated ST analysis further improves ECG sensitivity.[11,13,14]

Preconditioning, Stunning, and Hibernation

When the heart muscle experiences brief periods of ischemia that last less than 20 minutes, necrosis or cell death is prevented, but reversible contractile dysfunction, known as *stunning*, can occur and last for several hours.[15-17] As a result of stunning, many cardiac surgical patients may require 12 to 24 hours of inotropic support after cardiopulmonary bypass (CPB).

Ischemic preconditioning refers to the phenomenon whereby a short period of ischemia improves the heart's ability to tolerate subsequently longer periods of ischemic insult.[16] All inhalational anesthetics mimic this preconditioning effect. Consequently, there has been a resurgence of inhalation anesthesia as a primary technique for cardiac surgery, especially in patients with near-normal ventricular function. In past decades, there was a concern that the vasodilatory properties of isoflurane caused coronary steal.[18] However, clinical studies have shown that if blood pressure is controlled, ischemic episodes do not increase and outcomes are unchanged when inhalation agents, including isoflurane, are used.[19-21]

When stable coronary plaque causes chronic reductions in coronary perfusion, steady-state ischemia occurs, which results in left ventricular perfusion-contraction matching or *hibernation*. This phenomenon is considered a self-preservation mechanism whereby left ventricular contractile function is reduced to match the amount of oxygen available.[22,23] Unlike stunned myocardium, patients with hibernating left ventricles (LVs) often have significantly improved function after CPB and coronary artery bypass grafting (CABG). Differentiation of ischemic myocardium that is considered "viable" is important because approximately 20% to 40% of patients with chronically ischemic LV dysfunction will have a significant improvement after revascularization.[23,24] Multiple nuclear imaging tests and dobutamine stress echocardiography are used to help determine the presence of ischemia and viability. Some of the more common cardiovascular tests that are performed to identify ischemia and viability studies are outlined in Table 24-2.

The need to balance myocardial oxygen supply and demand is not limited to patients with CAD. Angina and myocardial infarction in patients with normal coronaries were demonstrated as far back as 1959.[25] Many other patients, such as those with chronic hypertension, aortic stenosis, or obstructive cardiomyopathy, will also benefit from a relatively high perfusion pressure

TABLE 24-2 Significant Findings on Cardiac Preoperative Testing

Diagnostic Tool	Significant Findings	
ECG and/or AECG	ST-T wave changes and presence of significant Q-waves If recent ACS: STEMI vs. NSTEMI vs. unstable angina Presence of *significant* arrhythmia BBB (concern if placing PAC) and LVH Presence of pacemaker	
Chest X-ray	Cardiomegaly Pulmonary vascular congestion/pulmonary edema Pleural effusion Presence of pacemaker or implantable cardioverter defibrillator	
Echo	**Valves**	
	Stenotic	***Regurgitant***
	• Degree (mild, moderate, severe) • Cross-sectional area • Pressure gradient across valve	- Grade (1+ to 4+) - Mechanism
	LV ejection fraction (systolic dysfunction) and RV function Presence and grade of diastolic dysfunction Amount and type of LVH Pericardial effusion/tamponade Presence of PFO (extra concern for air R to L) Presence of plaque on the ascending aorta (problem cannulating and/or clamping)	
Exercise Stress Test	Level and severity of ischemic changes, leads involved Patient characterization of symptoms	
Medications used to induce stress: adenosine and dipyridamole or dobutamine	Adenosine and dipyridamole cause vasodilation in normal coronaries leading to *steal* or *supply* ischemia in areas with CAD; used to identify viable myocardium Dobutamine (β-1 agonist) ↑ HR and contractility inducing *demand* ischemia; used for stress echo as well	
Nuclear Imaging	Radionuclides with varying tracer actions and kinetics are used to evaluate myocardial perfusion and function	
SPECT	Two sets of images are obtained: after stress and after rest. Defects that are initially seen (ischemic area) that fill later indicate viable myocardium, whereas fixed defects indicate scar	
PET	Ischemia shifts metabolism from fatty acids to glucose; an isotope is given that attaches to glucose; the scan can show flow as well as identify areas of uptake; uptake indicates ischemic areas and viable myocardium	
Stress Echo: Exercise or Dobutamine	Segments with new wall-motion abnormalities during stress are considered ischemic and therefore viable	
Cardiac Catheterization	LVEDP, cardiac index Presence of L main, triple vessel disease, or equivalent Quality of targets Type and timing of PCI Type, location, and timing of coronary stents Presence of pulmonary hypertension	

↑, Increase; +, with; − without; *ACS*, acute coronary syndrome; *AECG*, ambulatory electrocardiogram; *BBB*, bundle branch block; *CAD*, coronary artery disease; *ECG*, electrocardiogram; *HR*, heart rate; *L*, left; *LV*, left ventricle; *LVEDP*, left ventricular end-diastolic pressure; *LVH*, left ventricular hypertrophy; *NSTEMI*, Non-ST elevation myocardial infarction; *PAC*, pulmonary artery catheter; *PCI*, percutaneous coronary intervention; *PET*, positron emission tomography; *PFO*, patent foramen ovale; *RV*, right ventricle; *SPECT*, single-photon emission computed tomography; *STEMI*, ST elevation myocardial infarction.

and low heart rate. This is because of the structural, functional, and neurohumoral changes that occur in the ventricle in response to ischemia, infarction, and/or abnormal pressure or volume loads.

Heart Failure

Heart failure is a complex pathophysiologic process that causes a clinical syndrome characterized by pulmonary congestion resulting from the heart's inability to fill with or eject blood in a sufficient quantity to meet tissue requirements.[23] The heart was once thought of as simply the pump of the circulatory system, but it is now known that it evolves into "an endocrine organ" under stress, actively secreting neurohormonal factors in an attempt to meet the needs of the body. For example, atria natriuretic peptide (ANP) is released from the atria in response to volume overload and B-type natriuretic peptide (BNP) is released primarily from the ventricle in response to increased wall stress. These peptides help protect the myocardium by inducing physiologic effects such as diuresis, natriuresis, and vasodilation.[26] In fact, BNP has been recognized as a powerful biomarker for diagnosis, determination of severity, and prognostication of heart failure.[27] Heart failure is caused by an insult that alters perfusion and leads to a state of neurohumoral imbalance. Activation of the sympathetic nervous system (SNS) and the

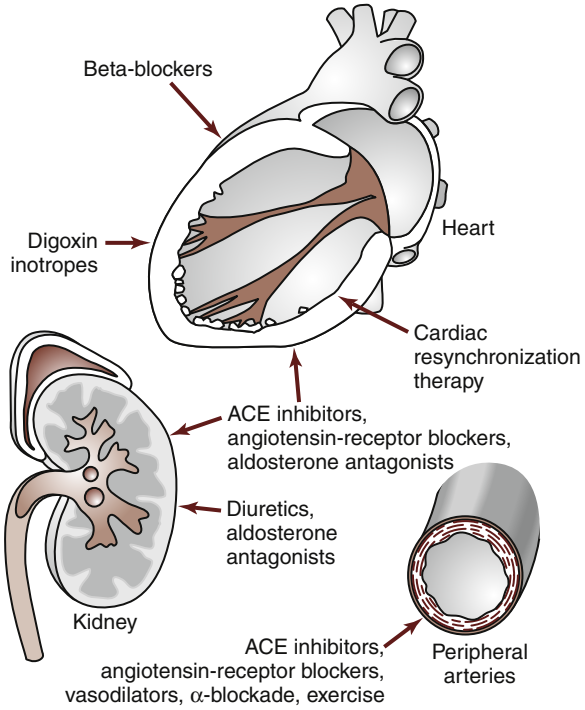


FIGURE **24-5** Pharmacologic treatments target the pathophysiologic changes caused by heart failure. Drug mechanisms produce one or more beneficial mechanisms including decreased preload, afterload, heart rate, blood pressure, deleterious ventricular hypertrophy and remodeling, sodium retention, and sympathetic stimulation. They improve renal and peripheral blood flow, reverse remodeling, and inotropicity. (From Jessup M, Brozena S. Heart failure. *N Engl J Med.* 2003;348:2007-2018.)

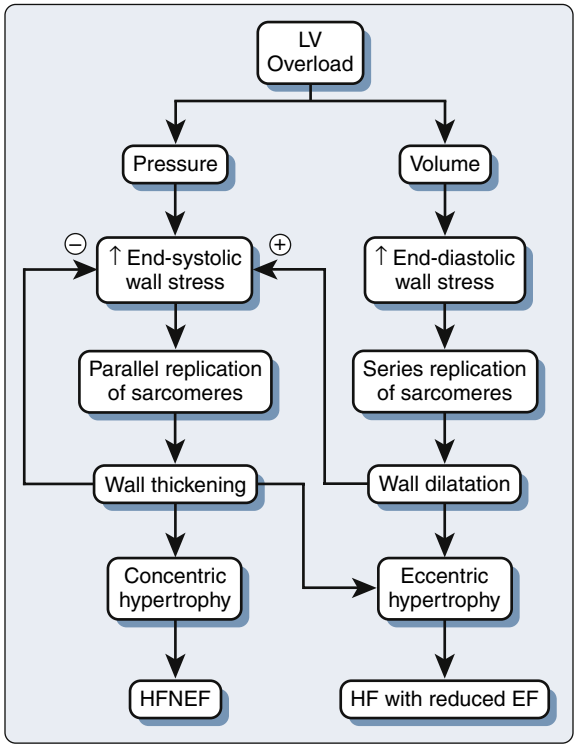


FIGURE **24-6** Left ventricular (LV) pressure and volume overload produce compensatory responses based on the nature of the inciting stress. Wall thickening reduces (−), whereas chamber dilation (+) increases, end-systolic wall stress as predicted by Laplace's law. LV pressure-overload hypertrophy has been linked to heart failure with normal ejection fraction (HFNEF), but LV volume overload most often causes heart failure (HF) with reduced ejection fraction (EF). (From Kaplan JA, Reich JA, Savino JS. *Kaplan's Cardiac Anesthesia: The Echo Era*. 6th ed. Philadelphia: Saunders; 2011.)

renin-angiotensin-aldosterone system (RAAS) induces a host of pathologic responses. Consequently, many patients will receive multimodal drug therapy aimed at interrupting the response and slowing disease progression[4] (Figure 24-5). Beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, and aldosterone antagonists can have a synergistic effect when combined with anesthetics. Although dealing with the resulting vasodilation and/or myocardial depression can be challenging for the anesthetist, medications used to control the patient's heart failure should be continued in the perioperative period because their benefit is well documented.[23,26-28] In fact, on the basis of multiple large-scale randomized, controlled clinical trials, it is estimated that 465 lives are saved for every thousand patients treated with a combination of beta-blockers, ACE inhibitors, and aldosterone antagonists.[29]

Left Ventricular Failure and Remodeling. In the face of sympathetic activation coupled with alterations in perfusion, pressure, and volume, the heart changes its size, shape, and function; that is, it *remodels* itself in an attempt to maintain cardiac output. *Supply* ischemia causes an increase in ventricular compliance (dilation) and a decrease in contractility, whereas *demand* ischemia reduces compliance (stiffening) without initially impacting contractility.[22,23] The primary characteristics of remodeling are hypertrophy or dilation, myocyte death, and increased interstitial fibrosis. The clinical impact manifests as a change in systolic and diastolic function. Figures 24-6 and 24-7 help summarize and visualize the process.

Systolic Dysfunction. As demonstrated in Figure 24-7, *A*, *supply ischemia* resulting in myocardial infarction, or chronic volume overload of the left ventricle causes *eccentric* hypertrophy or dilation. The chamber size increases in an attempt to preserve stroke volume. In the dilated state, the heart loses its normal elliptical football shape and becomes more spherical, resembling a basketball.[4] In this shape, the heart is unable to contract effectively (systolic dysfunction) and the mitral apparatus is stretched potentially to a point that results in mitral regurgitation (MR). Of patients with heart failure, 35% to 50% will experience MR.[30] The degree of systolic dysfunction is commonly expressed as ejection fraction (EF). The EF is calculated as stroke volume (SV) divided by end-diastolic volume (EDV). According to the American Society of Echocardiography's guidelines, normal EF is 55% or greater, and dysfunction is graded as mild (45%-54%), moderate (30%-44%), and severe (less than 30%). When SV is reduced, the body compensates by activating the SNS to raise the resting heart rate in an effort to maintain cardiac output. Systolic heart failure (SHF) is caused by CAD, dilated cardiomyopathy (DCM), chronic volume overload (regurgitant valves, high output failure), and the later stages of chronic pressure overload (aortic stenosis and chronic hypertension). Myocardial infarction causes regional defects that can eventually encompass the entire myocardium, whereas other causes of heart failure typically reduce global function from the onset.[26] As shown in Figure 24-6, SHF is associated with a volume overload of the left ventricle that is managed using multiple drug therapies as shown in Figure 24-5.

Diastolic Dysfunction. Diastolic dysfunction is a more difficult concept to explain, but one that is equally important.

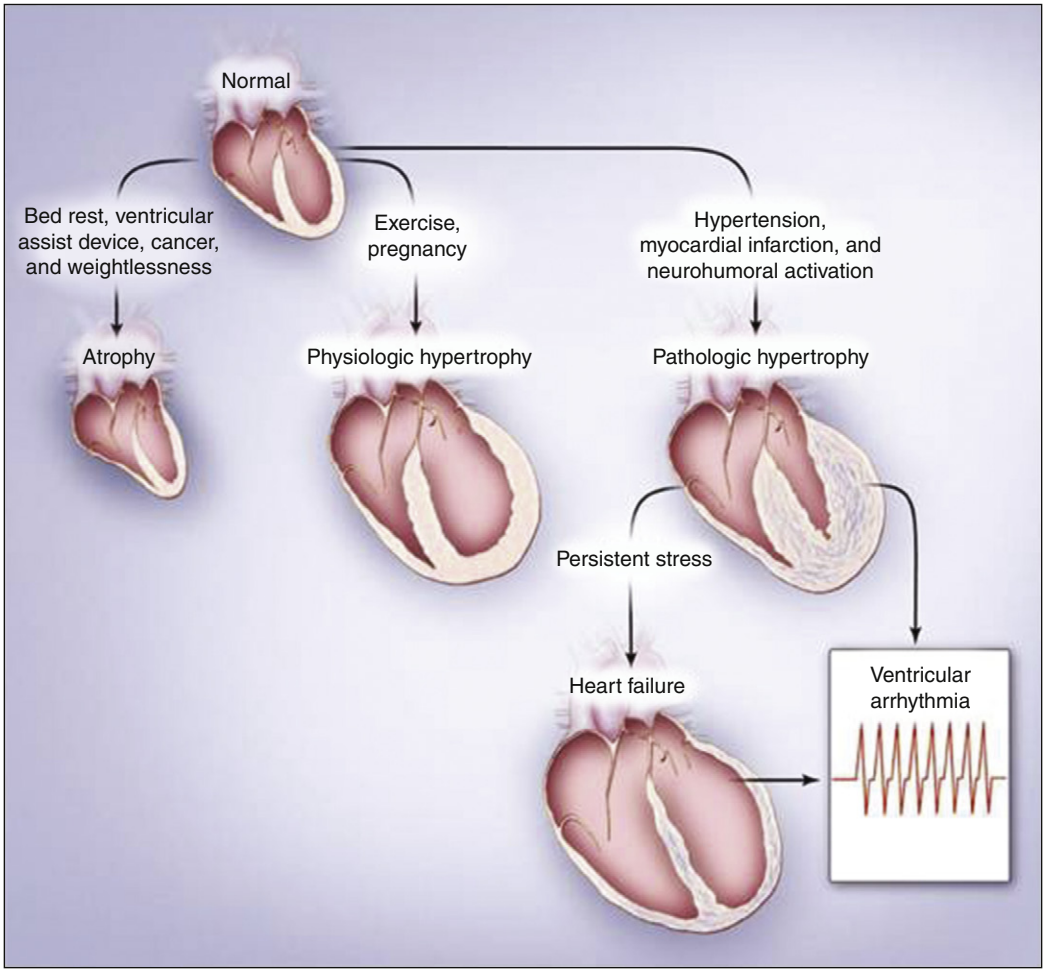


FIGURE **24-7** Conditions leading to remodeling of the heart and resulting in atrophy or hypertrophy. Depending on the circumstances, remodeling can be normal or pathologic. Pathologic remodeling is associated with a propensity toward decompensation, ventricular dilation, systolic dysfunction, and electrophysiologic changes leading to malignant ventricular arrhythmia. (From Hill JA, Olson EN. Cardiac plasticity. *N Engl J Med.* 2008;358:1370-1380.)

Pulmonary congestion and all the symptoms of heart failure can indeed develop with a normal EF. In fact, diastolic heart failure (DHF) is often called *heart failure with preserved EF* (greater than 40%) (see Figure 24-6). *Demand ischemia*, resulting from chronic pressure loads from stenotic heart valves, obstructive cardiomyopathy, chronic hypertension, or obesity, causes the myocardium to thicken (*concentric hypertrophy*) and compliance to decrease (see Figure 24-7).[4,284] Pulmonary congestion develops because the fibrosed, nondistensible LV, with an increased LVEDP, is unable to fill adequately despite near-normal systolic function. Diastolic failure is graded class I to IV based on echocardiographic examination findings.[31] The hypertrophied LV is prone to ischemia; therefore maintenance of a high MAP and slow normal heart rate is crucial.[32] Hypotension should be treated promptly, usually with phenylephrine to avoid rapid decompensation that can potentially lead to cardiac arrest. In the hypertrophied heart, chest compressions rarely generate enough pressure to perfuse the noncompliant LV. The mortality and hospitalization rates are similar in both systolic and diastolic failure. Table 24-3 compares the characteristics of patients with systolic and diastolic failure, and Table 24-4 outlines the anesthetic management strategies for systolic and diastolic dysfunction. Oftentimes, as DHF progresses, SHF will develop and the two will co-exist.[26]

Right Heart Failure. Right heart failure (RHF) is most often secondary to left heart failure (LHF), but can also be caused by pulmonary hypertension or a right-sided infarct. RHF causes systemic venous congestion, hepatomegaly, and peripheral edema.[23,26] Management of RHF can be more difficult to manage than left-sided failure because fewer options exist for unloading and supporting the right ventricle. The goal in managing RHF is to improve contractility while reducing right heart afterload. Thus anything that would increase right heart afterload should be avoided, including hypercarbia, hypoxemia, acidosis, and similar conditions that can potentially cause pulmonary hypertension. Nitrous oxide can cause pulmonary hypertension so it, too, should be avoided. Normally the right heart is perfused throughout the cardiac cycle (see Figure 24-3); however, when the right ventricle is distended, coronary perfusion occurs primarily during diastole as it does in the left ventricle.

Cardiopulmonary Bypass

Principles

Most cardiac surgeries must be accomplished with the aid of cardiopulmonary bypass (CPB). The machine is operated by a perfusionist, but it is imperative that the anesthetist have a clear understanding of the components and physiologic impact of CPB.

The purpose of CPB is to provide a motionless, bloodless heart for the surgical procedure. This goal is achieved by temporarily diverting venous blood away from the heart to an extracorporeal circulation that adds oxygen and removes CO_2 and then filters it before returning it to the body, most often via the ascending aorta. The CPB circuit is continuous with the systemic circulation and provides artificial ventilation, perfusion, and temperature regulation while diverting the blood from the surgical field. The technique results in stopping nearly all blood flow to the heart and lungs. To stop the heart's electrical activity and to protect it during the procedure, the heart is intermittently perfused and cooled with a chemical solution called *cardioplegia*. Although the goal is to provide near physiologic hemodynamics and acid/base balance, the technique is nonphysiologic. A near-normal cardiac index is usually maintained with an arterial flow of 2.0 to 2.4 L/minute/m^2, but it is nonpulsatile. There is some controversy over what is the most appropriate MAP on bypass, but most advocate no less than 50 to 60 mmHg. Older patients or those with known carotid disease should have a higher MAP, closer to 60 to 70 mmHg, to assure that there is adequate cerebral perfusion pressure.[9] The patient's blood and components are exposed to nonendothelial surfaces, which increase the incidence of platelet dysfunction and coagulopathy. CPB incites a host of inflammatory responses; these are outlined after the discussion of the circuit components.

TABLE 24-3 Characteristics of Patients with Diastolic and Systolic Heart Failure

Characteristic	Diastolic HF	Systolic HF
Age	Often in the elderly	Usually 50-70 years
Gender	Often in females	Most often in males
EF	Preserved, greater than 40%	Depressed, less than 40%
LV cavity size	Normal with concentric LVH	Dilated with eccentric LVH
Chest x-ray	Congestion ± cardiomegaly	Congestion + cardiomegaly
HTN	+++	++
DM	+++	++
Previous MI	+	+++
Obesity	+++	+
COPD	++	0
Sleep apnea	++	++
Dialysis	++	0
Atrial fibrillation	+ Usually paroxysmal	+ Usually persistent
Gallop rhythm	4th Heart sound	3rd Heart sound

Adapted from Popescue WM. Heart failure and cardiomyopathies. In: Hines RA, Marschall KE. *Stoelting's Anesthesia and Co-Existing Diseases*. 6th ed. Philadelphia: Saunders; 2012.
+, Occasionally associated with; ++, often associated with; +++, usually associated with; 0, no association; *COPD*, chronic obstructive pulmonary disease; *DM*, diabetes mellitus; *EF*, ejection fraction; *HF*, heart failure; *HTN*, hypertension; *LV*, left ventricle; *LVH*, left ventricular hypertrophy; *MI*, myocardial infarction.

Basic Circuit

The CPB machine consists of five basic components: a venous reservoir, a main pump, an oxygenator, a heat exchanger, and an arterial filter (Figure 24-8). The following is a simple explanation of full CPB: (1) venous (deoxygenated) blood is drained from the right side of the heart and carried by tubing to a reservoir; (2) a pump then propels the blood to (3) an oxygenator and (4) a heat exchanger; and (5) the oxygenated blood passes through a filter before returning to the arterial circulation to perfuse the rest of the body. The modern bypass machine also performs several other functions, including delivering cardioplegia by means of accessory pumps. The heart is vented and blood is salvaged from the field by means of suction devices.

Cannulae. The CPB circuit includes cannulae and tubing made of medical grade polyvinyl chloride (PVC), with a biocompatible coating to decrease the inflammatory response associated with CPB and to preserve blood components. One or two "staged" (meaning more than one hole to drain the blood) venous cannulae are used to remove the deoxygenated blood from the heart. A large-bore *two-stage* or *multistage* cannula that drains blood from both the right atrium and the inferior vena cava is used for CABG and aortic valve procedures in which the heart is actually closed and small amounts of retained blood will not interfere with the surgery (Figure 24-9). Open-cavity procedures, such as mitral, pulmonic, and tricuspid valve surgery, or procedures that repair defects such as atrial septal defects (ASD),

TABLE 24-4 Anesthetic Considerations for Systolic and Diastolic Dysfunction

	Systolic Dysfunction	Diastolic Dysfunction
Preload	Already ↑, avoid overload, especially coming off pump NTG helps reduce preload and ↑ subendocardial perfusion	Volume will be needed to stretch noncompliant LV Evaluate with echo as LVEDP falsely ↑
Contractility	Reduced →, avoid agents that cause further reductions May need inotropic support	Usually good, but caution with agents that suppress function Does NOT tolerate hypotension
Afterload	Reductions will enhance forward flow as long as coronary perfusion pressure maintained SNP works well if volume is adequate	Already ↑ Higher MAP needed to perfuse thick myocardium Treat hypotension aggressively with phenylephrine
Heart rate	Usually high normal due to sympathetic activation	Slow normal to maximize diastolic time for coronary perfusion and ↓ MvO_2 Prone to ischemia Maintain SR →; cardiovert early
CPB	Expect large pump volumes Consider ultrafiltration, diuretic	Pump volume normal

↓, Decreased; ↑, increased; →, therefore; *CPB*, cardiopulmonary bypass; *LVEDP*, left ventricular end-diastolic pressure; *MAP*, mean arterial pressure; MvO_2, myocardial oxygen consumption; *NTG*, nitroglycerin; *SNP*, sodium nitroprusside; *SR*, sinus rhythm.

patent foramen ovale (PFO) defects, or ventricular septal defects (VSD) all require a bloodless field. For such procedures, two separate venous *single-stage* cannulae are individually inserted into the superior and inferior vena cava, and the vessels are snared with elastic loops to prevent systemic venous blood from entering the heart (Figure 24-10). This technique is also known as *bicaval* cannulation.

Prime. *Prime* is the fluid used to fill the CPB circuit and components. It is composed of an isotonic balanced electrolyte solution, such as lactated Ringer's, Plasmalyte-A, or Normosol-R, that closely matches the principal ionic composition of blood. During setup, the perfusionist must take great care to de-air the circuit. Traditionally the priming volume for the CPB is 1 to 2 L. However, the development of minimally invasive cardiac procedures required the use of smaller cannulae and tubing to enable the surgeon to visualize the field. Medications and other solutions are often added to the prime for a variety of purposes; for example, colloid to decrease postoperative edema, blood to treat anemia, mannitol to promote diuresis, heparin to ensure adequate anticoagulation, and bicarbonate to treat acidosis. When the prime fluid is added to the circulating blood volume, a dilutional anemia occurs, and it is not unusual for the hematocrit to fall to 22% to 25%. The dilution offsets some of the increase in blood viscosity that occurs when the blood cools during CPB.

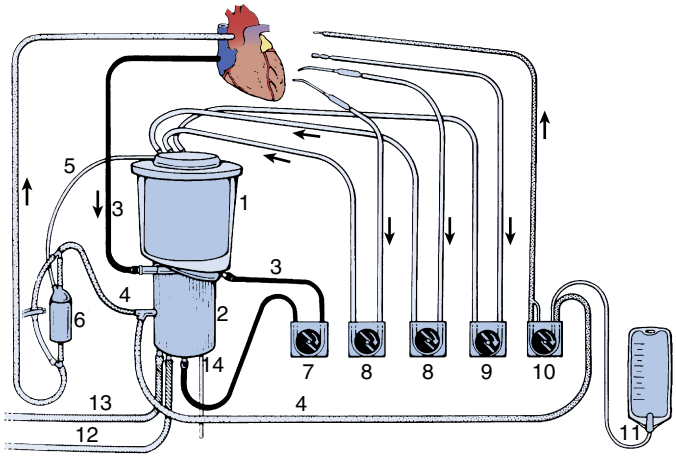


FIGURE **24-8** Components of the extracorporeal circuit. *(1)* Integral cardiotomy reservoir; *(2)* membrane oxygenator bundle; *(3)* venous blood line; *(4)* arterial blood line; *(5)* arterial filter purge line; *(6)* arterial line filter; *(7)* venous blood pump (also called the *arterial pump head*; this pump forces venous blood through the membrane oxygenator and arterialized blood to the patient's aortic root); *(8)* cardiotomy suction pump; *(9)* ventricular vent pump; *(10)* cardioplegia pump; *(11)* crystalloid cardioplegia; *(12)* water inlet line; *(13)* water outlet line; and *(14)* gas inlet line. (From Davis RB, Kauffman JN, Cobbs TL, Mick SL. *Cardiopulmonary Bypass*. New York: Springer-Verlag; 1995.)

Venous Reservoir. Venous reservoir (Figure 24-8 *[1]*) CPB is initiated when the perfusionist removes a clamp that occludes the tubing connecting the venous cannulae to the venous reservoir. The venous reservoir is typically hard-shelled and divided into two compartments, one for the venous drainage from the heart and the other for the blood suctioned or vented directly from the surgical field. This portion of the reservoir is known as *cardiotomy*; it is discussed in detail later. Traditionally blood drains from the patient to the reservoir by gravity. The rate of venous drainage is determined by the size and placement of the cannulae, height of the bed, and the patient's intravascular volume. With the introduction of minimally invasive techniques, gravity drainage was inadequate due to the small cannulae and tubing, so the practice of vacuum-assist venous drainage (VAVD) was established. A vacuum regulator is added to the venous reservoir with a piece of Y tubing and a pressure of −40 mmHg is applied. This Y tubing is used to turn on the suction or open the system to atmospheric pressure. Improved drainage can facilitate surgical exposure and decrease the necessity of adding more crystalloid and/or blood to the CPB circuit. The inherent risks include hemolysis of blood cells and air embolism. VAVD at a suction of −40 mmHg causes less hemolysis than when the suction is increased to −80 mmHg.[33] It is critical that the fluid level in the venous reservoir be kept sufficiently high to prevent air from entering the main pump and causing an air embolism. An alarm is incorporated into the venous reservoir to alert the perfusionist if the fluid level drops

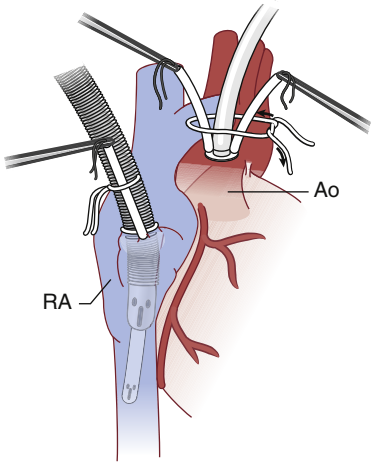


FIGURE **24-9** Aortic (Ao) and single, double-staged, right atrial (RA) cannulation. Notice the drainage holes of the venous cannula in the right atrium and inferior vena cava. (From Connolly MW. *Cardiopulmonary Bypass*. New York: Springer-Verlag; 1995.)

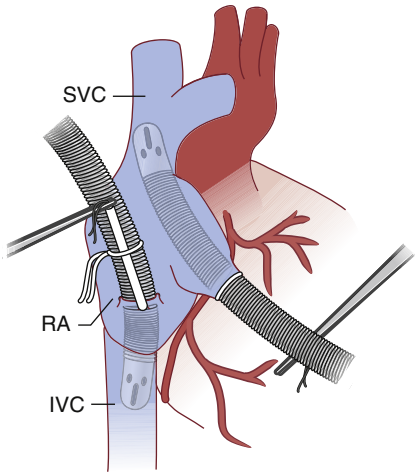


FIGURE **24-10** Position for two-vessel cannulation of the right atrium (RA) with placement of drainage holes into the superior vena cava (SVC) and inferior vena cava (IVC). The aortic cannula is not shown. (From Connolly MW. *Cardiopulmonary Bypass*. New York: Springer-Verlag; 1995.)

below a specific level. The perfusionist may add fluid and medications to the venous reservoir.

Main Pump. Blood is propelled through the CPB machine by an electrical pump (Figure 24-8 *[7]*). Two types of pumps are available. A *roller pump* produces flow by subtotally compressing large bore tubing against a tract and propelling the blood forward. Constant nonpulsatile flow is produced that is directly proportional to the number of revolutions per minute of the roller heads regardless of arterial resistance in the circuit. A *centrifugal pump* uses a magnetically controlled impeller that rotates rapidly, causing a pressure drop that causes blood to be sucked into the housing and ejected. A major difference between the two pumps is that the flow from the centrifugal pump will vary with changes in preload and afterload. For this reason, a flowmeter must be attached to the arterial side of the pump. The roller pump is economical and simple to use; however, unlike the centrifugal pump, it has the disadvantage of increasing the destruction of blood elements. As a result, centrifugal pumps are replacing roller head pumps in contemporary practice. In the event of a power failure, a hand crank can be used to operate either pump.

Oxygenator. The oxygenator performs the functions of oxygenating venous blood and removing carbon dioxide (CO_2) (Figure 24-8 *[2]*). In the past, bubble oxygenators were used, but today only membrane oxygenators are in use. The membrane oxygenator is a coated bundle of hollow microporous polypropylene fibers tightly wound to create a large surface area. Blood flows around the tightly packed fibers and gas flows through the fibers. The gas, consisting of oxygen or a mixture of oxygen and medical-grade air, diffuses passively across the membrane and into the blood. The oxygen level in the blood can be controlled by changing the Fio_2. The amount of CO_2 removed from the blood is controlled by changing the liter gas flow rate or "sweep" of gas through the oxygenator. Volatile anesthetic can also be added to the fresh gas inlet that enters the oxygenator.

Heat Exchanger. The blood enters a heat exchanger either separately or in combination with the oxygenator (Figure 24-8 *[2]*). The heat exchanger is usually made of stainless steel tubes with heated or cooled water flowing through them. Blood flows around the tubes and the temperature is adjusted to the desired level. Traditionally patients were cooled in an effort to protect the heart and other vital organs during CPB. Today, active cooling is less common. Instead the patient's temperature is allowed to naturally drop or *drift* while the surgery is performed. The patient is then actively rewarmed in preparation for the termination of CPB.

For some procedures, the patient is actively cooled to decrease the metabolic rate. This process is discussed later in the chapter under the heading "Surgery on the Ascending Aorta and Aortic Arch." As the patient is rewarmed, gas solubility decreases, and it is possible for air bubbles to form in the CPB circuit. Consequently, the oxygenated blood passes through a filter before it is returned to the patient.

Arterial Filter. Finally, the blood passes through an arterial filter before returning to the arterial cannula and the rest of the body (Figure 24-8 *[6]*). The arterial filter has a pore size of 21 to 40 μm and acts as an air bubble trap and particulate filter preventing thrombi, fat globules, calcium, and tissue debris from entering the circulation. The arterial cannula is most often placed in the ascending aorta, but alternate sites include the femoral or the subclavian artery.

Accessory Pumps and Devices

Cardiotomy and Basket Suction. As illustrated in Figure 24-8, the perfusionist also operates several accessory roller pumps (generally located to the right of the main pump), used to control suction devices and deliver cardioplegia. An assistant helps improve the surgeon's view by aspirating blood from the surgical field using a Yankauer or other suction tip. A "basket" type suction device can be placed in an open cardiac cavity to help drain the blood (Figure 24-8 *[8]*). This *shed* blood can then be returned to the patient in one of two ways. First, the blood can be returned to a portion of the venous reservoir known as the *cardiotomy*. The cardiotomy portion of the venous reservoir has a separate integrated filter that defoams the blood and removes air and debris that is picked up by the suction tip (*pump sucker*) used in the surgical field. Blood returned via the suction may contain fat, bone, and other debris. For that reason some surgeons prefer to return this blood to a separate cell-saver reservoir. Cell-saver blood is later centrifuged, washed, and returned to the patient. Research shows that systemic inflammatory markers decrease when shed blood is not returned to the patient undergoing CABG on CPB.[34,35] Using a cell-saver device instead of returning blood to the venous reservoir reduces the inflammatory response.[36] The disadvantage of this approach is that the volume of blood in the pump is reduced, especially if there is significant bleeding. If bleeding is a problem, the cell-saver blood can be washed and returned to the venous reservoir.

Left Ventricular Vent. The LV vent is a catheter placed in the left ventricle through the right superior pulmonary vein for the purpose of draining blood that accumulated in the cavity (Figure 24-8 *[9]*). Although blood is diverted from the heart during CPB, over time blood enters the LV from the bronchial arteries (which arise directly from the aorta or the intercostal arteries) or Thebesian vessels (coronary veins that drain directly into the heart). Blood and cardioplegia can also fill the LV if the patient has aortic insufficiency. This volume can cause the LV to distend, raise LVEDP, and compromise preservation by opposing the cardioplegia flow into the coronary arteries. Prior to inserting the vent, it is placed in a bowl of water to confirm that it is suctioning rather than blowing because accidental blowing of the vent could lead to an air embolism The vented blood returns to the cardiotomy.

Cardioplegia Pump. The perfusionist controls the infusion of cardioplegia by means of an accessory roller pump (Figure 24-8 *[10]*). A separate heat exchanger allows the temperature, as well as rate and pressure, to be controlled. Cardioplegia is discussed further in the section on myocardial preservation.

Anticoagulation

Systemic anticoagulation is *always essential* prior to cannulation and initiation of CPB. Without anticoagulation, clots can form in the pump that can lead to serious neurologic injury or death. Heparin, derived from porcine intestinal mucosa or bovine lung, is the preferred anticoagulant for cardiac surgery. It is a mucopolysaccharide that potentiates circulating antithrombin (AT III). It binds to AT III and increases its inhibitory action on the procoagulant effect of thrombin by 1000-fold. Heparin increases the speed of the reaction between AT III and multiple clotting factors including II, IX, X, XI, XII, and XIII. The standard cardiac dosage is 300 to 400 units/kg, administered preferably through a central intravenous line. Adequate anticoagulation is measured most commonly with point-of-care testing that includes activated clotting times (ACT) or heparin concentration assays (Hepcon). A baseline ACT is obtained sometime prior to heparin administration. The normal value is approximately 80 to 120 seconds. The ACT is measured 3 to 5 minutes after heparin administration. An ACT of more than 400 seconds (or more than 480 seconds, in some centers) is necessary before CPB is initiated. The lower limit ACT of 400 was determined in 1978 using monkeys on CPB. This level prevented the appearance of fibrin monomers in the CPB circuit.[37]

A heparin concentration monitor (Hepcon) can be used in place of, or in addition to, the ACT measure. The Hepcon generates a heparin dose response (HDR) curve that can then be used to calculate the most appropriate dose of heparin to initiate CPB and maintain an adequate anticoagulation level during bypass. The amount of protamine needed to reverse the heparin after bypass is also calculated. The level of anticoagulation should be checked every 20 to 30 minutes during bypass so that more heparin can be given as needed to maintain a safe level of anticoagulation.

Patients who have been recently exposed to heparin may become "heparin resistant" and require higher doses of heparin to obtain therapeutic anticoagulation. Heparin resistance is defined as an ACT of less than 380 seconds despite administration of 400 units/kg of intravenous heparin.[9] ATT III deficiency should be suspected if the patient does not become anticoagulated with additional heparin administration. ATT III deficiency can be treated empirically with 2 units of fresh frozen plasma, AT III concentrate, or recombinant AT III (rh AT III). Recombinant AT III has been shown to be effective in reducing heparin resistance by increasing circulating AT III without exposing patients to FFP.[38]

Heparin-induced thrombocytopenia (HIT) is an immune reaction that occurs as a direct consequence of exposure to heparin. A comprehensive review of this disorder is found in Chapter 34. The 14C-serotonin release assay (SRA) and an enzyme-linked immunosorbent assay (ELISA) that detects antibodies to the platelet factor 4 (PF4) are used to definitively diagnose the disorder. For patients with a history of HIT, but a negative HIT antibody screen at the time of cardiac surgery, the American College of Chest Surgeons guidelines recommend the use of heparin only during CPB. There is a decreased risk of a patient being rediagnosed with HIT if the prior diagnosis of HIT was greater than 100 days before the scheduled cardiac surgery. Use of an anticoagulant other than heparin is recommended in the preoperative and postoperative period. In all cases, there should be no heparin added to the flush solution or heparin lock intravenous ports, and heparin-bonded catheters are avoided. Surgery should be postponed if feasible in patients with acute HIT and those who are antibody positive (subacute HIT). If urgent surgery is required, an alternative thrombin inhibitor such as bivalirudin or lepirudin is preferred. A secondary alternative is to block platelet activation using aspirin and an antiplatelet drug such as epoprostenol or tirofiban, and then proceed with heparin administration intraoperatively. [39]

Myocardial Preservation

Mild to moderate systemic hypothermia and cold cardioplegia are used for myocardial preservation. The patient can be actively cooled by the CPB circuit or his or her temperature can be allowed to *drift* toward the ambient room temperature. Some surgeons cool the heart topically by packing icy slush around it. The goal is to achieve hypothermic diastolic circulatory arrest to decrease the metabolic rate, oxygen consumption, excitatory neurotransmitter release, and to preserve high-energy phosphate substrates.[9] The brain also benefits from the hypothermia and may be at least partially shielded from neurologic injury as a result. The cerebral metabolic rate decreases 6% to 7% for every degree Celsius decrease in brain temperature.

A hyperkalemic crystalloid solution mixed with blood is the most commonly used cardioplegia solution today. The ratio of the mix varies, but is most often a 4:1 blood to crystalloid solution. The exact composition in the mixture of cardioplegia solution is variable, but the first dose (*induction dose*) is cold (2° C to 5° C) with 20 to 30 mEq/L of potassium. Maintenance doses are also cold and contain 12 to 16 mEq/L of potassium. The goal is to maintain myocardial temperature between 8° C and 10° C.[40] Just before releasing the aortic cross-clamp, many surgeons administer a single terminal dose of warm blood (37° C) cardioplegia (TWBC). This so-called "hotshot" contains metabolic substrates (i.e., glucose, glutamine, and aspartate), which have been found to accelerate myocardial recovery from global ischemia.[41] The amount of cardioplegia given in any single dose can be based on time, volume, or myocardial temperature according to the surgeon's preference. It is generally redosed every 15 to 20 minutes while the aorta is clamped. ECG activity and/or an increase in myocardial temperature indicate that cardioplegia may need to be redosed sooner.

There are two possible approaches to delivering cardioplegia: *antegrade*, that is, down the coronary arteries; or *retrograde*, via the coronary sinus and cardiac veins. The first dose of cardioplegia is usually antegrade, and it is given just after placement of the aortic clamp. A catheter is inserted into the aortic root, just proximal to the aortic clamp, and cardioplegia is administered into the root and flows antegrade down the coronary arteries. Hypothermic diastolic circulatory arrest usually follows in 1 to 2 minutes depending on how well the heart is perfused. Antegrade cardioplegia can also be given directly down the coronary ostia when the aorta is opened for surgeries that involve the aorta or aortic valve. In CABG surgery, it is also infused directly into the new vein or arterial bypass grafts once the distal anastomosis is completed. Maintenance cardioplegia is administered every 15 minutes so the heart remains asystolic. Myocardial preservation is occasionally incomplete because the cardioplegia does not reach the entire myocardium either because the coronaries are blocked by atherosclerotic disease or because the solution has leaked into the left ventricle because of an incompetent aortic valve. When myocardial preservation is inadequate, there may be difficulty achieving diastolic arrest and electrical activity may reappear on the electrocardiogram (ECG) between doses of cardioplegia. Additionally, the fluid that leaks into the left ventricle when the patient has AI can cause the ventricle to distend. The increased pressure caused by the distension opposes the antegrade flow of the cardioplegia in the coronaries, thereby increasing the risk of myocardial ischemia. The purpose of the left ventricle vent is to suction out this fluid and prevent distension. In these cases, retrograde cardioplegia can significantly improve myocardial preservation. In fact, many surgeons choose to maximize myocardial protection by routinely giving both antegrade and retrograde cardioplegia.

In the *retrograde* approach, a catheter is blindly inserted into the right atrium and advanced into the coronary sinus, the largest venous drainage vessel of the heart. To place the catheter, the surgeon often lifts the heart to help locate the sinus and advance the catheter. If this catheter is placed before CPB, lifting and manipulation of the heart frequently results in dysrhythmias and hypotension. It is not unusual for this maneuver to cause atrial fibrillation (AF). Synchronized cardioversion of the AF may be required if the patient becomes hemodynamically unstable. Once the catheter is in place, cardioplegia is administered to the myocardium in a retrograde fashion through the cardiac veins. Retrograde perfusion protects the myocardium that is distal to the coronary obstructions.

Blood Conservation

According to the Society of Thoracic Surgeons (STS) database, 50% of cardiac surgical patients receive a blood transfusion.[42] Currently 10% to 15% of the nation's blood supply is used for patients having cardiac surgery. The risks of transfusion are well documented (see Chapter 20), and blood transfusions during cardiac surgery are associated with worse short-term and long-term

survival.[43,44] Additionally, the donor blood supply is either stable or decreasing.[45,46] Blood is considered a finite, scarce, and expensive resource, and there is a national effort to limit its use. Three preoperative risk factors have been linked to bleeding and blood transfusion: (1) advanced age (70 years or older); (2) low red cell volume either from preoperative anemia and/or small body size; and (3) urgent or complex surgery involving prolonged CPB times.[47]

In 2011 the STS and the Society of Cardiovascular Anesthesiologists (SCA) published instructions for blood conservation in clinical practice guidelines.[47] Practitioners of cardiac anesthesia are encouraged to review this important document; this chapter discusses only the highlights. The recommended techniques that promote the conservation of blood and blood products include the administration of antifibrinolytics, blood salvage, limiting the quantity of pump prime, ultrafiltration when appropriate, and the development of multidisciplinary blood management teams.

Antifibrinolytics. Antifibrinolytics are commonly administered to cardiac surgical patients requiring CPB. Use of antifibrinolytics reduces surgical bleeding and decreases the incidence of blood transfusion.[47] Aminocaproic acid (Amicar) and tranexamic acid (Cyklokapron) are both lysine analogs that inhibit plasmin, the key enzyme in the fibrinolytic cascade. Both drugs form a reversible complex with plasmin that then inhibits fibrinolysis or the natural breakdown of clot. Dosing regimens vary, but a common recommendation for aminocaproic acid is a 50 mg/kg bolus over 20 to 30 minutes followed by an infusion of 25 mg/kg/hr into the immediate postoperative period. A standard dosing regimen of tranexamic acid is 10 mg/kg over 20 minutes followed by 1 to 2 mg/kg/hr maintenance infusion into the immediate postoperative period. Dosing regimens vary among institutions. Tranexamic acid is known to be 5 to 10 times more potent than aminocaproic acid, but also more expensive. The use of aprotinin, a kallikrein inhibitor, was suspended in the United States in 2007 after an increase in mortality was noted in comparison to the other antifibrinolytics in the *B*lood Conservation Using *A*ntifibrinolytics in a *R*andomized *T*rial (BART).[48]

Blood Salvage. Blood that is suctioned from the surgical field while the patient is not on CPB, as well as the residual blood that remains in the CPB circuit at the end of bypass, should be directed into a centrifugal red-cell salvage device. As previously discussed, the blood aspirated from the field during CPB can return to the pump cardiotomy or to the cell-salvage reservoir depending on the surgeon's preference. The *shed* blood is kept in a reservoir until it reaches a quantity specified by the device manufacturer, and then it is washed, a process that removes the serum, coagulation factors, and platelets. The red cells are preserved and placed in a bag that can then be infused into the patient. Cell-salvaged blood has a hematocrit of about 55% to 70%. Infusing large quantities of salvaged blood can contribute to a dilutional coagulopathy, because this blood is devoid of coagulation factors and platelets. Contraindications to the use of salvage include infection and the use of topical hemostasis agents. Malignancy used to be considered a contraindication to salvage. However, the new guidelines state, "In high-risk patients with known malignancy who require CPB, blood salvage using centrifugation of salvaged blood from the operative field may be considered because substantial data supports benefit in patients without malignancy and new evidence suggests worsened outcome when allogeneic transfusion is required in patients with malignancy." Blood shed from mediastinal chest tubes can also be salvaged, washed, and reinfused.[47]

Limiting Pump Prime. Traditionally, the addition of pump prime to the patient's blood volume at the initiation of CPB resulted in significant hemodilution. Several mechanisms have been devised that help limit the volume of pump prime. Minicircuits that require a smaller volume of pump prime are available and should be considered for patients at high risk for anemia. Vacuum-assisted venous drainage in conjunction with these minicircuits has also proved helpful. Retrograde autologous priming (RAP) is a perfusion technique in which the CPB prime is displaced by passive exsanguination (back-bleeding) through the arterial and venous lines back into an empty bag that is out of the main circuit prior to initiating CPB. This means that once the primed CPB circuit is attached to the arterial and venous cannulae, the blood is allowed to back up, filling the circuit, and the crystalloid prime fluid is discarded. A recent meta-analysis found that RAP significantly reduces allogenic blood transfusion for adult cardiac surgery patients that require CPB.[49]

Ultrafiltration. Ultrafiltration is a process in which the perfusionist diverts the patient's blood to a hemultrafilter made of hollow capillary fibers that act as a membrane to separate the aqueous portion of blood from the cellular and proteinaceous elements. The aqueous portion is then discarded while the red cells and coagulation factors are *hemoconcentrated*. Ultrafiltration raises the hematocrit, so the technique is most often performed in an effort to prevent transfusing a patient who has a low hemoglobin level. An adequate pump volume is needed for ultrafiltration. When a patient is volume overloaded preoperatively, there is excess volume in the pump, and ultrafiltration can be used to remove the excess volume.[9]

Of course, the most critical questions are "What to transfuse, and when?" Even the 2011 STS/SCA Blood Conservation Guidelines do not provide clear answers to these complicated questions. Oxygen-carrying capacity is extremely important in cardiac surgical patients, but research has not been able to elucidate what hemoglobin (Hgb) level correlates with organ failure or long-term adverse outcomes. The guidelines suggest transfusion for patients on CPB with a hemoglobin of 6 g/dL or less, but a higher hemoglobin may be justified in patients at risk of decreased cerebral oxygen delivery. If the patient's hemoglobin is greater than 6 g/dL and the patient's clinical situation (including comorbidities, clinical setting, and laboratory or clinical data) warrants transfusion, it is reasonable to transfuse earlier.[47] Based on the increased age and comorbidities of the typical cardiac surgical population, it is generally accepted to keep a patient's hematocrit in the 22% to 25% range. Another recommendation is that a multidisciplinary team be created to manage blood resources.[47]

Physiologic Effects of Cardiopulmonary Bypass

Despite improvements in perfusion, anesthesia, and cardiac surgery, patients are still at risk for developing organ dysfunction after CPB. CPB causes a systemic inflammatory response syndrome (SIRS) that potentially can impact every organ system of the body. The inflammatory response to CPB can be mild and asymptomatic or result in multiple organ dysfunction syndrome (MODS). SIRS and ischemia related to emboli or hypoperfusion at the end organ seem to be the common pathophysiologic mechanisms for organ dysfunction after CPB. The heart, brain, lungs, kidneys, and gastrointestinal system are all at risk for negative impact or trauma. Finally, hemostasis is impaired as related to CPB.

Systemic Inflammatory Response. Systemic inflammatory response syndrome (SIRS) is thought to be activated as a result of CPB when the blood is exposed to the foreign surfaces of the CPB

machine and ischemia-reperfusion injury or embolizations occur that cause the release of endotoxin primarily from the splanchnic hypoperfusion. Endothelium damage occurs and the cellular immune response is activated, as are the complement and coagulation cascades. When bypass is initiated, the body exhibits a marked stress response; cortisol, catecholamines, arginine vasopressin, and angiotensin levels are elevated. Large amounts of oxygen-free radicals are also produced. More research is needed into protective strategies. Some therapies may include corticosteroids, protease inhibitors, (e.g., Aprotinin—not available in United States at this writing), cyclooxygenase inhibitors (i.e., aspirin or nonsteroidal antiinflammatory drugs [NSAIDs]), free radical scavengers, and antioxidants.[50]

Heart. Myocardial injury can occur even when protection strategies seem adequate. The injury can vary from being asymptomatic with only an elevation of cardiac enzymes postoperatively to severe with a marked decrease in cardiac function that results in failure to separate from bypass. Substantial increases in cardiac enzymes resulting from the activation of SIRS and/or ischemic injury can occur from embolization and hypoperfusion during CPB. Due to the very nature of the surgery, cardiac insult and ischemia after CPB may occur even with use of myocardial protection techniques. The extension of myocardial injury may result only in mild elevation of cardiac enzymes postoperatively. However, severe myocardial injury may occur, resulting in failure to wean or separate from CPB. Myocardial injury manifested as increased cardiac enzymes after CABG has been shown to increase the risk of both early and late death.[51] Management strategies and devices that may become necessary after myocardial injury during cardiac surgery and bypass are discussed later in the chapter.

Brain. Injury to the brain or the central nervous system (CNS) after cardiac surgery is a devastating outcome for both the patient and his or her family. Neurologic deficits have been categorized into type 1 outcomes, which include death due to stroke/encephalopathy, stroke, coma, or transient ischemic attack (TIA) and type 2 outcomes, which include new deterioration in intellectual function such as confusion, agitation, disorientation, memory deficit, or seizure. A classic prospective study of 2108 CABG patients found the incidence of type 1 injury was 3.1% and the incidence type 2 was 3.0%. The patients who experienced the type 1 outcomes had a substantial increase in mortality, length of hospital stay, and need for long-term care.[52] Atherosclerotic disease of the ascending aorta is the biggest predictor for type 1 injury, but increased age is also predictive. Most of the type 2 outcomes have been shown to improve in the first 3 months after surgery.[53] Late cognitive decline of CABG patients that was originally attributed by many to CPB, has been shown to occur to the same degree in patients of similar age with CAD who have not undergone CPB.[54] TEE and epi-aortic echocardiography may diagnose atheroma in the aorta, and minimizing manipulation of the aorta may decrease the risk of this neurologic insult. Filters on the CPB circuit decrease embolic debris, and flooding the operative field with CO_2 is thought to decrease gaseous emboli. A wide array of neuroprotective strategies and CNS monitoring have been introduced into practice to combat the causes of post-CPB neurologic dysfunction; however, only the efficacy of hypothermia has been proven.

Lungs. Pulmonary complications after CPB can range from mild atelectasis that develops because the lungs are not ventilated on bypass to severe pulmonary dysfunction that was at one time known as *pump lung* but is now known as acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) depending on the severity. Atelectasis and pleural effusions, which occur in 60% of cardiac surgery patients, are the most common injuries, but hemothorax, pneumothorax, and pulmonary edema may also occur.[40] Patients with chronic obstructive pulmonary disease (COPD) or any other preexisting respiratory disease are at increased risk for exacerbation of their existing pulmonary illness after CPB. Embolic insults, prolonged CPB, and the CPB-induced systemic inflammatory response, which causes an increase in pulmonary endothelial permeability, pose the biggest risk to the development of ALI and ARDS.[50]

Kidneys. Renal dysfunction manifested as acute kidney injury (AKI) is one of the major complications of cardiac surgery and serves as a major predictor of morbidity and mortality for postoperative cardiac surgical patients. Bove et al.[55] found 3.4% of 5068 patients who underwent cardiac surgery with CPB developed acute renal failure (100% creatinine increase) and 1.9% required renal replacement therapy. Hospital mortality was over 40% for the patients with acute renal failure (ARF) and increased to over 63% in patients who required renal replacement therapy. Optimizing cardiovascular volume status and cardiac output as well as limiting CPB time are suggested to decrease the incidence of ARF.

Gastrointestinal. System dysfunction is a relatively rare occurrence but significantly increases the incidence of perioperative myocardial infarction, renal failure, stroke, and even death.[56] Gastrointestinal dysfunction seems to also be affected by hypoperfusion and/or embolic events related to CPB. Splanchnic hypoperfusion causes the release of endotoxins that can initiate SIRS.

Coagulation. Even with adequate heparinization, CPB activates the extrinsic and intrinsic hemostatic pathways as well as fibrinolysis. Contact of the blood with the internal surface of the CPB circuit results in the activation of compliment, the coagulation cascade, platelets, plasminogen, and kallikrein. During CPB, platelets and clotting factors are first diluted and then denatured by the mechanical trauma from the bypass circuit and suction devices. Platelets and leukocytes are also activated by mechanical trauma. The end result is the development of coagulopathies that manifest as increased perioperative bleeding.

Anesthetic Considerations in the Perioperative Period

Preoperative Evaluation

Because of the serious nature of the primary disease and the high prevalence of comorbidities, all patients undergoing cardiac surgery should have a thorough preoperative evaluation, including a history of the patient's medical condition(s) and a complete physical examination. The preoperative assessment should focus on the cardiovascular system, but information must also be gathered and recorded about the airway as well as pulmonary, neurologic, endocrine, renal, hepatic, and hematologic functions.

Cardiovascular System. The medical record should be examined and the results of all cardiovascular tests noted. Table 24-2 summarizes many of the common tests and findings that are used to identify cardiac pathology. Ventricular function and a history of heart failure are important considerations that affect anesthetic choice, hemodynamic management, and requirements for pharmacologic support. The New York Heart Association's (NYHA) functional class of heart failure has prognostic significance and predicts postoperative quality of life. The American Heart Association (AHA) and American College of Cardiology (ACC) stages of heart failure emphasizes disease progression (Table 24-5).

Patients with a history of severe heart failure are likely to have a cardiac electronic implantable device (CEID) including

a pacemaker alone or in combination with implantable cardioverter defibrillators (ICDs). Many patients will have biventricular pacemakers for cardiac resynchronization therapy (CRT). CRT improves cardiac output, hemodynamics, heart failure symptoms, and quality of life.[57] All implantable devices should be evaluated prior to cardiac surgery, and the results of the device interrogation should be readily available.

Antitachyarrhythmia functions on AICDs (if present) and the rate response (if present) on pacemakers is most often suspended in the surgical suite just prior to surgery by reprogramming to prevent electrocautery-induced discharge.[58] Means for pacing and defibrillation are immediately available. Patients with ICDs have defibrillation pads placed prior to induction. The pads are positioned away from the generator to prevent damage to the device should defibrillation be necessary. A magnet must be available and the magnet response identified. In emergency situations, the magnet can most often be used to deactivate ICD devices and place most modern pacemakers in an asynchronous mode. If the programmed backup asynchronous pacing rate is less than 70, it is often advisable to have the pacemaker reprogrammed to a higher rate.[57]

Patients with CAD or aortic stenosis often have carotid disease and/or peripheral vascular disease (PVD) as well. The presence of PVD may limit the locations available for invasive monitoring. The presence of aortic disease can impact the surgeon's ability to cannulate or clamp the aorta. If alternate cannulation sites are selected, this too can impact invasive line placement. The blood pressure is kept within a relatively higher range in patients with carotid disease to ensure adequate cerebral perfusion pressure.

Comorbidities. For elective surgery, patient comorbidities should be optimized prior to the time of the operation. Multiple studies have correlated the following conditions with increased risk in the cardiac surgical population: diabetes mellitus, compromised renal function, depressed ventricular function, and heart failure.[59,60]

Diabetes mellitus and perioperative hyperglycemia are associated with increases in sternal wound infections, extended length of stay, recurrence of angina, postoperative mortality, and decreased long-term survival.[61-64] Given the increased risks associated with hyperglycemia, postoperative glucose control has become a Health and Human Services cardiac surgical care measure associated with Medicare reimbursement.[65] In 2009 the Society of Thoracic Surgeons (STS) developed evidence-based practice guidelines for blood glucose management in the perioperative period.[66] Highlights of the STS recommendations are found in Box 24-1.

Preoperative renal impairment is correlated with increases in morbidity and mortality. Despite research into reducing postoperative risk, thus far, only maintenance of normovolemia has proven effective in preventing further decline in renal function.[67]

Laboratory Studies. Laboratory studies that will assist in the perioperative period include a room-air arterial blood gas, electrolytes, serum blood urea nitrogen (BUN) and creatinine, fasting lipid profile, complete blood count, coagulation profile, hemoglobin A1c, and a fasting blood glucose. Any serum biomarkers drawn to evaluate ischemia, infarction, or failure should be noted. Methicillin-resistant *Staphylococcus aureus* (MRSA) infection has a low prevalence but high mortality associated with cardiac

TABLE 24-5 Comparison of the Primary Heart Failure Classifications

ACC/AHA HF Stage	NYHA Functional Class
A—At high risk for HF but without structural heart disease or symptoms	None
B—Structural heart disease without symptoms	I—Asymptomatic
C—Structural heart disease with prior or current symptoms	II—Symptoms with moderate exertion III—Symptoms with minimal exertion
D—Refractory heart failure requiring specialized interventions	IV—Symptoms at rest

Adapted from Popescue WM. Heart failure and cardiomyopathies. In: Hines RL, Marschall KE. *Anesthesia and Co-Existing Diseases*. 6th ed. Philadelphia: Saunders; 2012.
ACC, American College of Cardiology; *AHA*, American Heart Association; *HF*, heart failure; *NYHA*, New York Heart Association.

BOX 24-1

Highlights of STS Perioperative Glucose Management Recommendations

Preoperative
- Hold oral hypoglycemic for 24 hours prior to surgery
- Hold nutritional insulin after dinner night before surgery
- Continue basal insulin dose (NPH dose may be cut ½ to ⅓)
- Check glucose level frequently day of surgery
- Maintaining glucose at 180 mg/dL or less is reasonable

Intraoperative
- Intermittent bolus acceptable if nondiabetic and glucose less than 180 mg/dL
- Continuous infusion preferred if glucose 180 mg/dL or greater
- Continuous infusion preferred for diabetics, maintain postoperatively
- Adjust infusion per institutional protocol with a goal of maintaining glucose at 180 mg/dL or less
- Check glucose level every ½ to 1 hour or more frequently

Postoperative in ICU
- Consult endocrinology for diabetic patients
- If glucose persistently greater than 180 mg/dL, continue infusion
- If patient in ICU more than 3 days, target should be 150 mg/dL or less
- Before stopping infusion, transition to subcutaneous insulin

In Step-Down or Floor
- Endocrinology to adjust basal and nutritional insulin doses
- General goal is 180 mg/dL or less after meals and 110 mg/dL or less fasting
- Restart oral hypoglycemic if target achieved and no contraindications

Data from The Society of Thoracic Surgeons (STS) Guidelines on Blood Glucose Management During Adult Cardiac Surgery. *Ann Thorac Surg*. 2009;87:663-669.
ICU, Intensive care unit; *NPH*, neutral protamine Hagedorn; *STS*, Society of Thoracic Surgeons.

surgery. Preoperatively, nasal swab cultures are taken and those patients colonized with MRSA (≈ 3.9%) have vancomycin added to their antibiotic routine.[68]

Airway Assessment and Pulmonary Function. Airway assessment and pulmonary function deserve special attention. A plan must be developed to safely secure the airway and appropriately ventilate the patient. This is where the *art of anesthesia* care becomes evident. It can be especially challenging for the anesthetist to maintain hemodynamic stability in the face of a difficult airway, severe pulmonary hypertension, lung disease, or compromised ventricular function. A double-lumen tube and a pediatric fiberoptic scope are required for procedures performed through a thoracotomy incision. If prolonged postoperative ventilation is reasonably anticipated, a slightly larger endotracheal tube (ETT) aids mechanical ventilation and pulmonary toileting.

Surgical Risk. After collecting the aforementioned information, the preoperative team can estimate surgical risk. Risk-scoring schemes for cardiac surgery were first published in 1983. Today several validated scoring systems are available. Each system uses different demographic data, laboratory markers, and type of surgery to calculate risk. One of the most widely cited systems is the STS score. The STS maintains a robust national database that estimates the risk of operative mortality and morbidity after adult cardiac surgery on the basis of patient demographics and preoperative clinical variables. The risk calculator is accessible on the internet.[69] Risk can be calculated for primary procedures as well as combined CABG and single valve surgeries. The risk calculation includes overall morbidity and mortality, length of stay, risk of reoperation, and several other quality measures.

A somewhat simpler on-line risk analysis tool is the European System for Cardiac Operative Risk Evaluation.[70] The most recent version was released in October 2011. The validity and utility of one tool over the other is a subject of academic debate, but both are reliable; therefore use is institutionally specific. Seven variables—age, female gender, left ventricular function, body habitus, re-operation, type of surgery, and urgency of surgery—correlate with major risk across very diverse study settings.[66] In addition, the cardiac surgeon must also consider the extent of his or her training and clinical experience, and the breadth of professional support offered by his or her institution because these factors also have been correlated to risk.[71,72] In tertiary care centers specializing in cardiac care, there are likely to be many patients and procedures that exceed any risk model's ability to accurately calculate risk. Procedures such as re-operations for multiple valve replacement in a patient with endocarditis or placement of an assist device are not included in these models.

Management of Preoperative Medications. Cardiac surgical patients are likely to be on multiple medications to manage their primary disease and comorbidities. As a general rule, the patient should receive all of his or her usual long-term medications on the morning of surgery with a sip of water.[73] However, a few medications merit further discussion. Clinical research has demonstrated the benefit of perioperative beta-blocker therapy to improve hemodynamic stability, decrease dysrhythmias, and reduce morbidity and mortality.[74-76] As with postoperative glucose control, preoperative beta-blocker administration is now a Health and Human Services surgical care measure required for Medicare reimbursement.[65]

Medical management of heart failure includes the use of several drugs (see Figure 24-5). Controversy has arisen regarding administering angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) within 10 hours prior to induction. Some studies report moderate to profound intraoperative hypotension in patients who have received these drugs,[77-79] whereas other studies claim that the medications actually improve hemodynamic stability.[79-81] It is generally recommended that these medications be continued[9,73,82] and that hypotension be treated as needed. These medications also have been implicated as a cause of postoperative vasoplegic syndrome. Patients that seem resistant to Neo-Synephrine may exhibit increased responsiveness to small doses of norepinephrine (16 mcg) or vasopressin (1 unit).[83] (See Chapter 13 for a further discussion of vasoplegic syndrome.)

With regard to medications that affect coagulation, most institutions follow the STS recommendations.[47,84] A complete review of these recommendations is beyond the scope of this chapter, but a few important points are addressed as follows. Aspirin (acetylsalicylic acid [ASA]) and heparin are vital in the treatment of CAD, especially in patients with acute coronary syndrome. Heparin and ASA are administered to patients requiring emergency surgery, and heparin is continued until shortly before skin incision. Despite the proven therapeutic benefit of ASA, it is also associated with increased risk of bleeding; therefore the consensus guidelines recommend discontinuing ASA therapy 3 to 5 days before an elective procedure. ASA should be resumed early in the postoperative period because it improves graft patency and reduces mortality.[84] An alternative antiplatelet agent Clopidogrel (Plavix) blocks adenosine diphosphate (ADP)-mediated platelet activation by binding with the P2Y12 receptor. It should be withheld for 5 to 7 days before surgery, but "newer P2Y12 inhibitors are more potent than clopidogrel and differ in their pharmacodynamic properties. Point-of-care testing may help identify patients with incomplete drug response who can safely undergo urgent operations."[47] Because all of these medications increase the risk of bleeding, they should be discontinued 3 to 7 days before surgery depending on the individual pharmacodynamics. GPIIb/IIIa inhibitors also vary in their pharmacodynamics; the intravenous agent eptifibatide (Integrilin) should be discontinued 4 hours before surgery and patients should receive their last dose of abciximab (ReoPro) 12 hours before incision.[85]

Because cardiac surgical procedures are associated with significant blood loss, the anesthesia provider must confirm with all patients their willingness to accept blood products. In patients with specific religious beliefs or personal preferences, specific products that are permissible should be confirmed.[47]

Psychological Preparation and Preoperative Sedation. Because the cardiac operating room (OR) is a fast-paced, high-intensity environment, it is easy for the team to become task-oriented, inadvertently overlooking the emotional needs of the patient. Patients facing major surgery are acutely aware of their mortality and often apprehensive about the procedure and pain. Concerns about the future of their families and others who might be dependent upon them and what those loved ones would do if they (the patients) were not there to support or care for them are common. The preoperative interview provides a unique opportunity to gather needed data and share information to allay their fear. This visit will also help establish rapport and address the patient's and family's concerns. Patients who are mentally prepared will be more calm, confident, and cooperative in the OR and in the intensive care unit (ICU).

Preoperative sedation is selected on an individual basis, considering the patient's functional status and anxiety level. Generally patients with normal LV function and few comorbidities can tolerate heavier sedation, whereas the frail are lightly sedated. Sedation should not be so heavy as to prevent coherent patients from

participating in the identification and interview process. When in doubt, sedation is withheld preoperatively and then administered in the OR while the patient is monitored during line placement.

Preparation for Surgery

Operating Room Preparation. The surgical suite should be readied in preparation for the planned surgical incision before the patient's arrival. Communication with the surgical and perfusion teams is essential to ensure that all parties are ready to act appropriately if the patient should rapidly deteriorate requiring emergent surgical intervention and/or institution of cardiopulmonary bypass. The basic set-up and monitoring is similar to most major cases, with a few additions as outlined in Table 24-6.

Monitoring. Standard and extended monitors for cardiac surgery are listed in Table 24-6. ECG monitoring should include lead II for detection of dysrhythmias and lead V_5 with automated ST analysis for detection of ischemia. The ECG is limited because it cannot detect posterior wall ischemia and is less sensitive than

TABLE 24-6 Typical Anesthesia Preparation of the Cardiac Operating Room

Anesthesia Machine	Routine Check	
Airway	Nasal cannula or mask as needed Facemask, laryngoscope handle and blades Oral airways and appropriate endotracheal tubes Suction (Yankauer and endotracheal) Ambu bag and any anticipated difficult airway equipment	
Vascular Access	Large-bore PIV cathether (14 or 16 gauge preferred) 2nd PIV catheter on a warmer for complex cases or expected blood loss Arterial line (radial or brachial based on institutional preference) R may be preferred for LITA conduit L may be preferred for "redo's" if R subclavian cannulation Avoid side of radial artery conduit and sites distal to prior brachial cut-down for cardiac catheterization Central Venous Access CVP for normal LVF and primary, simple cases PAC with cardiac output for poor LVF and complex surgery	
Monitors	**Standard Monitors**	**Extended Monitors**
	BP (noninvasive + invasive) ECG (II, V_5 + automated ST analysis) Pulse oximetry Capnography Temperature (core ± peripheral) CVP Urine output Intermittent arterial blood gases (ABGs) Neuromuscular blockade monitor Machine with cassettes for monitoring anticoagulation (ACT or HepCon) Paper or electronic medical record	PAC Specialized PACs (pacing, etc.) Cardiac output measurement Mixed venous saturation TEE Left atrial pressure Infrared absorption spectrophotometry BIS monitoring Cerebral oximetry Retrograde coronary sinus cardioplegia perfusion pressure Spinal drain (intrathecal) pressure
Medications	Anesthetic Sedation Line placement (midazolam) Transport to ICU (propofol or dexmedetomidine) Induction (propofol or etomidate) Muscle relaxant (succinylcholine for difficult airway + nondepolarizing) Narcotic (fentanyl, sufentanil, or remifentanil) Inhalation Heparin (300-400 units/kg in a syringe) Vasoactive Bolus: Nitroglycerine, phenylephrine, ephedrine, epinephrine, atropine, ± calcium Infusions on pumps: Aminocaproic acid or tranexamic acid Nitroglycerin (NTG) for patients with CAD or volume overload Sodium nitroprusside (SNP) for patients with HTN, regurgitant valve lesions, or systolic HF Inotrope (epinephrine or dobutamine) for patients with poor left or right ventricular function Vasopressor for septic or vasoplegic individuals Insulin	
Miscellaneous	Pacemaker with battery Warm water mattress or forced-air warming device with appropriate blanket	

ACT, Activated clotting time; *BIS*, bispectral index; *BP*, blood pressure; *CAD*, coronary artery disease; *CVP*, central venous pressure; *ECG*, electrocardiogram; *HepCon*, machine for determining circulating heparin concentration; *HF*, heart failure; *HTN*, hypertension; *ICU*, intensive care unit; *L*, left; *LITA*, left internal thoracic artery; *LVF*, left ventricular function; *PAC*, pulmonary artery catheter; *PIV*, peripheral intravenous; *R*, right; *TEE*, transesophageal echocardiography.

TEE for detection of ischemia. Core temperature can be recorded using esophageal or nasopharyngeal probes or the pulmonary artery catheter (PAC). If deep hypothermic arrest is planned, the nasopharyngeal recording most accurately reflects brain temperature. To avoid excessive nasopharyngeal bleeding, the probe should be placed at the beginning of the case before heparinization. A peripheral temperature monitor (bladder or rectal) is useful to compare core and shell temperatures during cooling and rewarming.

Arterial Line (A-Line). It is generally safest to place the arterial line (A-line) before induction, using sedation as tolerated and local anesthesia for patient comfort. A noninvasive blood pressure cuff should be placed as a backup monitor in case of arterial line malfunction. The A-line can be used to obtain a blood gas with the patient breathing room air or the supplemental oxygen being used before surgery. This will provide an estimate of lung function and can assist providers when weaning the patient from mechanical ventilation in the postoperative period.

Most importantly, the A-line will provide an instantaneous and continuous monitoring of hemodynamics during induction of anesthesia. This is crucial when the patient has life-threatening cardiac pathology, including severe aortic stenosis, left main coronary artery disease, severe pulmonary hypertension, or moderate to severe decreased left or right ventricular function. In stable patients with less severe disease, the A-line can be placed shortly after induction. The choice between placing a brachial or radial A-line is usually made on a personal or institutional preference. Radial artery cannulation is considered safer secondary to redundant blood flow to the hand via the ulnar artery. However, the radial pressure waveform may dampen during sternal and/or chest wall retraction as a consequence of subclavian artery compression between the clavicle and first rib, especially during dissection of the internal thoracic artery. Additionally, radial A-lines should not be placed below the site of a previous brachial cut-down (for prior cardiac catheterization) because they are prone to thrombosis and waveform distortion. Hence, some providers prefer the brachial artery because it is a more reliable measure of central aortic pressure before and after cardiopulmonary bypass (CPB).[86,87] Although concerns for thrombosis persist, the safety of its use in heparinized patients has been well documented.[87,88] The surgeon may wish to avoid aortic cannulation if the patient has aortic atheroma. As an alternative to aortic cannulation, the right subclavian artery is often cannulated. The right subclavian artery also may be used for redo sternotomy if the surgeon is concerned about inadvertently damaging cardiac structures during opening. In cases of right subclavian cannulation, the A-line is usually placed in the left upper extremity. If the radial artery is being removed as a conduit for CABG, the A-line must be placed in the opposite arm or in the ipsilateral brachial artery proximal to the antecubital fossa. Occasionally other cannulation sites must be considered, most commonly the femoral artery.

Central Venous Access. A central venous access is mandatory in cardiac surgery for volume resuscitation and administration of vasoactive medications. The right internal jugular vein is the preferred cannulation site because it is relatively easy to access and provides a straight, short course to the right atrium. If the left internal jugular vein is used, the anesthetist must be careful to avoid the thoracic duct and the left brachiocephalic vein, which crosses the internal jugular vein at a right angle. Some providers prefer to use a short introducer on the left for this reason. Catheters placed in the external jugular or subclavian vein, especially on the left, are prone to kinking during chest wall retraction. The use of ultrasound to guide placement is becoming increasingly common, especially if the patient has had prior neck surgery or has carotid atherosclerosis. Studies suggest decreased rates of infection and complications when ultrasound is used.[89]

A pulmonary artery catheter (PAC) is frequently placed instead of a central venous pressure (CVP) monitor when more hemodynamic information is desired. Although considered an extended monitor, it is quite useful because changes in intracardiac pressures can be monitored (Table 24-7) and cardiac output measured using thermodilution. The information obtained can then be used to derive several other hemodynamic parameters to assist patient management (Table 24-8). Generally, a PAC is preferred in patients who are undergoing complex surgery or procedures in which large volume shifts are anticipated, or who have left ventricular systolic or diastolic dysfunction, pulmonary hypertension, or right ventricular failure. During CPB, the PAC can advance and become wedged; therefore it is recommended that the catheter be retracted 2 to 3 cm during this time and the baloon inflated slowly after weaning from bypass. To avoid the possibility of pulmonary artery damage or rupture in patients that receive full heparinization, some providers avoid wedging completely and base management on the PAEDP. Special precautions must be taken when a PAC is placed in a patient with a left bundle branch block (LBBB). About 3% of the time, the patient develops complete heart block (CHB) because the catheter causes a right bundle branch block (RBBB) as it enters the right ventricular outflow tract.[90] If a PAC must be placed in a patient with a LBBB, defibrillation/pacing pads should be prophylactically placed before insertion of the catheter. Alternatively, the catheter can be left in the superior vena cava until the chest is open, and then advanced. If CHB does develop, rapid CPB is an option.[91] PACs should generally be avoided in patients that have had pacemaker leads placed in the past 6 weeks because of the possibility of lead displacement.[57] If a PAC is deemed necessary, pacemaker pads for external pacing are placed prior to insertion. Occasionally in cardiac surgery, specialized PACs are useful, including those that can pace or continuously measure mixed venous saturation or cardiac output. In cases in which large blood loss or volume shifts are anticipated, a 9-French two-lumen introducer is useful.

Transesophageal Echocardiography. Transesophageal echocardiography (TEE) requires extensive specialized training, but it has become an invaluable source of information about anatomy

TABLE 24-7 Normal Intracardiac Pressures

Location	Mean (mmHg)	Range (mmHg)
Right atrium	5	1-10
Right ventricle	25/5	15-30/0-8
Pulmonary arterial systolic/diastolic	23/9	15-30/5-15
Mean pulmonary arterial	15	10-20
Pulmonary capillary wedge pressure	10	5-15
Left atrial pressure	8	4-12
Left ventricular end-diastolic pressure	8	4-12
Left ventricular systolic pressure	130	90-140

From Reich DL, Mittnacht AJ, Manecke GR, Kaplan JA. Monitoring of the heart and vascular system. In: Kaplan JA, Reich DL, Savino JS, eds. *Kaplan's Cardiac Anesthesia: The Echo Era*. 6th ed. Philadelphia: Saunders; 2011.

TABLE 24-8 Derived Hemodynamic Parameters

Formula	Normal Values
Cardiac Index	
CI = CO/BSA	2.8-4.2 L/min/m^2
Stroke Volume	
SV = CO x 1000/HR	50-110 mL (per beat)
Stroke Index	
SI = SV/BSA	30-65 mL/beat/m^2
Left Ventricular Stroke Work Index	
LVSWI = 1.36 x (MAP – PCWP)*SI/100	45-60 gram-meters/m^2
Right Ventricular Stroke Work Index	
RVSWI = 1.36 x (MPAP – CVP)*SI/100	5-10 gram-meters/m^2
Systemic Vascular Resistance	
SVR = (MAP – CVP) x 80/CO	900-1400 dynes/sec/cm^{-5}
Systemic Vascular Resistance Index	
SVRI = (MAP – CVP) x 80/CI	1500-2400 dynes/sec/cm^{-5}/m^2
Pulmonary Vascular Resistance	
PVR = (MPAP – PCWP) x 80/CO	150-250 dynes/sec/cm^{-5}
Pulmonary Vascular Resistance Index	
PVRI = (MPAP – PCWP) x 80/CI	250-400 dynes/sec/cm^{-5}/m^2

From Reich DL, Mittnacht AJ, Manecke GR, Kaplan JA. Monitoring of the heart and vascular system. In: Kaplan JA, Reich DL, Savino JS, eds. *Kaplan's Cardiac Anesthesia: The Echo Era*. 6th ed. Philadelphia: Saunders; 2011.
BSA, Body surface area; *CI*, cardiac index; *CO*, cardiac output; *CVP*, central venous pressure; *HR*, heart rate; *LVSWI*, left ventricular stroke work index; *MAP*, mean arterial pressure; *MPAP*, mean pulmonary arterial pressure; *PCWP*, pulmonary capillary wedge pressure; *PVR*, pulmonary vascular resistance; *PVRI*, pulmonary vascular resistance index; *RVSWI*, right ventricular stroke work index; *SI*, stroke index; *SV*, stroke volume; *SVR*, systemic vascular resistance; *SVRI*, systemic vascular resistance index.

and function during cardiac surgery. It is the most sensitive clinical monitor for detecting wall motion abnormalities caused by myocardial ischemia. Additional uses include evaluation of right and left systolic and diastolic ventricular function, valvular area, function and pathology, intravascular volume status, intracardiac air, aortic atheroma and dissection, and to guide catheter or cannula placement. Unless there is a contraindication, the 2010 American College of Cardiology (ACC)/American Heart Association (AHA)/American Society of Echocardiography (ACE) practice guidelines recommend TEE for all open chamber (e.g., valvular) procedures and catheter-based valvular procedures. The guidelines also state that TEE should be considered for coronary artery bypass graft surgeries as well.[92] The only absolute contraindications to TEE are pathologic conditions of the esophagus including strictures, diverticula, tumors, traumatic interruption, or recent suture lines. A complete study encompasses at least 20 views and is completed before CPB by a credentialed provider to identify baseline pathology and function. This is then used for comparison after bypass to immediately evaluate the surgical repair(s) and identify new pathology or dysfunction after cardiopulmonary bypass. Although even an introductory discussion of TEE is beyond the scope of this chapter, a basic understanding of TEE is valuable for nurse anesthetists to help them monitor ventricular function and intravascular volume status. More advanced diagnoses are best made by credentialed providers.

The use of other extended monitors is related to personal preference (e.g., bispectral index [BIS] monitor) or case requirement (e.g., spinal fluid pressure in descending thoracic aneurysms). Although the BIS monitor has not been shown to reliably prevent recall,[93] the trend is useful in detecting changes in anesthetic depth. Occasionally during times of hemodynamic instability, the inhalation agent is titrated down during the resuscitation. The BIS can serve as a reminder to the practitioner(s) to administer a medication to prevent recall.

Selection of Medications. An enormous body of information has accumulated regarding the cardiovascular effects of various anesthetic agents. The most significant considerations are highlighted here. Traditionally the choice of anesthetic has been based primarily on preexisting ventricular function and comorbidities, coupled with the desired length of action. However, the same anesthetic combination may cause different responses in patients with similar histories and hemodynamic profiles. Therefore the combination of medications selected for the anesthetic is far less important than the skill and judgment with which they are administered.

Volatile Anesthetics. Volatile anesthetics can potentially cause myocardial depression, vasodilation, and hypotension. They lower the arrhythmogenic threshold to catecholamines[94] and do not provide pain relief in the postoperative period. Consequently, they are often combined with a narcotic in a balanced technique. Inhalation agents are now considered beneficial because of their preconditioning effect. A recent meta-analysis demonstrated for the first time that the choice of an anesthetic regimen based on administration of halogenated anesthetics is associated with a better outcome after cardiac surgery than a total intravenous technique.[95] Most cardiac surgical patients will benefit from the myocardial protection of volatile agents; the exception may be those with severe LV dysfunction who cannot tolerate any further cardiac depression. Desflurane is a potential concern because sudden increases in inspired concentration can lead to tachycardia and hypertension that can be detrimental in patients who have CAD, hypertrophic cardiomyopathy, or stenotic valvular lesions. Desflurane and nitrous oxide raise pulmonary vascular resistance, pulmonary artery pressure, and wedge pressure.[96] Nitrous oxide should be avoided just before, during, and after CPB because of the potential for expansion of air introduced into the circulation during bypass. Nitrous oxide also may cause catecholamine release and LV dysfunction. The use of nitrous oxide in noncardiac surgery was associated with increased long-term risk of myocardial infarction.[97]

The trend today favors fast-track or early extubation in cardiac surgery because decreased length of stay translates into reduced cost without increases in adverse outcomes.[98,99] Thus the goal of early extubation, generally within 6 hours, is now a major consideration in the selection of medications. Early extubation can be achieved using a variety of techniques, including low- to moderate-dose narcotics (fentanyl 5-20 mcg/kg or sufentanil 2-10 mcg/kg) combined with a volatile agent or total intravenous anesthesia with short-acting drugs such as remifentanil, propofol, or dexmedetomidine.

Opioids do not cause myocardial depression, and they maintain stable hemodynamics. Consequently, a high-dose narcotic technique (fentanyl 100-200 mcg/kg) was popularized in past decades. Problems with the technique included significant bradycardia, recall, chest wall rigidity, and prolonged intubation. Today moderate doses of the fentanyl derivatives are most popular, but

morphine, hydromorphone, and other narcotics also can be used effectively. A primary narcotic technique is reserved for hemodynamically unstable patients.

Sedation. Sedation prior to induction can be accomplished with low doses (1-5 mg) of midazolam. Caution is advised because the combination of a benzodiazepine and fentanyl-type drugs reduces systemic vascular resistance (SVR) and myocardial depression leading to hypotension. Sedation for transport to the ICU is often facilitated with infusions of propofol or dexmedetomidine.

Induction Agents. Induction of anesthesia can be accomplished with any of the agents alone or in combination with narcotics, volatile agents, or benzodiazepines. Etomidate causes less myocardial depression than propofol; therefore it may be preferable for patients who have reduced left ventricular function. A large review of studies involving single-dose etomidate induction versus other standard induction agents showed an increase in adrenal insufficiency in critically ill patients.[100] If adrenal insufficiency is suspected, a dose of steroid such as hydrocortisone 100 mg may be administered. Etomidate and propofol may cause pain with injection, but this can be blunted with prophylactic IV lidocaine or narcotic.

Muscle Relaxants. Muscle relaxants are needed to facilitate tracheal intubation, prevent movement during cannulation, and to attenuate shivering and skeletal muscle contraction from defibrillation. Most nondepolarizing muscle relaxants used today lack significant cardiac effects except for pancuronium, which is longer acting and vagolytic. The increased heart rate is potentially detrimental in patients with CAD, hypertrophic cardiomyopathy (HCM), or valvular stenosis, but beneficial in patients with regurgitant valvular lesions. Choice of relaxant is based on the airway examination, patient history, and procedure length. Succinylcholine is often preferred for difficult airways.

Antibiotic Prophylaxis. The STS has published guidelines for antibiotic prophylaxis in cardiac surgery. A beta-lactam antibiotic (cephalosporin) is the prophylactic antibiotic of choice (Class 1A) for cardiac surgical patients who are *not* at increased risk for MRSA. Cefazolin 1 g (or 2 g for patients weighing more than 60 kg) IV is recommended every 3 to 4 hours while the surgical incision is open. Cefuroxime 1.5 g IV is another alternative. Patients at increased risk for MRSA (known or presumed), including those undergoing an operation using prosthetic valvular or vascular material, should have vancomycin 1 to 1.5 g (or 15 mg/kg weight adjusted) added. Patients with known beta-lactam allergy should be dosed with vancomycin as above, and an aminoglycoside such as gentamicin 4 mg/kg should be added for gram-negative coverage. Redosing of vancomycin and the aminoglycoside are not recommended. The guidelines also recommend that the antibiotic should be administered within 1 hour of incision or 2 hours for vancomycin.[101]

Intraoperative Management

This section focuses on management of general cardiac surgery from the time the patient enters the OR until his or her care is safely transitioned to the ICU team. What follows is a sequential description of events that occur during most cases, so that the anesthetist can gain an understanding of important perioperative milestones. The rationale for pharmacologic and hemodynamic management, as well as patient monitoring, was discussed previously. Management of specific cases and specialized equipment follow.

The cardiothoracic OR is a fast-paced, high-intensity environment where up to a dozen practitioners must focus for extended periods. The patient population is high risk because of the prevalence of multiple comorbidities in addition to the primary cardiac pathology. The surgical procedures can be quite complex, and manipulation of the heart and vasculature can profoundly impact hemodynamic function. Thus the anesthetist is required to intently focus on both the surgical procedure and the patient's response to widely varying levels of stimulation. Problems must be anticipated and interventions prompt. Throughout the process, communication between the anesthesia, surgical, nursing, and perfusion teams is critical. Failure to communicate can have devastating consequences. Closed-loop communication, the practice of clearly repeating back information when one team member makes a request of another, is imperative for safety.

Precardiopulmonary Bypass Period. The precardiopulmonary bypass period refers to the period beginning when the patient arrives at the operating suite and ends when the patient is on cardiopulmonary bypass (CPB.) A review of the patient's preoperative vital signs and cardiac function will help the anesthetist determine the "normal" range for that particular individual. The general goal during the period is to maintain hemodynamic stability. Individual hemodynamic perturbations must be considered within the context of the patient's baseline status. For example, a patient with an acceptable heart rate, mean arterial pressure (MAP), oxygen saturation, and arterial pH does not need an inotropic agent if the cardiac index is below the "normal range." In this particular instance, general anesthesia reduces oxygen demand, and the decreased cardiac output is probably adequate to meet demand. Starting an inotrope to increase the cardiac index within the normal range (higher than 2.2 L/min/m^2), might paradoxically lead to ischemia by increasing myocardial oxygen demand.

The prebypass period is marked by periods of variable stimulation. The most intense stimulation occurs at intubation, incision, sternal split and spread, sympathetic nerve dissection, pericardial incision, and aortic cannulation. Hypertension and tachycardia that occur as a result of inadequate analgesia or sympathetic activation can lead to ischemia, dysrhythmias, or heart failure. The anesthetist must anticipate these events and consider a preemptive dose of narcotic and/or an increase in the concentration of the volatile agent. Hyperdynamic individuals may also need the addition of a short-acting beta antagonist, such as esmolol (0.1-0.5 mg/kg) or an intravenous infusion of a titratable vasodilator such as nitroglycerin or sodium nitroprusside to treat the adrenergic response to these events. During the remainder of the prebypass period, including preincision and the harvesting of conduit, there is little stimulation and the blood pressure and heart rate tend to decrease. Hypotension and bradycardia may decrease coronary perfusion pressure and lead to ischemia; oftentimes intermittent boluses of phenylephrine or ephedrine are used to support coronary perfusion.

Preinduction Period. During the preinduction period, the patient is interviewed before entering the OR to confirm proper identification and the information reviewed from the preoperative assessment. The airway is reexamined and the patient is interviewed to ascertain whether there have been any changes in the patient's medical condition, with a particular focus on worsening symptoms and recent infectious illness. Medications taken within the last 24 hours are recorded. The interview also gives the anesthesia provider an opportunity to assess patient anxiety, communicate expectations, and provide emotional support.

Once in the OR, the patient is moved to the OR table and standard monitors are applied (see Table 24-7). Some institutions use external, adhesive defibrillation pads for those patients that may require emergent defibrillation, that is, patients with a history of ventricular tachycardia or those with an automatic implantable cardioverter defibrillator. Pulse oximetry volume should be

loud enough to provide an audible warning to the clinician in case of decreasing oxygen saturation while the clinician's attention is focused on another task. Some centers routinely administer supplemental oxygen during the preinduction phase whereas others use oxygen as needed. A large-bore peripheral intravenous catheter (14 or 16 gauge) is placed using local anesthesia for patient comfort. Patients with normal left ventricular function will often benefit from supplemental sedation, especially if invasive monitors need to be placed. The decision as to the location and timing of invasive monitoring was previously discussed in the monitoring section of the chapter. Once the arterial line is placed, a baseline arterial blood gas (ABG) and activated clotting time (ACT) are measured. Central cannulation is most often deferred until after induction, but regardless of the timing, baseline measurements including the cardiac output are recorded after placement. When the patient and all teams (nursing, perfusion, surgery, and anesthesia) are prepared, induction can commence.

Induction and Intubation. The plan for induction is based on the length and complexity of the proposed procedure as well as multiple patient-specific considerations including cardiac pathology, comorbidities, ventricular function, and the airway examination. No combination of induction medications has proven superior in cardiac anesthesia. Rather the artful skill each practitioner uses to administer preferred drugs to achieve hemodynamic stability and block the stimulating effects of laryngoscopy is most important. Most often a combination of a sedative, hypnotic, opioid, volatile agent, and muscle relaxant with or without lidocaine, and a beta-blocker are used. Achieving hemodynamic stability can be especially challenging when a difficult airway must be secured, or when 100% oxygen has been advocated for cardiac surgery to maximize O_2 tensions, but a lower inspired concentration may prevent absorption atelectasis and reduce the risk of oxygen toxicity. Because inhalation anesthetics have been correlated with improved outcomes in cardiac anesthesia (most likely because of the preconditioning effect), they are usually included in the maintenance plan**.** Patients with severe LV dysfunction may require a primary narcotic technique because all inhalational agents cause some degree of myocardial depression and afterload reduction.

Preincision Period. The preincision period is generally not very stimulating, therefore the anesthetic level often needs to be reduced and occasional boluses of phenylephrine may be required for hemodynamic support. A second PIV is inserted if necessary and central access obtained. Use of a multiple-access large-bore introducer should be considered for redo sternotomy patients and other cases in which large volume shifts are anticipated. The stomach is decompressed with an oral gastric tube before placement of the TEE probe. It is important to ensure the TEE probe is not in the locked position prior to insertion and a generous amount of water-soluble jelly is placed in the oropharynx to facilitate placement. The combination of a tongue and jaw lift together with turning the head slightly to the right usually helps the probe advance smoothly to the 30-cm marking. To prevent damage to the esophagus, never use force in placing the TEE probe. The TEE examination is completed by a credentialed provider. The urinary catheter, which often incorporates a temperature monitor, is inserted and a nasopharyngeal temperature probe (if used) is placed.

Next, the patient is carefully positioned and pressure points are padded. All routine positioning precautions apply, along with some areas of special concern. Brachial plexus injury can occur if the arms are hyperextended or chest wall retraction is excessive. Brachial and radial artery or nerve compression can occur if the upper arm is compressed by the ether screen or the post used to support the chest wall retractor during dissection of the internal thoracic artery (ITA). The heels and sacrum are prone to ischemia, especially during long procedures with hypothermia, so commercial foam dressings can be prophylactically applied. Occipital alopecia is a common problem that develops in the weeks after surgery; the head should be on a well-padded surface and repositioned frequently during the operation.

After final positioning the anesthetist should reconfirm the position of the endotracheal tube. The antibiotic infusion should be completed (vancomycin may take longer) and the antifibrinolytic agent initiated. Proper placement of monitors and lines should be verified, transducers should be balanced, and given the multiple access ports and IV's used in cardiac surgery, stopcocks should be neatly secured for easy access. Hemodynamic parameters, blood gasses, and blood chemistry are all rechecked and any abnormalities treated. Hypokalemia is not typically treated during the pre-CPB period because cardioplegia solution contains significant amounts of potassium. Insulin infusions may be required to lower the serum glucose level, especially in those with diabetes mellitus. The STS guidelines recommend that blood glucose should be treated for levels greater than 180 mg/dL intraoperatively in both diabetic and nondiabetic patients (see Box 24-1).[94] Insulin should be titrated cautiously to avoid dramatic changes in serum glucose.

Incision to Bypass. The incision to bypass period begins with intensely stimulating events: incision, sternotomy, and sternal spread. The anesthetist should prepare for these events by deepening the anesthetic and administering additional muscle relaxant if needed. The highest rate of recall in cardiac surgery has been recorded during this period; therefore an amnestic can be given if not previously administered. The lungs should be deflated during sternotomy to decrease the risk of cardiac or pulmonary laceration.

Repeat, or redo sternotomy requires greater preparation and vigilance. Patients that have had a prior CABG may have an arterial or venous bypass graft lying directly beneath the sternum. Patients that have had prior chest radiation (often for breast cancer or lymphoma) can also have adherent scar tissue that is difficult to dissect. In these situations, the surgical team will examine the patient's lateral radiograph and possibly a magnetic resonance image (MRI) or computed tomography (CT) scan to determine the proximity of the cardiac structures to the sternum. If the heart appears to be adherent to the sternum, there are several management options for sternotomy and dissection. Some surgeons may expose the femoral vessels so they can quickly cannulate and institute CPB if arterial or cardiac trauma occurs at sternotomy, whereas other surgeons will cannulate before sternotomy and institute CPB during dissection (the heart is not arrested and continues beating). An oscillating saw is used for slow, cautious sternotomy. Communication between the surgeon and anesthetist is crucial, because the lungs may need to be deflated several times for short periods. In the rare event that a cardiac structure or great vessel is entered and bleeding becomes uncontrollable, intravenous heparin (300-400 units/kg) should be administered centrally. If the patient is not already cannulated, the surgeon will emergently place the arterial cannula in the femoral artery or aorta and the cardiotomy suckers will be used for venous return in what is sometimes called "sucker bypass." Blood pressure should be kept high enough to maintain adequate coronary perfusion, yet hypertension should be avoided to minimize excess bleeding. Crystalloid or colloid can be administered if necessary, but hemodilution will exacerbate preexisting anemia. Packed red blood cells should always be prepared and ready for rapid transfusion in all redo sternotomies because the potential for inadvertent vascular injury is significantly increased, as previously discussed.

After sternotomy, the conduit will be harvested if the procedure involves a CABG. The anesthetic considerations related to conduit are reviewed later in the chapter during the discussion of CABG. If no conduit is required, the heart and vascular structures are dissected as individual exposure requirements of the surgical procedure dictate. The period of harvesting and dissection is generally less stimulating so anesthetic levels can be reduced. Often dissection requires considerable manipulation of the heart and vasculature that can result in hypotension and dysrhythmias. Vigilance is required on the part of the anesthetist so the surgeon can be alerted when excessive manipulation results in hypotension and/or dysrhythmias. Hypotension usually responds to placing the patient in Trendelenburg position (head down) and administering small doses of phenylephrine. The surgeon may ask for ventilation to be held and the lungs deflated to improve the surgical view. When the lungs are down, it is recommended that the anesthetist either leave the ventilator alarm sounding or keep his or her hand on the anesthesia bag as a reminder to resume ventilation. Inadvertent failure to ventilate is a real hazard in cardiac anesthesia that can have devastating consequences. Both sympathetic nerve dissection and opening of the pericardium are additional stimulating events that may require increased levels of anesthesia. After the anterior pericardium is opened, it may be lifted (especially in the ministernotomy approach) and sutured to improve the surgical view. This surgical maneuver is likely to cause bradycardia and hypotension because the position of the heart in the pericardium is changed, decreasing venous return with activation of the parasympathetic nervous system. Most patients respond to small doses of phenylephrine or ephedrine, but occasionally the anesthetist must ask the surgeon to decrease tension on the pericardial sutures. After the pericardium is opened, surgical preparation for cannulation is begun.

Cannulation. Cannulation is the next major event in the prebypass period. Full heparinization is essential before cannulation. Heparin (300-400 units/kg) should be administered through a central line after aspiration of blood confirms line patency and to ensure intravascular administration. The ACT or heparin concentration assay should be checked 3 to 5 minutes after the heparin is administered. Muscle relaxation is given if needed because movement during cannulation could prove disastrous. The aortic cannula is placed first, followed by the single venous cannula or double venous cannulae (see Figures 24-9 and 24-10). Then the antegrade and retrograde cardioplegia cannulae may be inserted, or the surgeon may wait until after CPB is initiated.

Surgical manipulation of the heart and great vessels during cannulation often leads to hypotension and dysrhythmias; therefore careful attention and clear communication between the anesthetist, surgeon, and perfusionist are critical. Before the aortic cannula is placed, blood pressure should be decreased to a systolic blood pressure (SBP) of 90 to 100 mmHg or a MAP less than 70 mmHg to decrease the risk of aortic dissection. To achieve this goal, the anesthetic level can be deepened or vasodilators can be carefully titrated. The aortic cannula and aortic line from the CPB machine should be connected and inspected, and all air bubbles should be purged. Complications of aortic cannulation include arterial dissection, hemorrhage, plaque or air embolization, and inadvertent placement of the distal tip of the cannula in an aortic arch vessel. Once aortic cannulation is completed, the perfusionist will confirm intraarterial placement of the arterial cannula by verifying pressure variation in the manometer connected to the aortic line (called *checking the swing*) and administer a test transfusion to confirm normal flow into the cannula. The anesthesia provider may then allow the blood pressure to increase by either decreasing the anesthetic or discontinuing vasodilators. The perfusionist can give volume through the aortic line to augment MAP.

BOX 24-2

Preparation for Bypass: Prebypass Checklist

1. Anticoagulation
   a. Heparin administered
   b. Desired level of anticoagulation achieved
2. Arterial cannulation
   a. Absence of bubbles in arterial line
   b. Evidence of dissection or malposition?
3. Venous cannulation
   a. Evidence of superior vena cava obstruction?
   b. Evidence of inferior vena cava obstruction?
4. Pulmonary artery catheter (if used) pulled back
5. Are all monitoring/access catheters functional?
6. Transesophageal echocardiograph (if used)
   a. In "freeze" mode
   b. Scope in neutral/unlocked position
7. Supplemental medications
   a. Neuromuscular blockers
   b. Anesthetics, analgesics, amnestics
8. Inspection of head and neck
   a. Color
   b. Symmetry
   c. Venous drainage
   d. Pupils

From Grocott HP, Stafford-Smith M, Mangano CT. Cardiopulmonary bypass management and organ protection. In: Kaplan JA, et al. *Kaplan's Cardiac Anesthesia*. 6th ed. Philadelphia: Saunders; 2011.

Next the venous cannulae are placed. Again the anesthetist should watch for hypotension, dysrhythmias, or hemorrhage. Once placement is completed, the perfusionist may initiate the RAP (retrograde autologous priming) process. As described earlier, this process requires an increased blood pressure. Finally, the surgeon may choose to place the retrograde cardioplegia cannula. Because this is done by palpation of the coronary sinus, a posterior structure, it almost inevitably leads to hypotension and dysrhythmias. For this reason, some surgeons place this cannula after bypass has been initiated. The retrograde cannula is sometimes connected to a pressure transducer to watch the mean. The baseline retrograde pressure is generally reflective of venous pressure and should increase about 20 mmHg when retrograde cardioplegia is infused. If the retrograde pressure is low, it could indicate the cannula has fallen into the atria; if it is too high (greater than 40 mmHg), the catheter could be positioned too distally, increasing the risk of coronary sinus rupture. Box 24-2 contains a preparation-for-bypass checklist.

Cardiopulmonary Bypass Period

Initiation. Initiation of cardiopulmonary bypass (CPB) can begin after the ACT is greater than 400 seconds. The venous clamp is first released, allowing blood to fill the venous reservoir; then the arterial clamp is removed, initiating CPB. Adequate venous drainage is necessary for the pump flow to be gradually increased to reach a calculated cardiac index of 2.0 to 2.5 L/min/m^2. Acceptable venous drainage usually correlates with a CVP of less than 5 mmHg (and even negative with vacuum-assisted venous drainage [VAVD].) The heart should appear empty and not distended. Hypotension is common at the initiation of bypass and is most likely related to the instantaneous hemodilution and reduced blood viscosity that occurs, which can then result in a reduction of SVR. Phenylephrine boluses administered by the perfusionist

are routinely necessary to augment the MAP during the initial phase of CPB. The most ominous reason for significant persistent hypotension (MAP less than 30 mmHg) is an aortic dissection. The diagnosis can be confirmed by TEE, and the surgeon may note a hematoma on the wall of the aorta. If a dissection is suspected, CPB must be discontinued until the aorta can be recannulated distal to the dissection. Other causes of persistent hypotension while on CPB include vasoplegia and sepsis.

When the CPB machine reaches full flow, there will no longer be a pulsatile trace visible on the pulmonary artery (PA) or A-line indicating that blood is now bypassing the lungs; mechanical ventilation can be held. Passive insufflation of the lungs with oxygen (200 mL/min) is usually continued. During CPB, the anesthetist must ensure adequate levels of anesthetic and muscle relaxant are maintained. Equipment integrity should be verified throughout the duration of CPB. If a volatile agent is to be used, the vaporizer must be properly seated on the oxygenator gas inlet of the CPB machine and turned on. An improperly seated vaporizer can obstruct gas flow to the oxygenator, resulting in hypoxemia. The infusion of all intravenous fluids and medications is stopped with the exception of aminocaproic acid. Insulin is often necessary because hyperglycemia usually manifests during CPB. The PA catheter, if present, should be pulled back 2 to 3 cm to prevent inadvertent wedging. Sometimes the surgeon will complete the dissection of the heart while it is still beating on CPB before aortic cross-clamp. The vent for the left ventricle is inserted most often through the left superior pulmonary vein.

Next the surgeon will ask the perfusionist to temporarily decrease the CPB flow while the aortic cross-clamp is applied. The clamp time is noted because this represents the beginning of cardiac arrest. After the cross-clamp is applied, full CPB flow will be resumed and cardioplegia infused through a catheter placed in the aorta between the cross-clamp and the heart. As the infusion of the high-potassium solution reaches the myocardium via the coronary arteries, the heart arrests in diastole, and electrical and mechanical asystole should ensue quickly. As explained earlier, achieving diastolic arrest can be difficult in patients with significant aortic regurgitation because some of the cardioplegia leaks into the ventricle rather than perfusing the coronaries. Any heart rhythm besides asystole indicates incomplete myocardial protection and the need for additional cardioplegia. Retrograde cardioplegia through the coronary sinus may also be administered or cardioplegia may be given directly into the coronary ostia if the aorta is opened. To further enhance myocardial and cerebral protection, the surgeon may allow the patient's temperature to "drift" toward the ambient room temperature or begin active cooling centrally through the CPB circuit. Some surgeons cool topically by packing ice around the heart. Box 24-3 contains a checklist of items the anesthetist should check after bypass is initiated.

Maintenance. The flow rate on CPB is maintained at 50 to 60 mL/kg/min to reach a calculated cardiac index of 2.0 to 2.5 L/min/m^2. The ideal systemic pressure on CPB is 50 to 70 mmHg, depending on the patient's age and comorbidities. The mixed venous oxygen saturation should be monitored and maintained at 70%. Hypertension may indicate a light anesthetic level. This can be treated by increasing the vapor or administering a supplemental dose of narcotic or benzodiazepine. If hypertension persists, a vasodilator may be added. Hypotension is usually treated with bolus doses of phenylephrine by the perfusionist, but occasionally an infusion of a vasopressor may be needed. The train-of-four (TOF) should be completely suppressed to prevent movement or shivering during CPB. Shivering may not be obvious, but it greatly increases O_2 consumption, which may be manifested as low O_2 on the venous gas.

BOX 24-3

Anesthesia Checklist at the Initiation of Bypass

Face	Examine for color, temperature, plethora, edema, and symmetry.
Eyes	Examine pupils for size and symmetry and conjunctiva for edema.
CPB lines	Arteriovenous color difference should be visible.
PAC	If present, pull back 3 to 4 cm. Pressure should be less than 15 mmHg mean.
CVP	Less than 5 mmHg, possibly negative with VAVD.
Heart	Avoid distension.
Ventilation	Stop when PA ejection and/or aortic ejection ceases.

CPB, Cardiopulmonary bypass; *CVP*, central venous pressure; *PA*, pulmonary artery; *PAC*, pulmonary artery catheter; *VAVD*, vacuum-assisted venous drainage.

ABGs and ACTs should be monitored every 30 minutes. Acid/base balance should be corrected as needed. Blood may be needed depending on the patient's hematocrit and comorbidities as well as on the complexity of the surgical procedure. Blood glucose usually increases to a level that requires treatment with an insulin infusion. Patients often develop some level of hyperkalemia probably related to the potassium in the cardioplegia solution. The insulin infusion counters this problem by driving K+ into the cell. Urine output should be monitored: 1 mL/kg/hr is considered satisfactory. If urine output is low and the pump volume is adequate, the addition of a diuretic should be considered, especially if the patient was taking a diuretic preoperatively. If the hematocrit is low, hemoconcentration (ultrafiltration) through the cardiopulmonary bypass circuit can be considered as a blood conservation technique.

Preparation for Separation from CPB. Box 24-4 outlines many of the factors that must be considered in preparation for separation from CPB. The need for possible inotropic or vasopressor support should be anticipated and infusions prepared. Rewarming begins as the surgeon is completing the repair. The process should begin early enough to facilitate slow, gradual warming to 36° to 37° C nasopharyngeal or esophageal.[95] During rewarming, the bladder temperature may lag 2° to 4° C behind the nasopharyngeal or esophageal temperatures.[96]

Arterial and venous blood gases should be normalized before termination of CPB. Potassium should be treated if greater than 5.5 mEq/L or less than 4.0 mEq/L to decrease the incidence of dysrhythmias. If the patient is hyperkalemic, calcium also may be given to counteract the potassium and stabilize the membrane to prevent dysrhythmias. The administration of calcium is somewhat controversial. Some clinicians have a low threshold for treating low ionized Ca^{2}+ given its beneficial positive inotropic effects and essential role in the coagulation cascade. Other clinicians avoid calcium because it contributes to coronary vasospasm and may exacerbate reperfusion injury. Magnesium (2-4 g IV) is frequently administered prophylactically to minimize dysrhythmias. In a recent review, CABG patients who received IV magnesium intraoperatively experienced a significant reduction in postoperative atrial fibrillation.[97] Treatment for high glucose levels should continue, but the rate of insulin infusion often can be lowered significantly, especially in a nondiabetic patient after separation from CPB.

BOX 24-4

Preparation for Separation-from-Bypass Checklist

1. Air clearance maneuvers completed
2. Rewarming completed
   a. Nasopharyngeal temperature 36°-37° C
   b. Rectal/bladder temperature ≥ 35° C, but ≤ 37° C
3. Address issue of adequacy of anesthesia and muscle relaxation
4. Obtain stable cardiac rate and rhythm (use pacing if necessary)
5. Pump flow and systemic arterial pressure
   a. Pump flow to maintain mixed venous saturation ≥ 70%
   b. Systemic pressure restored to normothermic levels
6. Metabolic parameters
   a. Arterial pH, P_{O_2}, P_{CO_2} within normal limits
   b. Hct: 20%-25%
   c. K^+: 4.0-5.0 mEq/L
   d. Ionized calcium
7. Are all monitoring/access catheters functional?
   a. Transducers re-zeroed
   b. TEE (if used) out of freeze mode
8. Respiratory management
   a. Atelectasis cleared/lungs re-expanded
   b. Evidence of pneumothorax?
   c. Residual fluid in thoracic cavities drained
   d. Ventilation reinstituted
9. Intravenous fluids restarted
10. Inotropes/vasopressors/vasodilators prepared

From Grocott HP, Stafford-Smith M, Mangano CT. Cardiopulmonary bypass management and organ protection. In: Kaplan JA, et al. *Kaplan's Cardiac Anesthesia*. 6th ed. Philadelphia: Saunders; 2011.
Hct, Hematocrit; *TEE*, transesophageal echocardiography.

An adequate circulating blood volume is necessary for separation from CPB. The amount needed varies with the patient's weight, prebypass volume status, ventricular function, and comorbidities. As previously indicated, the ideal hematocrit is a matter of debate, but most cardiac surgical patients require a hematocrit of 22% to 25% to ensure adequate tissue perfusion.[47]

As the cardiac chambers are surgically closed, the lungs are inflated to remove air from the heart and pulmonary veins and to assist in filling the heart. Warm reperfusion cardioplegia solution ("*Hot Shot*") is administered, and the perfusionist lowers the pump flow temporarily as the surgeon removes the aortic cross-clamp. The time of clamp removal is noted. It is not uncommon for the heart to fibrillate, especially if there was insufficient myocardial preservation or electrolyte imbalances. Intracardiac air can migrate into the coronary artery, most commonly the right coronary artery, because it is anatomically superior and air will rise. Ischemic changes may manifest on the ECG and echo. The surgeon may shake the heart or insert a needle through the muscle into the ventricle it in an attempt to displace residual air. Echocardiography and the ECG can aid the surgeon in determining when all air pockets have been removed.

If fibrillation occurs, the heart is defibrillated with internal cardiac paddles placed directly on the myocardium using 10 to 20 joules. Antidysrhythmics such as lidocaine or amiodarone also may be administered. The MAP can be increased using phenylephrine boluses if necessary to improve coronary blood flow to ensure optimal ventricular function. In some centers, magnesium (1-2 g) IV and lidocaine (100 mg) IV are administered prophylactically with discontinuation of CPB. The optimal heart rhythm is sinus, and a rate between 80 and 90 bpm represents a balance between adequate cardiac performance and myocardial oxygen demand. Temporary ventricular pacing wires are routinely placed because the intrinsic conduction system of the heart may be temporarily or permanently altered.

Atrioventricular pacing is preferred for bradycardia because the atrial contribution to the cardiac output can be preserved. Unfortunately, atrial tissue is more prone to disruption or damage when the pacing wires are removed in the postoperative period, so they are placed less commonly. Patients with chronic atrial fibrillation are generally unable to conduct with atrial pacing. After separation from CPB when electrocautery is used, the pacemaker may sense discharge from the electrocautery as intrinsic cardiac activity—the pacemaker will not discharge. Therefore an asynchronous pacing mode, VOO (ventricular asynchronous) or DOO (atrial ventricular sequential asynchronous), is frequently employed to prevent electrocautery-induced pacemaker inhibition. However, asynchronous pacing modes place the patient at risk for developing ventricular fibrillation as a result of the R-on-T phenomenon. The pacer should accordingly be converted to a synchronous mode as soon as electrocautery use becomes limited.

Once the heart begins ejecting, the lungs should be gently reinflated manually limiting the positive pressure to 30 cm H_2O and mechanical ventilation resumed. The anesthesia provider should visually inspect the lungs as they reinflate, in order to detect atelectasis and adequacy of reinflation. Positive end-expiratory pressure (PEEP) or manual sighs can be used to treat significant atelectasis. However, overinflation of the lungs must be avoided, especially in CABG patients because an in-situ ITA bypass graft may be stretched, or even disrupted, during hyperinflation of the lungs. Delivery of inhalation or intravenous anesthetic should be continued by the anesthetist. Monitors and transducers should be zeroed to atmospheric pressure and recalibrated. Ventricular function should be assessed using TEE and direct visual inspection of the heart in the surgical field. The surgeon should be notified of any echocardiographic findings that are of concern. Valvular integrity and ventricular wall motion are carefully examined. If ventricular function is marginal, an inotrope, most commonly epinephrine, dopamine, or dobutamine should be initiated. If hypotension persists, a vasoconstrictor such as norepinephrine may be started. Once the volume, hemodynamic function, and ventilation are satisfactory, weaning from CPB can begin.

Separation from CPB. The perfusionist uses a clamp to gradually occlude the venous return to facilitate filling of the right ventricle. The right ventricle moves volume through the pulmonary system and into the left ventricle. As the beating heart continues to fill, ejection resumes and arterial pressure rises. Then the perfusionist gradually decreases CPB flow. Volume (preload) can be added through the arterial pump line until loading conditions are optimized. Once adequate volume is given through the in-situ arterial cannula, the line is clamped and separation time from CPB is recorded. The immediate postbypass period demands close attention because hemodynamic instability and cardiovascular collapse may occur. If a radial arterial line is present, the practitioner must be aware of the potential discrepancy between radial and aortic pressure.[78] If a PAC was pulled back during the procedure and is now in the right ventricle, it can be repositioned into the pulmonary artery.

If pulmonary pressures rise precipitously with concurrently falling arterial pressures, this may indicate severely decreased ventricular function and an inability to separate from CPB. If the patient fails separation despite significant efforts at support, CPB can be

reinstituted, and the situation reevaluated focusing on potentially reversible causes of demise. TEE is an invaluable tool to assist in diagnosis and guide management. Visual inspection of the operative field may reveal a surgically correctable problem, such as a kinked bypass graft. If, however, no obvious anatomic problem is identified, a period of resting perfusion on CPB will help resolve cardiac stunning that commonly occurs after cardiac surgery. Pharmacologic inotropic or vasopressor support is initiated or increased. If pharmacologic support is insufficient for separation from CPB, an intra-aortic baloon pump (IABP) may be placed. As a last resort, extracorporeal membrane oxygenation (ECMO) or a ventricular assist device (VAD) may be used for ventricular support. The indications and use of these devices is discussed in the mechanical circulatory support of heart failure section of the chapter.

Postbypass Period

Decannulation. Blood from the pump is transfused to the patient either at a slow but continuous rate or in 100-mL increments. Caution is taken to prevent overdistention and volume overload of either ventricle. Once major surgical bleeding is controlled and hemodynamic stability is satisfactory, preparation for decannulation can begin. The blood pressure is usually lowered to 90 mmHg systolic or a MAP of 70 mmHg or less to reduce bleeding. The atrial (venous) cannula(e) are removed first, then the aortic cannula is removed and the time is recorded. Blood that remains in the CPB reservoir and pump tubing is sent to the cell saver device so that it can be washed and reinfused.

Protamine Administration. Protamine is used to reverse the anticoagulation caused by heparin. Protamine neutralizes heparin through electrostatic interaction, forming a heparin-protamine complex that renders heparin inactive. A test dose of 10 mg protamine is routinely given to check for anaphylaxis because allergies or intolerance to protamine are relatively common.[98] Protamine reactions can range from mild hypotension to anaphylaxis. Some surgeons prefer to give the test dose of protamine while the aortic cannula is in the aorta in case anaphylaxis develops. Otherwise, the protamine should not be administered until the patient is decannulated because clot formation in the CPB pump will have devastating consequences. Slow drug administration is the most effective strategy to use to avoid hypotension, which is common when protamine is delivered rapidly. Giving protamine over a period of 10 to 15 minutes will decrease the probability of both type I (systemic vasodilation) and type III (pulmonary vasoconstriction) protamine reactions. However, an anaphylactic reaction (type III) can occur at any rate of administration.[98] The normal dose of protamine is one milligram of protamine to reverse every 100 units of heparin that was given. Therefore a normal heparin dose of 30,000 units would require 300 mg of protamine for reversal. An ACT is obtained after the entire protamine dose is given to confirm that the clotting time has returned to baseline. Alternatively, a heparin dose response machine can be used to determine optimal protamine dose and check for residual heparin after protamine administration. Additional protamine doses of 50 to 100 mg are routinely administered to cover residual anticoagulation, and if inadequate, hemostasis is visualized in the surgical field.

Hemodynamic Management. After CPB, most patients fall into one of four groups.[50] The first group includes patients with good LV function preoperatively and few comorbidities; they usually separate from CPB easily and require little support. Patients with good ventricular function usually have a blood pressure, heart rate and rhythm, and cardiac output within the normal range. This group of patients may need some occasional adjustments of their volume or blood pressure, but they are generally stable during the postbypass period.

The second group consists of patients with significant concentric LVH and diastolic dysfunction. This group tends to be volume dependent. The intravascular volume status should be continually reassessed using TEE, because LVEDP may be falsely elevated secondary to decreased ventricular compliance. When volume is optimized, the patients may be hypertensive with an adequate cardiac index. As discussed in the beginning of the chapter, patients with concentric ventricular hypertrophy require a high MAP and adequate diastolic time to fill the noncompliant ventricle (see Table 24-4). If the MAP decreases, they are prone to ischemia; therefore they may benefit from a low-dose vasoconstrictor such as norepinephrine if the blood pressure is low after volume has been optimized. On the other hand, if they become hypertensive, cautious titration with a vasodilator infusion is indicated.

The third group of patients present with persistent hypotension in the post-CPB period. In this group, the cardiac output is usually normal or high. Patients in this group may be septic because of preexisting endocarditis or they develop vasoplegic syndrome. Vasoplegic syndrome is a type of well described vasodilatory shock that occurs after CPB. The reported incidence (9%-44%) varies widely, as do the purported causes.[99-101] Preoperative administration of angiotensin-converting enzyme (ACE) inhibitor and calcium channel blockers, amiodarone, and IV heparin are implicated as potential causative agents. Diabetes and moderate to poor LV dysfunction are also correlated with this syndrome.[100,102] Unfortunately, no particular medical history consistently predicts manifestation of this syndrome; however, hypotension early in the pump run is predictive of its development after CPB.[99,100,102] Patients with the syndrome often require large doses of phenylephrine or even norepinephrine while on CPB. Post-pump, they develop resistance to phenylephrine and respond much better to boluses of norepinephrine (16-32 mcg) or vasopressin (1-2 units.) A norepinephrine and/or vasopressin infusion is often needed to support the blood pressure. Vasopressin has been demonstrated as being more effective in the management of vasoplegic syndrome than norepinephrine.[101-104] Although a patient's cardiac output may fall into the normal or even hyperdynamic range, the heart may still benefit from low to moderate doses of inotropic support to sustain contractility in this state of vasodilatory shock.[103] Maintaining a relatively high hematocrit level augments preload and also improves blood pressure.[50]

The fourth and final group of patients comprises those that develop systolic failure after CPB. This group can be further subdivided into left, right, or biventricular failure.[50] Patients with poor preoperative left or right ventricular function, long CPB runs, complex procedures, and inadequate myocardial protection on CPB are at high risk for failure. The pathophysiology of failure was discussed early in the chapter (see Tables 24-3 and 24-4). LV systolic failure is managed with an inotrope such as epinephrine combined with gentle afterload reduction with a vasodilator such as nitroprusside if the SVR is high. An inodilator such as milrinone will provide inotropic support and reduce afterload and may be used alone or in conjunction with other inotropes and vasopressors. RHF can be initially managed with a combination of epinephrine to support contractility and nitroglycerin titrated to reduce afterload while maintaining blood pressure to support coronary perfusion. If this is ineffective, a bolus and/or infusion of milrinone can be helpful because it is particularly effective in reducing pulmonary vascular resistance, thereby lowering right ventricular afterload. Unfortunately, milrinone may cause an excessive decrease in the SVR that leads to hypotension. A norepinephrine infusion

may be initiated to augment blood pressure to a level sufficient for coronary perfusion. Rarely (due partly to cost) is nitric oxide used to selectively dilate the pulmonary vasculature and decrease right heart afterload. If maximal pharmacologic support fails, then mechanical support of the ventricle is considered, including the use of an IABP, ECMO, or VAD. Because management of these devices is complex and rather specialized, the anesthetic considerations are discussed separately in the section on the treatment of heart failure.

Additional Considerations. After the patient is decannulated, the surgeon may pack the chest to encourage hemostasis. Electrocautery is used routinely. During this period the surgeon may need to lift the heart to inspect for bleeding on the posterior surface. Lifting and manipulation of the heart and vasculature can cause significant dysrhythmias and hypotension. The surgeon should be informed if hypotension is severe or excessive in duration. As previously mentioned, electrocautery-induced suppression of the pacemaker can occur; often the pacemaker is placed in an asynchronous mode. Synchronous pacing should be resumed as soon as possible. Most patients require volume supplementation after the pump and often a combination of crystalloid, colloid, and cell saver blood is used. The combination usually results in a hematocrit of 25% to 30%.

Persistent bleeding after CPB occasionally develops, especially if the surgery was complex and required a long pump run. The causes are multifactorial, but readily treatable problems should be addressed. Adequate reversal of heparin should be confirmed via ACT or heparin concentration assay and additional doses of protamine given if needed. Hypothermia accentuates hemostatic defects, so the patient and room should be warmed to normothermia. Surgical causes of persistent bleeding should be sought because inadequate surgical hemostasis may develop and progress insidiously. If oozing persists, laboratory coagulation studies may reveal a deficiency in the coagulation cascade. Platelets, plasma, cryoprecipitate, and red cell transfusions may be required depending on the underlying deficiency. In severe bleeding situations, desmopressin (DDAVP) and factor VII can be administered.

As discussed in the section on physiologic effects of CPB, a host of other complications can arise including ARDS, renal failure, and neurologic injury. Although these are most evident in the postoperative period, problems with adequately ventilating the patient may occur in the OR as well. Most patients will respond to the addition of PEEP and other recruitment measures. Occasionally acute lung injury is so severe that an ICU ventilator with advanced ventilating modes is required.

Chest Closure. When hemostasis has been achieved and the patient is hemodynamically stable, preparations are made for chest closure and transport to the ICU. The lungs are deflated to facilitate chest closure. Cardiac output and echocardiogram (if available) are reviewed before and after chest closure because the preload decreases and afterload increases with chest closure. If the patient becomes unstable, the wires are released and the situation reevaluated. Patients that have received massive transfusions or require high-dose pharmacologic and/or mechanical support may not be able to tolerate the hemodynamic consequences of chest closure. In this situation, the patient may have the chest left open with surgical dressings and a sterile covering applied. The patient is maintained in the ICU for the next 24 to 48 hours. Later when hemostasis and hemodynamic stability are achieved, the patient will be returned to the OR for chest closure.

Once the chest is closed, preparations for safe transport to the ICU are initiated. Emergency medications and airway equipment are gathered for transport because transfer to the ICU represents a particularly vulnerable time period outside of the OR. Although some stable patients may be extubated at the end of the procedure, most surgeons prefer that fast-tracking occur in the ICU after they ensure minimal chest tube output as evidence of adequate hemostasis. Most patients are sedated with propofol or dexmedetomidine infusions until extubation. The echo probe is removed at the end of the procedure and an oral gastric tube inserted to decompress the stomach.

Transport. With the numerous monitors, invasive lines, chest tubes, pharmacologic infusions, and requisite airway equipment, moving a patient safely to the ICU can be complicated and hazardous; a thorough patient-handoff to ICU personnel is vital. A hand-off checklist helps to ensure that all critical information is communicated to the ICU team.

Postoperative Bleeding and Cardiac Tamponade

Bleeding is not uncommon after cardiac surgery and about 4% to 10% of cases are returned to surgery to have the chest re-explored for persistent bleeding, tamponade, or unexplained hemodynamic instability that is presumed to be tamponade.[9] Cardiac tamponade is reported to occur after cardiac surgery, between 0% and 8.8% depending on the complexity of the surgical procedure and patient comorbidities.[102,103] Cardiac tamponade occurs when fluid trapped in the pericardial sac increases in volume enough to cause myocardial compression. The compression then limits diastolic filling of the heart, thus reducing stroke volume and cardiac output. Severe hypotension, myocardial ischemia, and eventually cardiac arrest can ensue once venous pressures fall below pericardial pressures causing ventricular collapse. Pericardiocentesis, subxiphoid drainage, or mediastinal exploration must occur without delay once decompensated cardiac tamponade occurs to prevent complete cardiac collapse.

Cardiac tamponade can occur from nonloculated pericardial effusions, which can be caused by many medical conditions such as malignancies, viral pericarditis, uremia, and bacterial infections. Coagulopathy, postoperative bleeding, and/or localized compression from blood that is in contact with the heart, because of the open pericardium, may all contribute to tamponade that occurs in the immediate postoperative period after cardiac surgery. Cardiac tamponade should be suspected after cardiac surgery if there is a sudden dramatic decrease in chest tube drainage with concomitant hypotension, tachycardia, increased and equalizing filling pressures, and decreased cardiac indices despite increased inotropic and vasopressor support. Pulsus paradoxus, electrical alternans, and the Beck triad are all considered classic clinical indicators of cardiac tamponade. Pulsus paradoxus is defined as a drop in systolic blood pressure greater than 10 mmHg on inspiration. Venous return to the right ventricle increases on inspiration, causing the ventricular septum to bulge into the LV and decrease cardiac output. With positive pressure ventilation, venous return is greatest on exhalation, so the blood pressure drop occurs then. Electrical alternans is the cyclic alteration in the magnitude of P waves, QRS complexes, and T waves that occurs as a result of the tamponade. The Beck triad is characterized by low blood pressure, jugular venous distension, and distant heart sounds. A chest x-ray will often reveal an enlarged cardiac silhouette, and TEE examination will find diastolic collapse of the right atrium or right ventricle.[73,103]

Crystalloid, colloid, and/or blood should be administered to optimize preload until pericardiocentesis or mediastinal exploration can be undertaken in the ICU or operating suite. If the postoperative cardiac surgical patient is brought to the operative room for re-exploration because of tamponade, sedatives or narcotics

should be carefully titrated to prevent further cardiac depression until the tamponade is relieved. Ketamine, pancuronium, and small doses of epinephrine are often chosen for induction of anesthesia because sympathetic tone and myocardial function are supported. If cardiac arrest seems likely to occur with induction, a temporary improvement in cardiac function can be achieved by performing a pericardiocentesis under local anesthesia before induction to remove enough drainage to provide some relief. Postoperative cardiac surgical patients returning to the OR because of bleeding and tamponade, who no longer have invasive monitoring in place, will require insertion of an A-line and CVP. However, surgical drainage should not be delayed for placement of central access. TEE is useful for monitoring ventricular function and as an aid in guiding the surgeon in removing trapped fluid. The patient is sometimes kept spontaneously breathing to prevent further decreases in ventricular filling caused by positive pressure ventilation. If positive pressure ventilation is used, tidal volumes should be reduced. Once the tamponade is surgically relieved, an immediate improvement in hemodynamics is usually noted. At this time hypertension and tachycardia from endogenous catecholamine release should be anticipated by the anesthetist and treated accordingly.

ANESTHETIC CONSIDERATIONS FOR SPECIFIC CARDIAC DISEASES AND SURGICAL PROCEDURES

Coronary Artery Disease and Myocardial Revascularization

Pathophysiology

On-pump coronary artery bypass graft (CABG) surgery is the most frequently performed cardiac surgical procedure. Anesthetic management for these patients requires an understanding of coronary anatomy and physiology, as discussed in Chapter 23, as well as an understanding of the key physiologic principles covered at the beginning of this chapter. This section focuses on the considerations that pertain to CABG surgery.

Coronary artery disease (CAD) is a complex disease state that involves narrowing of the coronary arteries. The pathogenesis of CAD is not definitively clear, but several theories have been proposed. Scientists believe the endothelium or innermost layer of the artery becomes injured. Over time, cholesterol agents such as low-density lipoproteins and macrophages adhere to the endothelium and form plaques. The plaques continue to build and decrease the vessels' ability to distend. Because coronary oxygen extraction is maximal at rest, the only way to increase oxygen delivery to the tissues is to increase coronary flow. In normal coronaries, flow can increase 3 to 5 times over baseline when demand increases. However, this increase in flow, known as coronary reserve, is limited in patients with CAD. Thus when patients with CAD increase demand by exercise or stress, they develop *demand ischemia*, which can then be symptomatically experienced as predictable stable angina. General anesthetics protect against demand ischemia.

Acute coronary syndromes (ACSs) and perioperative ischemia are usually caused by *supply ischemia*.[104,105] Ischemia occurs when a piece of the plaque ruptures, causing a thrombus to form that significantly or totally occludes a segment of a coronary artery, leading to ischemia, dysrhythmias, and/or myocardial infarction (MI). The problem can be exacerbated by spasm, which can develop even in normal adjacent vessels.[9] Great strides have been made in the nonsurgical treatment of CAD and ACS in the past two decades. The development and evolution of coronary stents has revolutionized care. Most patients presenting for CABG surgery with CAD and/or ACS will have been referred for some type of percutaneous coronary intervention (PCI). Surgeons and anesthesia providers must take this into consideration when planning care. Much research has been done comparing the risk-benefit ratio of surgical intervention to optimal medical management. The ACC/AHA guidelines state that surgical intervention is indicated for patients with stenosis of greater than 50% in the left main trunk (LMT) or triple vessel disease. Additionally, patients who have failed PCI or who have coronary lesions not amenable to PCI will benefit from surgery.[106] In these situations, CABG has been found to have a lower mortality risk of major cardiovascular complications or cerebral events than optimal medical management.[106-109]

Anesthetic Considerations and Surgical Options for On-Pump CABG

The anesthetist should carefully review preoperative cardiac tests to determine the location and extent of the lesions, to assess ventricular function, and to detect the possible presence of concurrent cardiac abnormalities such as aortic stenosis. Table 24-2 reviews significant findings on cardiovascular preoperative testing. Preoperative ventricular function correlates with the risk of developing postoperative low cardiac output syndrome (LCOS). Patients with ACS or NYHA class IV heart failure (see Table 24-5) are at high risk of LCOS. If the patient develops cardiogenic shock, often requiring an IABP to maintain stable hemodynamics, the patient is in the highest risk category. Patients who have had bare metal stents implanted within 3 months of surgery and/or drug-eluting stents within 1 year of surgery will have special considerations because of their antiplatelet therapy. The general management of drugs affecting coagulation has already been discussed. However, in patients with recent coronary stents, the cardiologist and surgeon collaborate to determine the best management for the individual patient. For emergency procedures, both aspirin and glycoprotein IIb/IIIa inhibitors may be continued despite the increased risk of bleeding.[110]

Optimizing myocardial oxygen supply and minimizing demand are clearly key anesthetic considerations in CABG surgery (see Figure 24-1). The patient must be monitored carefully for ischemia throughout the procedure. Using a combination of ECG and TEE findings, together with direct inspection of the heart, is advised.[92] Table 24-1 outlines causes and treatments for myocardial ischemia. Anesthetic considerations are summarized in Table 24-9. It is most important to keep a relatively high MAP to maintain coronary perfusion, while keeping the heart rate and LVEDP low. Patients with left-main and triple-vessel disease should have an arterial line and large-bore IV in place before induction so that hypotension can be treated promptly. Beta-blockers are used to control heart rate, and the preferred vasodilator for CABG is nitroglycerin.[110] Preoperative beta-blockade is a quality metric for both the National Quality Forum and the STS database, which is used for quality report cards in conjunction with Consumer Reports.[111,112] In low doses, nitroglycerin acts immediately to reduce preload by decreasing vascular tone; in higher doses it also decreases coronary artery resistance. Kaplan showed that nitroglycerin is superior to nitroprusside in CABG patients.[113]

Volatile anesthetics should also comprise part of the anesthetic plan because of their preconditioning effect.[95] Nitrous oxide should be avoided because of the possibility of expanding gaseous spaces. Patients considered for fast-track protocols, generally those with EFs above 35%, should receive a limited dose of narcotics. The highest-risk patients may still require a primary narcotic technique to maintain hemodynamic stability.

Conventional on-pump CABG surgery is performed through a median sternotomy with CPB. Different types of conduit can be used to bypass occluded areas of the patient's native coronary arteries to revascularize the myocardium distal to the occlusions

TABLE 24-9 Anesthetic Considerations in the Management of CABG

Factor	Hemodynamic Consideration	Anesthetic Considerations
Preload	Decrease	↓ LVEDP will ↑ MvO_2 supply and ↓ demand Nitroglycerin selectively dilates coronary vessels
Heart rate	Slow normal	Too fast → ischemia; consider β-blockade Too slow → not enough CO for coronary perfusion
Rhythm	Maintain sinus	Maintains atrial contribution to cardiac output
Compliance	Decrease	Concentric ventricular hypertrophy common with history of hypertension
Contractility	Depress if normal LVF	↓ Contractility → ↓ MvO_2 demand If poor LVF, may not tolerate depression
SVR	Maintain	Hypertension better tolerated than hypotension Treat hypotension promptly with phenylephrine
PVR	Maintain	Usually not a problem

↓, Decrease; ↑, increased; →, leads to; β, Beta; *CABG*, coronary artery bypass graft; *CO*, cardiac output; *LVEDP*, left ventricular end-diastolic pressure; *LVF*, left ventricular function; MvO_2, myocardial oxygen demand; *PVR*, pulmonary vascular resistance; *SVR*, systemic vascular resistance.

(Figure 24-11). The surgeon must take into consideration the viability of the myocardium, quality of the target vessel, and the type and length of conduit needed to reach distal to the occlusions. The most commonly used conduits are the internal thoracic arteries (formerly internal mammary arteries) and greater saphenous veins. The free radial artery graft is popular with some surgeons whereas others question its long-term patency.[114] Arterial grafts are generally reserved for high-grade lesions because flow in the native coronary can compete with flow in the arterial bypass graft. If there is not enough flow in the muscular artery, it will spasm and shut down. Topical (papaverine) and intravenous antispasmodic drugs such as calcium channel blockers or low-dose nitroglycerin infused intraoperatively is used to treat spasm.

The left internal thoracic artery (LITA) is usually left in situ at its proximal origin from the left subclavian artery, dissected from the chest wall, and most commonly anastamosed to the left anterior descending (LAD) artery. A LITA graft to the LAD artery has a 10-year patency rate of 85% to 99.1%.[115,116] The right internal thoracic artery (RITA) is usually transected from its proximal origin to become a free graft with its proximal anastomosis off the aorta or another conduit. The surgical table is elevated and turned while the internal thoracic artery (ITA) is dissected. Lung volumes are reduced to improve the surgical view. The patient's arm should be well padded because the axillary artery can be compressed by the chest wall retractor, lowering radial A-line pressures. A noninvasive cuff on the contralateral arm helps confirm the diagnosis. Heparin is usually administered before the LITA pedicle is clamped.

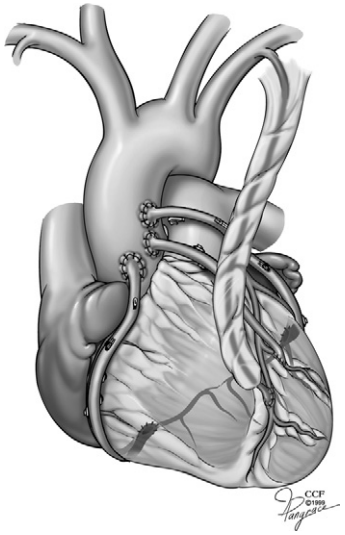


FIGURE 24-11 Coronary artery bypass graft (CABG) surgery. The in-situ left internal thoracic artery (ITA) is most often grafted to the left anterior descending (LAD) native coronary. Free grafts (saphenous vein grafts [SVGs], free radial artery, or right internal thoracic artery) are anastomosed proximally to the aorta (or branched from another bypass—not shown) and distally to a *target* area of the native coronary vessel that is beyond the obstruction. (Reprinted with permission from Cleveland Clinic Center for Medical Art & Photography © 2006-2012. All rights reserved.)

The saphenous vein graft (SVG) and radial artery conduit can be harvested by open surgery or endoscopically. As with any endoscopic procedure, the respiratory rate may have to be increased to compensate for the addition of carbon dioxide. Most vein grafts are now removed endoscopically, but there are concerns that endovascular vein harvest (EVH) might decrease long-term graft patency.[117,118] The surgeon reverses the vein to avoid the valves. The distal anastomosis to the native coronary artery is usually completed first and then the proximal portion is sewn to the aorta or bridged off another graft.

Several surgical and technical complications can result in ischemia. In addition to the previously mentioned concerns about reoperations, patients who have undergone prior CABG surgery may have a patent LITA or other grafts lying directly under the sternum. Sternotomy can lead to marked ischemia if flow in the vessel is accidentally disrupted. The surgeon must take care to make bypass grafts the perfect length. LITA grafts that are too short can be overstretched with vigorous lung inflation and SVGs can be overstretched when the heart is filled. On the other hand, grafts that are too long can kink when the chest is closed. Other causes of ischemia include coronary embolization of air or debris (discussed earlier) and coronary spasm.

Anesthetic Considerations and Surgical Options for Off-Pump CABG

The first off-pump coronary artery bypass (OPCAB) procedures were attempted in the 1950s, but there has been a resurgence in popularity since retractors and epicardial stabilizing devices such as the Octopus (Medtronic) were developed in the 1990s. Off-pump surgery is also called *beating heart bypass surgery*. Although the procedure is typically performed through a full median sternotomy without the aid of CPB, a perfusionist and a primed or dry pump (based on surgical preference) should be in the OR on standby throughout the case. Occasionally a limited anterior

thoracotomy (minimally invasive coronary artery bypass [MIDCAB]) approach is used. The implications of the MIDCAB incision are detailed in the section on minimally invasive surgery. It is estimated that OPCAB accounts for 20% to 30% of all CABG procedures.[110] OPCAB is performed to avoid the risks and complications associated with conventional CABG and CPB, but further research is necessary on its relative safety. Aortic cross-clamping is avoided, theoretically decreasing the risk of debris embolization. Recent studies comparing the techniques showed that patients from both groups had equivalent rises in inflammatory biomarkers[119] and similar neuropsychologic outcomes.[120] Additionally, incomplete revascularization was slightly more common in the OPCAB patients and 1-year patency significantly worse.[120] The STS recommends OPCAB as a blood conservation technique.[47]

Anesthetic implications and monitoring are similar to those of on-pump CABG with a few additional concerns. The procedure is usually limited to patients with relatively good LV function and bleeding is less of a concern, so patients are even more likely to be candidates for a fast-track anesthetic plan. Volume depletion is not uncommon in patients admitted to the OR. In contrast to on-pump cases, in which patients are going to be diluted by priming volume, OPCAB patients require crystalloid and/or colloid solutions to correct fluid deficit and the hemodynamic changes inherent to the procedure. Patient temperature likewise cannot be corrected on-pump; therefore hypothermia becomes a concern. Normothermia is maintained by warming the room and using fluid warmers, warm water mattresses, or forced-air warming devices. Anticoagulation is necessary, but the decision to partially heparinize (100-200 units/kg with an intended ACT of more than 300 seconds) or fully heparinize (300-400 units/kg with an intended ACT of more than 400 or 480 seconds) depends on the surgeon's preference. ACTs should be monitored at least every 30 minutes and heparin administered as needed to maintain adequate anticoagulation. Aminocaproic acid is not routinely used because the blood is not exposed to CPB. Arterial blood gases, electrolytes, and blood glucose should be monitored every half-hour to 1 hour and should be treated.

To perform the bypass on the beating heart, the surgeon employs specialized compressive footplate stabilizers (Figure 24-12) and retractors that use suction to lift and suspend the heart, *verticalizing* the apex (Figure 24-13). These maneuvers compress cardiac chambers and distort valvular apparatuses, resulting in well-documented hemodynamic compromise and acute ischemia.[121,122] Every team member needs to be prepared for the possibility of converting to an on-pump procedure in case of hemodynamic deterioration. Less myocardial manipulation is needed to bypass the LAD or diagonal coronary artery lesions (see Figure 24-12), but as shown in Figure 24-13, near verticalization of the apex is necessary to expose the posterior lateral wall for posterior descending artery (PDA) and circumflex lesions to be grafted. Some surgeons routinely shunt the coronary lesion being grafted, whereas others only shunt the lesion if regional ischemia develops. Close communication between the anesthesia providers and the surgical team is critical. Monitoring must be vigilant and interventions timely. The CPP is maintained by keeping a relatively high MAP (90-100 mmHg) during distal anastomosis. Hypotension is initially treated with volume and vasopressors, by bolus or infusion as needed to maintain the blood pressure. The Trendelenburg position will facilitate surgical exposure and help restore MAP and cardiac output.[123,124] Occasionally patients will also require an inotrope to maintain hemodynamic stability. Dramatic hemodynamic changes can occur when the heart returns to a physiologic position, necessitating the abrupt withdrawal of pharmacologic support. Later, when the surgeon uses a side-clamp to perform the proximal graft-aortic anastomoses, the MAP is routinely lowered to around 60 to 70 mmHg. Surgical drying and closure is often more rapid in off-pump than in on-pump procedures, because bleeding is minimized.

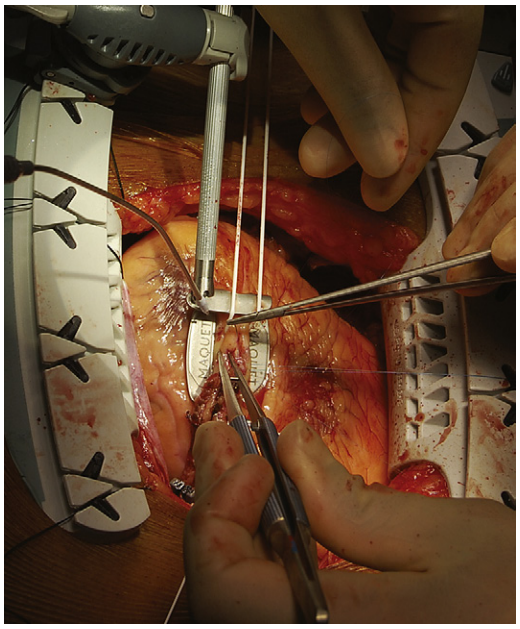


FIGURE **24-12** Left anterior descending (LAD) artery anastomosis during off-pump coronary artery bypass grafting using a left internal mammary artery (LIMA) graft. The view is from the head of the patient. The Maquet mechanical stabilizer (MAQUET, Wayne, NJ) is in place together with vascular snare sutures used to transiently occlude the artery. The LIMA is being anastomosed to the LAD, assisted by use of pressurized and heavily humidified carbon dioxide ("mister blower" metal cannula) to facilitate visualization of the vessel lumen. (Courtesy Alexander Mittnacht, MD, Mount Sinai School of Medicine, New York, NY.)

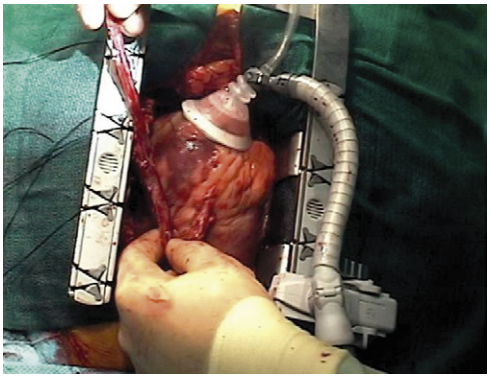


FIGURE **24-13** Verticalization of the cardiac apex in an off-pump coronary artery bypass (OPCAB) operation. (From Miller RD, et al. *Miller's Anesthesia*. 7th ed. Philadelphia: Churchill Livingstone; 2009.)

Valvular Heart Disease and Cardiac Valve Surgery

Although the prevalence of rheumatic heart disease has decreased in industrialized countries, degenerative heart disease, which correlates closely with advanced age, is increasing. It is estimated that 2.5% of the overall U.S. population has valvular heart disease, but prevalence rises dramatically with increasing age, reaching 13.2% after the age of 75.[125] Infective endocarditis is also an important cause of valvular disease, and patients who have this condition can

be unusually challenging for both the surgeon and the anesthetist. The proportion of cardiac surgeries that include valvular procedures has doubled over the past two decades.[126] Currently 20% of cardiac surgeries involve valve repair or replacement, and a significant proportion of these cases will include multiple lesions or concurrent myocardial revascularization. Aortic stenosis is the most common valvular defect requiring surgical intervention, followed by mitral regurgitation, aortic regurgitation, and finally, mitral stenosis. Right-sided valvular disease occurs much less often.[125] Often multiple lesions are present and a valve may exhibit both stenosis and regurgitation. In this condition, usually one problem predominates and management is dictated by the pathology causing the majority of the patient's symptoms.

Valvular heart disease causes abnormalities in the pressure and volume-loading conditions of the heart that result in structural and functional changes. Management requires a clear understanding of the anatomy, pathophysiology, and natural history of each lesion as discussed in Chapter 23. Echocardiography is an invaluable tool in the diagnosis and management of valvular heart disease. Three factors determine valvular flow: valve area, the pressure gradient across the valve, and the duration of flow in systole or diastole. Management of valvular heart disease requires hemodynamic manipulation of heart rate and rhythm, preload, afterload, and contractility to enhance forward flow in stenotic lesions and to minimize backward flow in regurgitant lesions. Although hypertrophic cardiomyopathy (HCM) is not technically a valvular defect, its hemodynamic management is similar to that of aortic stenosis, so it is addressed in this section of the chapter.

Aortic Stenosis

Aortic stenosis (AS) is the most common valvular lesion among patients in industrialized countries. About 1% to 2% of the population has a congenitally bicuspid valve. This valve has a smaller orifice, which subjects the valve apparatus to increased sheer stress and degeneration. Hence the majority of younger patients (30-50 years of age) undergoing valve replacement have bicuspid valves.[127] Risk factors for the development of acquired aortic stenosis are the same as those for atherosclerosis: increased age, male gender, smoking, hypertension, and hyperlipidemia. The prevalence markedly increases with age.[9] About two thirds of aortic valve replacements are combined with CABG.[125] Some patients will be referred for aortic valve replacement (AVR) in preparation for subsequent noncardiac surgery because aortic stenosis is one of the active cardiac conditions for which the AHA and ACC recommend intensive management before noncardiac surgery.[128]

Pathophysiology. The normal aortic valve measures 3 cm^2 ± 1 cm^2. Stenosis is considered severe when the valve area decreases to 1 cm^2 and critical when it is 0.7 cm^2 or less. The stenotic orifice obstructs the LV outflow and the ventricle compensates by becoming thicker (concentric hypertrophy), attempting to generate enough pressure to push the blood forward past the stenosis. This forward motion causes accelerated, turbulent blood flow as it crosses the valve, somewhat like the water flow when a garden hose is partially occluded. Secondary to the Venturi effect, this increased flow results in a pressure drop as it crosses the valve so that pressure in the aorta is significantly less than the pressure in the LV. A jet velocity 4.0 m/sec or more and a mean pressure gradient drop of 40 mmHg or more suggests severe AS. The pressure drop results in a characteristic slow upstroke and high dicrotic notch on the A-line with a classic narrow pulse pressure (systolic − diastolic) associated with AS. The thick, hypertrophied cardiac muscle mass has a high oxygen requirement and increased LVEDP. The high ventricular pressure inhibits coronary perfusion. Because there is a high prevalence (more than 50%) of coexisting CAD, the patient with AS is very prone to ischemia. The fibrosed ventricle is noncompliant; consequently, diastolic filling becomes compromised even though LV systolic function is initially normal. Patients with AS are dependent on atrial augmentation of their cardiac output. Atrial kick can contribute up to 40% of LVEDV. The classic triad of AS symptoms—angina, syncope, and congestion causing dyspnea—correlate closely with 5-, 3-, and 2-year survival, respectively.[9] Ventricular function remains normal until late in the course of the disease, when the LV loses systolic function and dilates.

Anesthetic Considerations and Surgical Options. Valve replacement is indicated in symptomatic patients or in patients who manifest a reduction in LVF.[127,129] Preoperatively, great caution is required in treating angina with nitrates because hypotension can initiate a rapidly developing downward spiral of decreasing coronary perfusion, which can result in cardiac arrest and sudden death. Cardiac compressions can rarely generate enough pressure to provide adequate coronary perfusion to permit resuscitation. In patients with AS, hypotension should therefore be treated aggressively with phenylephrine to prevent this hemodynamic decompensation.[73]

Anesthetic management follows directly from an understanding of cardiovascular pathophysiology. Table 24-10 outlines the anesthetic considerations. The anesthesia provider must be prepared for hemodynamic instability on induction and should choose the medications and speed of their administration accordingly. Patients often present with a significant degree of hypertension preoperatively. The blood pressure may rise or fall abruptly during the case depending on the level of stimulation. Hypertension is better tolerated than hypotension, but keep in mind that hypertension can also be a source of increased myocardial oxygen demand. Patients with severe AS have at least a 40 to 50 mmHg mean pressure gradient between the left ventricle and the aorta. Consequently, a systolic pressure of 180 mmHg in the aorta means that systolic pressure in the left ventricle is at least 220 mmHg.[130] Tachycardia decreases the diastolic time needed for adequate coronary perfusion and ventricular filling while increasing myocardial oxygen demand at the same time. Hypotension or tachycardia must be treated promptly to avoid increased myocardial consumption, which can provoke the cycle of ischemia that can be disastrous. All vasodilators should be titrated cautiously. High-dose inhalation anesthesia can be problematic if it leads to a nodal rhythm with loss of atrial augmentation of cardiac output.

Stenotic aortic valves rarely lend themselves to repair. The choice of valve depends on patient preference, age, and comorbidities, but about 80% are replaced with a bioprosthetic (tissue) valve. Other options include a mechanical valve, aortic homograft (cadaver valve), or a Ross procedure, which uses the native pulmonic valve. Table 24-11 shows various surgical options and key points about each alternative. Mechanical valves can theoretically last a lifetime, but the patient is required to take Coumadin and occasionally prophylaxis against endocarditis.[131] It should be noted that the recommendations for antibiotic prophylaxis in patients with valvular heart disease have undergone important revisions that are clearer and should improve compliance. Although tissue valves do not require Coumadin, they nevertheless degenerate over time. In a 50-year-old patient, there is a 50% chance that the valve will have to be replaced in 15 years. A tissue heart valve tends to last longer as the recipient's age increases. The STS mortality risk benchmark for an isolated aortic valve replacement is

TABLE 24-10 Anesthetic Considerations in the Management of Aortic Stenosis

Factor	Hemodynamic Consideration	Anesthetic Considerations
Preload	Increase	Need volume to stretch noncompliant LV Increased preload reduces the gradient across LVOT LVEDP greater than LVEDV—Use echo to evaluate
Heart rate	Slow Normal	Too fast →, ischemia Too slow →, not enough CO for coronary perfusion
Rhythm	Maintain Sinus	Atrial kick can contribute up to 40% of LVEDV Cardiovert early
Compliance	Reduced	Thick, sclerotic LV prone to diastolic failure ↑ LVEDP reduces coronary perfusion Cautiously treat with NTG maintaining LVEDV and MAP
Contractility	Normal LVF till late in course	Concentric hypertrophy with normal chamber size Normal or ↑ EF initially Late dilation and falling EF
SVR	Elevated and relatively fixed	Hypertension better tolerated than hypotension Treat hypotension promptly with phenylephrine Dilate cautiously for severe hypertension
PVR	Normal till late in course	Diastolic failure can lead to dyspnea

↑, Increased; ↓ leads to; *CO*, cardiac output; *EF*, ejection fraction; *LV*, left ventricle; *LVEDP*, left ventricular end-diastolic pressure; *LVEDV*, left ventricular end-diastolic volume; *LVF*, left ventricular function; *LVOT*, left ventricular outflow tract; *MAP*, mean arterial pressure; *NTG*, nitroglycerin; *PVR*, pulmonary vascular resistance; *SVR*, systemic vascular resistance.

2.4% in an otherwise healthy patient, but can increase to over 15% if the patient has multiple comorbidities and the surgery is combined with other procedures.[69] According to the STS database, in 2010 there were 25,219 isolated aortic valve replacements (AVR) and 18,040 combined AVR and CABG.[132]

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is the preferred contemporary nomenclature for this disease, but it was formerly known as idiopathic hypertrophic subaortic stenosis (IHSS) or hypertrophic obstructive cardiomyopathy (HOCM). HCM is a common familial inherited disease that affects globally about 1 in 500 persons of all ages. It is a heterogeneous disease with diverse clinical presentations ranging from asymptomatic to life-threatening. When complications of HCM develop, they fall into three categories, which are not mutually exclusive: ventricular tachydysrhythmias, which can lead to sudden cardiac death, especially in young athletes; progressive diastolic heart failure, despite normal LV function; and atrial fibrillation, with a predisposition to stroke. It is recommended that diagnosis and treatment of HCM take place in a clinical center that specializes in management of this disease.[127]

Pathophysiology. Concentric LVH is the primary problem in HCM as opposed to AS, in which the LVH is secondary to stenosis. The pathophysiology of HCM is complex and can include left ventricular outflow tract (LVOT) obstruction, mitral regurgitation, diastolic dysfunction, ischemia, and dysrhythmias. HCM can be either obstructive or nonobstructive, based on the degree of outflow tract obstruction and the presence or absence of systolic anterior motion (SAM—discussed later.) Clinical management is guided by this finding. Echocardiography is used to determine the presence of obstruction and to document the gradient across the obstruction. A gradient of more than 30 mmHg is considered significant, and greater than 50 mmHg is the conventional threshold for surgical or percutaneous intervention if symptoms persist despite optimal medical management. About one third of patients manifest nonobstructive HCM, one third manifest obstruction even at rest, and finally, one third have variable obstruction based on loading conditions. About 25% of patients exhibit autonomic dysfunction that causes their blood pressure to decrease or increase only slightly in response to exercise, which increases the degree of obstruction.[133]

Because of LVH, patients can have angina and ischemia even without significant CAD.[9] Some patients will present with dyspnea, angina, and syncope; but in more than half the cases, sudden death or cardiac arrest is the presenting finding. It is imperative that HCM patients be evaluated for the risk of sudden cardiac death (SCD).[73] In the subset of patients in whom septal hypertrophy has become so extensive as that it obstructs the LVOT, ventricular contraction becomes hyperdynamic, forcing the blood to eject at high velocity to pass the obstruction. This rapid blood flow can then lead to a Venturi effect that causes the anterior leaflet of the mitral valve to be pulled into contact with the septal wall during systole, a phenomenon called *systolic anterior motion* (SAM) of the mitral valve. SAM increases LVOT obstruction and causes mitral regurgitation (MR). Any reduction in ventricular volume, directly or reflexively, will increase the degree of SAM–septal wall contact and exacerbate LVOT obstruction. Therefore, increases in heart rate and contractility and/or decreases in preload and afterload must be avoided.[134]

Medical management of HCM includes treatment of comorbidities, β-blockers to prevent sympathetically induced tachycardia and to treat atrial fibrillation, calcium channel blockers to improve diastolic relaxation, and disopyramide or other antidysrhythmics to reduce contractility and treat dysrhythmias. It is also important to maintain sinus rhythm, because as with AS, the atrial contribution to cardiac output can be considerable. Patients with a history of cardiac arrest or symptomatic ventricular dysrhythmias will likely have internal cardiac defibrillators (ICDs). ICDs should have their antitachyarrhythmia function suspended before surgery to prevent electrocautery-induced discharge. Other nonsurgical invasive therapies include septal ethanol ablation and biventricular pacing, in which the goal is slight pre-excitation of the RV apex, resulting in paradoxical septal motion that decreases the ejection velocity and reduces SAM.[135] Biventricular pacing is reserved for patients who are inappropriate candidates for surgical correction or alcohol ablation or who have a biventricular pacer implanted for another reason.[11,127,136]

Anesthetic Considerations and Surgical Options. Patients who remain symptomatic with gradients of 50 mmHg despite optimal medical management are candidates for septal reduction therapy. Surgical septal myotomy via the aortic approach at an experienced surgery center is preferred over alcohol septal ablation.[133] Approximately two thirds of patients will also have structural malformations of the mitral valve. It is not uncommon to find that the mitral valve will need repair or replacement at the time of myectomy.[73] Anesthetic management (Table 24-12) is

TABLE 24-11 Surgical Options for the Aortic Valve

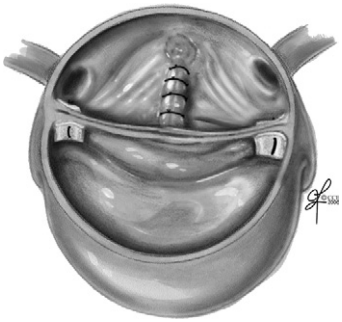
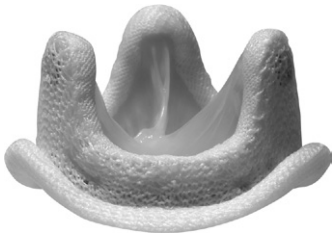
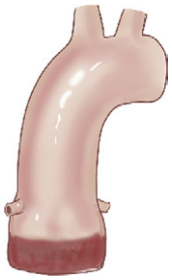
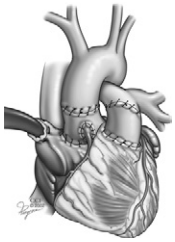
Surgical Option	Surgical Considerations
Repair	
 (Reprinted with permission from Cleveland Clinic Center for Medical Art & Photography © 2006-2012. All rights reserved.)	Used for aortic regurgitation, usually due to bicuspid valve Technically more difficult than mitral repair Can last a lifetime, but 20%-25% need replaced in 10 years Preserves heart muscle strength and natural heart anatomy Decreased risk of infection Decreased requirement for life long anticoagulation
Replacement with a Mechanical Valve	
 (Courtesy Medtronic Inc., Minneapolis, Minn.)	Designed to last a lifetime Require the use of lifetime anticoagulation so lifestyle, childbearing, and compliance must be considered Some antibiotic prophylaxis Some make a clicking noise
Replacement with a Bioprosthetic (Tissue) Valve	
 (Courtesy Medtronic Inc., Minneapolis, Minn.)	Made of cow (bovine) or pig (porcine) pericardium sewn on a frame Coumadin not required unless patient is in atrial fibrillation At age 40, 50% chance of lasting 15 years, but generally less durable if younger and more durable if older at age of implantation Straightforward, relatively low risk
Replacement with a Homograft (Also Called Allograft)	
 (From Otto CM, Bonow RO. *Valvular Heart Disease: A Companion to Braunwald's Heart Disease.* 3rd ed. Philadelphia: Saunders; 2009.)	Human aortic or pulmonic valve Ideal for endocarditis because they are least prone to infection May be good choice for athletes because of excellent flow characteristics and no need to take Coumadin Technically challenging and limited availability Last only about 15 years; durability varies with age
Ross Procedure (Also Called Switch Procedure)	
 (Reprinted with permission from Cleveland Clinic Center for Medical Art & Photography © 2006-2012. All rights reserved.)	Patient's own pulmonary valve is removed and used to replace the aortic valve; coronaries are reimplanted Pulmonary valve is replaced with a pulmonary homograft Main advantage is that the valves can grow, so a good choice in teens Lifetime anticoagulation is not required Pulmonary autograft (in aortic position) has about a 50% chance of lasting a lifetime; pulmonary homograft has a 10% chance of needing replacement in 10 years Technically difficult and reoperation is challenging

TABLE 24-12 Anesthetic Considerations in the Management of HOCM

Factor	Hemodynamic Consideration	Anesthetic Considerations
Preload	Increase	Volume is key → optimize preload to: Stretch noncompliant LV Reduces the gradient across LVOT Prevent SAM and MR Volume is first treatment for hypotension LVEDP greater than LVEDV—Evaluate with echo
Heart rate	Low-normal	Too fast → ischemia and not enough time for ventricular filling
Rhythm	Maintain Sinus	Atrial kick contributes LVEDV Cardiovert early
Compliance	Reduced	Due to concentric hypertrophy
Contractility	Usually hyperdynamic	Inhalation agents and/or β-blockers are used to depress
SVR	Avoid reductions	Hypertension better tolerated than hypotension Treat hypotension with volume and phenylephrine
PVR	Maintain	Not usually a problem

↑, Increased; ↓, decreased, leads to; *EF,* ejection fraction; *HOCM,* hypertrophic obstructive cardiomyopathy; *LV,* left ventricle; *LVEDP,* left ventricular end-diastolic pressure; *LVEDV,* left ventricular end-diastolic volume; *LVOT,* left ventricular outflow tract; *MR,* mitral regurgitation; *PVR,* pulmonary vascular resistance; *SAM,* systolic anterior motion of the mitral valve; *SVR,* systemic vascular resistance.

directed at optimizing preload, avoiding increases in septal wall–anterior leaflet contact caused by increases in heart rate or contractility, and preventing sudden reductions in afterload. Excision of the hypertrophied basal septum may result in disruption of the conduction system of the heart with new-onset heart block requiring pacing. After CPB is terminated, the outflow tract and mitral valve are examined using TEE.[9] To determine adequacy of surgical repair, the patient's heart rate and contractility are deliberately increased while the blood pressure is simultaneously decreased with an infusion of isoproterenol, dobutamine, or rapid ventricular pacing (rate of 120 bpm) The medications are used to mimic the physiologic hyperdynamic state, such as exercising. The echocardiographic examination will reveal whether obstruction, SAM, or MR develops with the tachycardia and hypotension. If more muscle needs to be excised or the valve needs repair or replacement to prevent SAM, CPB will resume so the surgeon can make the necessary adjustments.

Aortic Insufficiency or Regurgitation

Aortic insufficiency (AI) or regurgitation occurs because malcoaptation of the aortic valve leaflet or annular dilation allows a portion of the ejected stroke volume to be regurgitated or flow backward during diastole from the aorta into the LV. The regurgitant blood flow causes the left ventricle to be volume overloaded. AI can develop acutely or chronically and can be caused by a primary disease affecting the valve itself or secondary as a result of aortic root dilation. Acute AI results in rapid deterioration and is most frequently caused by trauma, endocarditis, or aortic dissection. Chronic AI can be tolerated for decades and can develop due to long-standing calcific degeneration, a congenitally bicuspid aortic valve, rheumatic fever, inflammatory or connective tissue diseases, idiopathic aortic root or valve dilation, hypertension-induced aortoannular ectasia, syphilis, or Marfan and Ehlers-Danlos syndromes.[137]

Pathophysiology. The increased LVEDV causes increased diastolic wall tension that leads to a pattern of LV enlargement known as *eccentric hypertrophy* whereby the sarcomeres replicate in series. By virtue of the Frank-Starling mechanism, the increased preload results in a large stroke volume that in turn rapidly raises aortic systolic pressure. Diastolic run-off is rapid as well, because blood can progress forward down the aorta or retrograde through an incompetent aortic valve back into the LV. The rapid systolic ejection and diastolic run-off leads to the well-described physical examination finding of widened pulse pressure (systolic − diastolic), a bounding pulse and an arterial waveform with rapid rise in systolic pressure and low dicrotic notch. Sometimes a double systolic peak called *pulsus bisferiens* can be seen on the arterial line. The magnitude of the regurgitant volume is directly proportional to regurgitant orifice size, diastolic time, and SVR. Ventricular compliance is increased and LVEDV can be three to four times greater than normal. The regurgitation is graded as mild (1+ [<40%]) to severe (4+ [>60%]), based on echocardiographic findings. As volume overload progresses, wall tension also increases, resulting in LV pressure overload and some degree of concentric hypertrophy.[103,138] The hypertrophy increases oxygen demand and angina can develop in patients with normal coronaries. However, the oxygen debt incurred for muscle shortening is relatively low so that ischemia is much less of a problem than with AS.[9] The natural history of chronic AI is such that dilation occurs slowly over years so that the ventricle compensates allowing the patient to be asymptomatic until AI is severe, causing permanent LV dysfunction. Surgery is recommended before ventricular function falls below 55%. Even after symptoms develop, life expectancy remains at 9 years as opposed to severe AS, for which the prognosis is more ominous.[138]

Acute AI can cause rapid deterioration because the normal ventricle is unable to compensate for the sudden increase in volume. Ventricular distension leads to increased LVEDV and pressure. As the LVEDP approaches aortic diastolic pressure, coronary perfusion decreases and this in turn causes ischemia and systolic dysfunction. Pulmonary congestion is likely because the forward blood flow from the LA is reduced due to higher LV diastolic volume and pressure. Mitral regurgitation can develop as the LV dilates further.[139] TEE is invaluable in the etiologic diagnosis and treatment of acute AI and can help determine the need for urgent or emergent surgery.

Anesthetic Considerations and Surgical Options. Hemodynamic management of AI (Table 24-13) is focused on enhancing forward flow and minimizing the regurgitant volume. A relatively high heart rate is used to minimize diastolic time. Judicious vasodilation lowers the SVR to enhance forward flow and reduce the regurgitant volume while still maintaining adequate pressure to support coronary perfusion.

During CPB, AI can lead to ventricular distention and pressure overload that directly opposes coronary perfusion and myocardial preservation. When CPB is initiated, a slow heart rate or ventricular fibrillation can lead to distension. After the aortic cross-clamp is applied, cardioplegia that is usually infused into the aortic root intended for antegrade flow down the coronaries can instead run into the LV secondary to the aortic valve's incompetence. Even mild to moderate AI can cause distention;

TABLE 24-13 Anesthetic Considerations in the Management of Aortic Insufficiency

Factor	Hemodynamic Consideration	Anesthetic Considerations
Preload	Increased	Need increased volume to maintain forward flow
Heart rate	High-normal	Decreased diastolic time minimizes regurgitation Avoid bradycardia
Rhythm	Usually sinus	Not usually a concern
Compliance	Increased	Eccentric hypertrophy can lead to a LVEDV 3-4 times normal Return large pump volume judiciously after bypass to prevent failure
Contractility	Normal LVF till late	Surgery indicated when EF less than 55% May need inotropes after pump
SVR	Decrease	Judicious vasodilation enhances forward flow
PVR	Increased with acute AI	Acute failure develops rapidly
CPB	LV distention	Can develop due to slow HR or nonbeating heart Consider LV vent; retrograde or ostial cardioplegia

AI, Aortic insufficiency; *CPB,* cardiopulmonary bypass; *EF,* ejection fraction; *HR,* heart rate; *LV,* left ventricle; *LVEDV,* left ventricular end-diastolic volume; *LVF,* left ventricular function; *PVR,* pulmonary vascular resistance; *SVR,* systemic vascular resistance.

consequently, the presence of AI increases the risk of other cardiac surgical procedures as well. Achieving diastolic standstill in these situations often requires cardioplegia to be delivered directly into the coronary ostia and/or retrograde through the coronary sinus. An LV vent is placed to suction away fluid, thereby alleviating or preventing distension. A positive inotrope is often useful after CPB, especially if there was LV dysfunction prebypass or questionable preservation during bypass.

Valve repair is possible but technically more challenging than mitral repair. Traditional replacement options are the same as for aortic stenosis (see Table 24-11). Percutaneous replacement is discussed later in the chapter, but this procedure is limited to severe inoperable stenotic lesions at this time.

Mitral Stenosis

Mitral stenosis (MS) is the least common left-sided valvular defect because it is caused primarily by rheumatic heart disease (RHD), which is now rare in developed countries. Although RHD affects men and women equally, MS is 2 to 3 times more prevalent in women. Occasionally MS also develops as the result of severe mitral annular calcification caused by the atherosclerotic process. Clinically, significant stenosis takes decades to develop and symptoms does not usually appear until the normal 4 to 5 cm^2 valve area is reduced to 2.5 cm^2.[140]

Pathophysiology. As the valve orifice narrows, diastolic filling of the LV is limited and a pressure gradient develops across the mitral valve. Initially, left atrial pressure increases, which can result in pulmonary hypertension (PHTN). Eventually right ventricular failure can develop if the PHTN is left uncorrected. Stenosis is considered severe when the valve area is less than 1.0 cm^2, the mean gradient exceeds 10 mmHg, and pulmonary artery systolic pressures are greater than 50 mmHg.[136] The presence of PHTN increases the risk of surgery by 4% to 9%.[141] Flow across the valve will decrease in response to an increase in cardiac output or a decrease in diastolic time. Hence, symptoms are usually first experienced during exercise or stress. Conditions such as pregnancy and sepsis may provoke atrial fibrillation (AF) in a previously asymptomatic patient, leading to decompensation. Approximately 40% of patients develop AF. The rapid heart rate is the primary cause of hemodynamic instability, rather than the loss of atrial kick. Patients with MS and AF have an embolic stroke rate of 7% to 15% per year. Long-term anticoagulation and heart rate control are important in the management of MS.[136]

Anesthetic Considerations and Surgical Options. Although avoiding tachycardia and treating AF helps control the symptoms, MS causes mechanical obstruction to ventricular filling. The three procedures used to relieve this obstruction are mitral baloon valvotomy, open commissurotomy of the mitral valve, and replacement with a mechanical or biologic valve. Closed commissurotomy is no longer recommended. Valvotomy or repair is generally preferred to replacement, but a left atrial thrombus, concurrent mitral regurgitation, or annular calcification may make replacement the treatment of choice. If the patient has a history of AF and the valve is approached through a full sternotomy, the surgeon will often elect to add a Maze procedure or pulmonary vein isolation to treat AF. Choice of the traditional cut-and-sew technique, radiofrequency (heat), or cryotherapy (cold) ablation is based primarily on surgical preference. Anesthetic considerations for the Maze procedure and other options for atrial ablation are discussed after the valve section of this chapter.

Anesthetic considerations for MS are outlined in Table 24-14. Keeping the heart rate low-normal is a priority so there is adequate time in diastole time to fill the LV. If atrial fibrillation is present or develops, the ventricular rate must be controlled. Conditions or situations that could exacerbate pulmonary hypertension should be avoided. These include hypercarbia, hypoxemia, nitrous oxide, and the Trendelenburg position. MS is the only valve defect that causes the LV to be chronically underloaded. Volume management can be challenging, because an adequate preload is needed to maintain flow across the stenotic valve, but too much volume can lead to pulmonary congestion. The majority of patients have normal left ventricular function; however, the increase in ventricular volume that occurs after valve replacement can cause the chronically underloaded left ventricle to dilate. If failure occurs, it is generally responsive to inotropic support.[142] Pulmonary hypertension with resultant RV failure can be more problematic. Patients may benefit from mild hypocapnea, judicious vasodilator therapy, and inotropic support with epinephrine or milrinone. In extreme cases, nitric oxide, an inhaled pulmonary vasodilator, may be beneficial in reducing RV afterload. Routine use of nitric oxide is limited by cost.

Mitral Regurgitation or Insufficiency

Mitral regurgitation (MR) or insufficiency occurs during systole when blood is ejected back into the left atrium because of an incompetent mitral valve. The causes of MR are considered organic or structural when the regurgitation is due to a problem with the valve leaflets or chordae; or functional, when insufficiency results from a dilated LV stretching a structurally normal valve. In developed countries, MR is usually caused by degenerative processes, but it can also arise secondary to infective endocarditis, mitral annular calcification, RHD, and connective tissue disorders such as Marfan syndrome. Functional MR is most often caused by ischemic heart disease, but it can also develop in patients who have idiopathic

TABLE 24-14 Anesthetic Considerations in the Management of Mitral Stenosis

Factor	Hemodynamic Consideration	Anesthetic Considerations
Preload	Reduced	LV chronically underloaded Adequate preload needed to maintain flow across valve Avoid hypovolemia
Heart rate	Low-normal	Need adequate diastolic time to fill LV Too fast →; ↑ gradient across valve
Rhythm	Atrial fibrillation in 40%	May decompensate if rapid ventricular response, otherwise reasonably well tolerated
Compliance	Normal	Not a problem
Contractility	LV usually okay but RV can be ↓	LV may need inotropic support after pump Administer volume cautiously after pump, watching for RV dysfunction and volume overload RV may need support with epinephrine or milrinone Judicious RV unloading with NTG or nitric oxide
SVR	Normal	May need vasoconstrictor to offset vasodilation from milrinone, but watch for pulmonary vasoconstriction
PVR	Increased	Pulmonary hypertension can be mild to severe Avoid hypercarbia, hypoxia, acidosis, Trendelenburg position, and nitrous oxide Severe cases may benefit from nitric oxide

↑, Increased; ↓, decreased; →, leads to; *LV*, left ventricle; *NTG*, nitroglycerin; *RV*, right ventricle; *PVR*, pulmonary vascular resistance; *SVR*, systemic vascular resistance.

cardiomyopathy.[142] The presentation of the patient with MR varies depending on the etiology or acuity of the condition.

Pathophysiology. In patients with MR, there is no isovolumetric contraction phase of systole because the LA acts as a low-resistance vent for ventricular ejection. Both the left atrium and ventricle are volume overloaded because the total stroke volume is equivalent to the volume of blood that goes antegrade down the aorta plus the amount of blood that is ejected retrograde into the LA. Consequently, the EF that is calculated by TEE overestimates the actual forward flow. Pressure and volume overload leads to LA dilation. Atrial fibrillation develops in about 50% of the patients who undergo surgery.[73] The amount of regurgitation is dynamic and based on the size of the mitral orifice, the pressure gradient between the LA and LV, the time available for regurgitant flow, and the compliance of the receiving chamber. The LA and LV compensate for the chronic volume overload by eccentrically dilating (parallel replication of sarcomeres), increasing compliance to accommodate the volume loads. Consequently, patients with MR may be asymptomatic for years. Large increases in volume can occur with minimal increases in LA or PAEDP. Increases in heart rate and decreases in preload and/or afterload help minimize the regurgitation and enhance forward flow.[9] Often TEE is used to evaluate the extent of regurgitation while the blood pressure is pharmacologically manipulated at various systolic driving pressures. Eventually volume overload induces pressure overload and LV dysfunction develops. Since cardiac output is an afterload-dependent measurement, it can be normal or only mildly reduced even in the face of significantly compromised ventricular function. An EF of less than 60% in a patient with severe MR represents significant LV dysfunction and is predictive of a poorer outcome.[138] The problem is often first unmasked during the attempt to separate from CPB after valve repair or replacement. Pharmacologic support with epinephrine or dobutamine should be considered if LV dysfunction occurs.[73]

Patients with acute MR often deteriorate rapidly. The LA cannot handle the abrupt increase in volume so the fluid backs up, resulting in acute pulmonary edema and right heart failure. The pulmonary capillary wedge pressure (PCWP) will classically show an enlarged V wave, but the size does not reliably correlate with the degree of MR.[142] Acute MR must often be treated on an urgent or emergent basis with mitral repair or replacement. Oftentimes an intra-aortic baloon pump will be used to increase coronary perfusion, decrease afterload, and support the patient during the perioperative period.[129]

Anesthetic Considerations and Surgical Options. The preload is elevated and must be judiciously maintained or gently reduced to enhance forward flow and minimize regurgitation. Inhalation agents and vasodilators are generally effective in reducing afterload and maintaining heart rate in the high-normal range (Table 24-15). Valve repair or replacement increases afterload and may unmask previously compensated LV dysfunction. An inotrope or inodilator may be needed after bypass. Occasionally SAM develops after repair, especially if the anterior leaflet is long or has redundant tissue. TEE is used to diagnose this problem.[9]

Mitral valve repair is almost always favored over replacement whenever possible, depending on the native valve pathology and on surgical expertise. The advantages of repair include improved postoperative LV function, increased long-term and short-term survival, improved quality of life, lower risk of complications, and less need for long-term anticoagulation.[129,139] Over the past decade, as surgeons have gained experience with valve repair techniques, the volume and approaches to mitral repair have risen dramatically. The mitral valve can be accessed through a traditional sternotomy, partial upper sternotomy, right minithoracotomy, and a robotically assisted endovascular approach. The latest advance in mitral valve repair involves a percutaneously introduced clip. These alternative approaches are discussed later in the chapter. Posterior leaflet problems are often repaired using a triangular or quadrangular resection with a complete or partial annuloplasty ring (Figure 24-14). Involvement of the anterior leaflet increases the complexity of the repair and requires greater surgical expertise because the chords must often be shortened, transferred, or replaced. If the patient has atrial fibrillation, a Maze procedure or ablation may be performed. Severe mitral annular calcification or rheumatic disease may make repair impossible, in which case the valve can be replaced with a tissue or mechanical device.[129]

Surgical Therapy for Atrial Fibrillation

Early in 1990, Cox et al. developed the "Maze" procedure in which several incisions are made in a specified pattern around the atria to create a maze of scar tissue that would block the reentry circuits that cause atrial fibrillation (AF) while still allowing conduction of an impulse from the sinus to the atrioventricular node.[143,144] The original procedure has been improved, so that the Cox-Maze III procedure cures AF 99% of the time. It is indicated for drug intolerance, arrhythmia intolerance, or recurrent embolic

TABLE 24-15 Anesthetic Considerations in the Management of Mitral Regurgitation

Factor	Hemodynamic Consideration	Anesthetic Considerations
Preload	Increased	Cautiously maintain or ↓ to enhance forward flow
Heart rate	High-normal	Decreased diastolic time minimizes regurgitation Avoid bradycardia
Rhythm	Sinus or atrial fibrillation	Not usually a concern as long as rate adequate
Compliance	Increased	Eccentric hypertrophy of LA and LV
Contractility	Normal early Reduced late	Surgery indicated when symptomatic or EF ↓ May have LV dysfunction even with mildly ↓ EF May need inotropes after pump
SVR	Decrease	Cautious vasodilation enhances forward flow
PVR	Avoid further increases	Acute pulmonary edema and/or RV failure can develop with acute MR or longstanding chronic MR May need to treat urgently with MV repair or replacement and/or an IABP
CPB	LV dysfunction	Can be unmasked after surgery

↓, Decrease; *CPB*, cardiopulmonary bypass; *EF*, ejection fraction; *IABP*, intra-aortic baloon pump; *LA*, left atrium; *LV*, left ventricle; *MR*, mitral regurgitation; *MV*, mitral valve; *PVR*, pulmonary vascular resistance; *RV*, right ventricle; *SVR*, systemic vascular resistance.

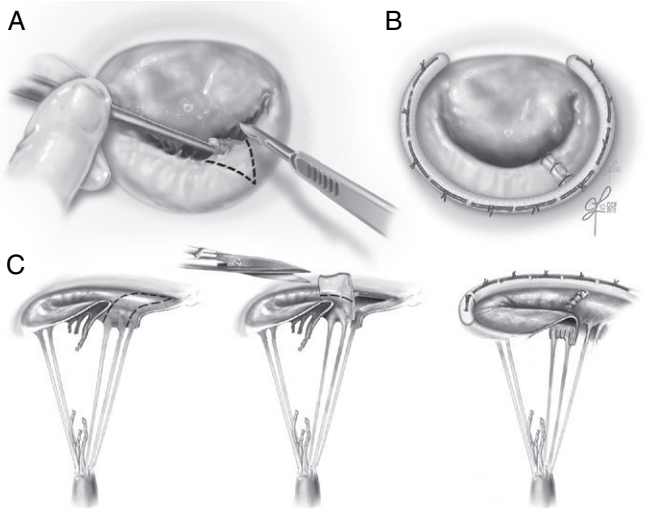


FIGURE 24-14 Mitral valve repair. **A,** Triangular resection is the technique used most often for posterior leaflet prolapse. Region to be resected is indicated. **B,** Abnormal segment has been removed. Leaflet edges are sewn together. An annuloplasty ring completes the repair. **C,** Chordal transfer to correct anterior leaflet prolapse. Posterior leaflet chordae are transferred to the unsupported free edge of the anterior leaflet. The posterior leaflet is repaired with a quadrangular resection. An annuloplasty ring completes the repair. (Reprinted with permission from Cleveland Clinic Center for Medical Art & Photography © 2006-2012. All rights reserved.)

events.[145] The number of surgical and catheter-based techniques used to treat AF has expanded greatly as the understanding of causation has grown. Today many catheter-based ablative procedures are available in the electrophysiology laboratory, but this discussion will be limited to procedures performed in the operating suite.

Surgical procedures used to ablate AF are often carried out in conjunction with, and usually just prior to, other cardiac procedures, but they can also be performed independently. Traditionally, the Maze requires CPB and includes the ligation or stapling of the left atrial appendage because it is considered a major source for emboli. The right atrial appendage is a significant source of atrial natriuretic peptide, so it is not removed. The procedure can be carried out through a traditional sternotomy or through a minimally invasive right anterior thoracotomy with femoral cannulation. Newer technology now allows surgeons to use a variety of alternate energy sources to quickly and simply make lesions that interrupt the reentry pathways.[73] The pulmonary veins have been found to be a site of reentry, so they are now frequently isolated using ablative energy.[146] Options for energy sources include radiofrequency (RF) and microwave energy, ultrasound, cryotherapy (freeze), and laser. The development of epicardial probes has enabled surgeons to now perform ablative procedures on beating hearts through keyhole incisions off-pump.[147,148]

Minimally Invasive Surgical Approaches

Overview

Minimally invasive cardiac surgical techniques have evolved considerably in the past two decades. Much of the technology was first developed for other surgical specialties and then adapted to cardiac surgery. The driving force behind the growth has been twofold—first to reduce the use of CPB and second to make the procedures less invasive. As the population ages, the prevalence of comorbidities and aortic atherosclerosis increases. Avoidance of CPB, aortic manipulation, and cross-clamping ideally would prevent some of the known complications. Indeed, transcatheter aortic valve implantation (TAVI) was recently approved for the population of patients with aortic stenosis that is deemed too high risk for traditional surgery. Additionally, the public assumes that less is more, so they seek out minimally invasive surgeons on the intranet.

What actually constitutes a minimally invasive approach is quite variable. In some cases, only the skin incision is smaller and the sternotomy is full. In other cases, the approach is robotic and/or endoscopic. Figure 24-15 shows some of the common incisions that are used in minimally invasive surgery. The field is rapidly evolving, but this chapter focuses on the most innovative approaches at the time of its writing.

Minimally Invasive Mitral Valve Procedures

Surgical Approaches. Minimally invasive mitral valve surgery involves repair or replacement of the mitral valve by a variety of less invasive surgical incisions and approaches than the traditional full median sternotomy. Minimally invasive mitral valve surgery has evolved extensively over the last 10 to 15 years, that is, since 1996, when Carpentier performed the first video-assisted mitral valve repair through a right minithoracotomy, and 1997, when Mohr performed the first robotic-assisted mitral valve repair.[149,150] Surgical approaches for repair of the mitral valve today may include partial sternotomy, right minithoracotomy, or total endoscopic approach through port chest incisions, with or without the use of video assistance or robotics (see Figures 24-15 and 24-16). The minimally invasive mitral valve approach has shown successful surgical results and positive outcomes in regard

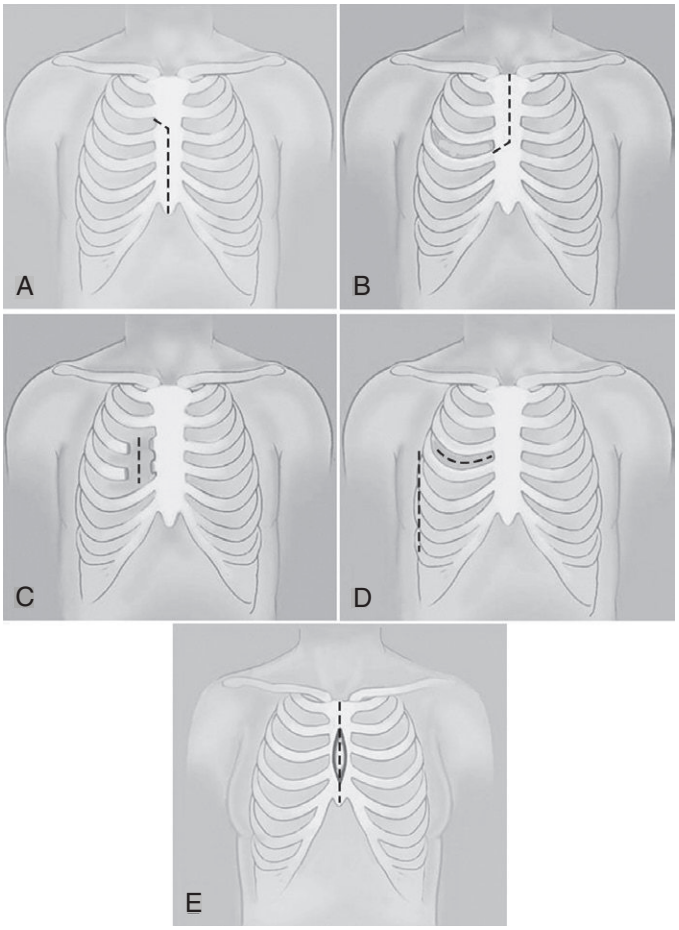


FIGURE **24-15** Minimally invasive incisions. **A,** Lower hemisternotomy. **B,** Upper hemisternotomy. **C,** Parasternal incision. **D,** Anterolateral minithoracotomy. **E,** Full sternotomy with small skin incision. (From Kaplan J. *Essentials of Cardiac Anesthesia*. 6th ed. Philadelphia: Saunders; 2008.)

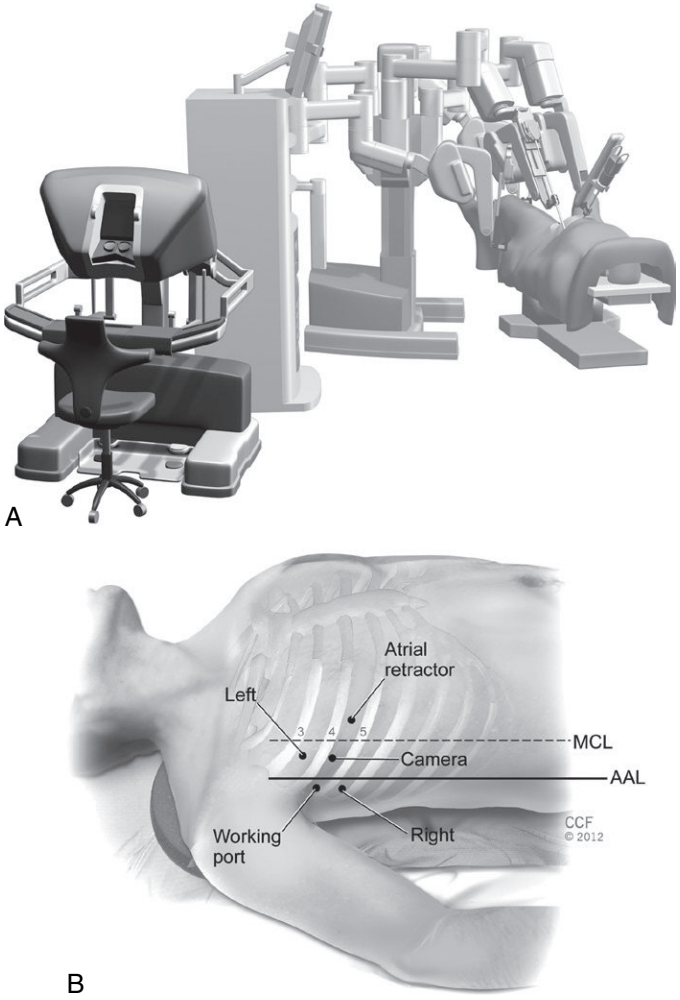


FIGURE **24-16** **A,** Robot used to assist cardiac surgery. The surgeon sits at the remote console and controls the two robotic arms. **B,** Port placement for lateral endoscopic approach. *AAL,* Anterior axillary line; *MCL,* midclavicular line. (Reprinted with permission from Cleveland Clinic Center for Medical Art & Photography © 2006-2012. All rights reserved.)

to mortality and morbidity.[149,151-153] Advantages of the minimally invasive approaches to the mitral valve include decreased hospital length of stay, faster patient recovery, decreased blood loss, and improved cosmetics compared to the traditional median sternotomy.[149,153-155] Successful surgical outcomes are dependent on proper patient selection. Contraindications to a minimally invasive approach to mitral valve repair include inability to obtain TEE, severe aortic regurgitation, aortic and/or thoracic disease, Marfan syndrome, and previous aortic and/or thoracic surgery.[156] Atherosclerosis of the descending aorta or femoral vessels preclude surgeries that require retrograde aortic cannulation through the femoral artery.

Anesthetic Considerations. Regardless of the surgical approach adopted, all minimally invasive mitral valve procedures require a general anesthetic. Principles applied to the anesthetic management of patients with mitral valve disease (discussed earlier in the chapter) are also applicable to the patient undergoing a minimally invasive mitral valve procedure, but with some additional considerations. A fast-track approach to the selection of induction and maintenance of medications is usually appropriate. Judicious use of narcotics and muscle relaxants will facilitate achieving the goal of early extubation. It is imperative that the level of muscle relaxation be closely monitored because unwanted patient movement during a robotic procedure could cause significant harm. Measures to maintain normothermia such as fluid warming devices, circuit humidifiers, forced air warming devices, and raising the room temperature must also be considered, especially if early extubation is a goal.

For robotic surgery, patients are positioned supine with a roll placed under the right scapula to elevate the hemithorax 25 to 30 degrees.[152,154] The right arm is carefully positioned (slightly deviated from body to allow port access) and padded along the right side of the patient's body to prevent it from interfering with the robotic device. External defibrillator pads should be placed on all patients because the use of internal defibrillation paddles is not possible with limited incisions.

If a mini-thoracotomy approach is selected, the surgeon makes a 3- to 4-cm right submammary, minithoracotomy incision at the fourth to fifth intercostal space along with separate smaller chest incisions for port access or for robotic instrumentation access.[149,150] If a total endoscopic approach is selected, only several small chest incisions are usually made in the right hemithorax for port access[152] (see Figures 24-16, 24-17, and 24-18). Lung isolation is not necessarily required, but is usually preferred (especially for robotic procedures), to allow more working room in the surgical field. Lung isolation can be accomplished with either a double-lumen endotracheal tube or a bronchial blocker,

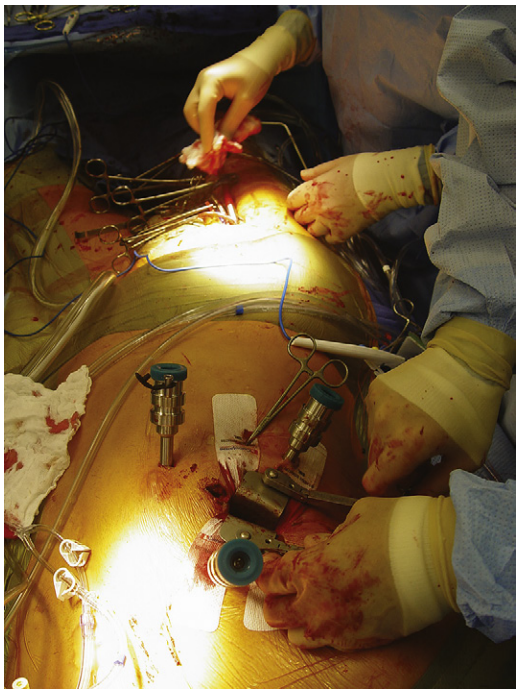


FIGURE **24-17** Intraoperative photograph taken from near the patient's head before robotic-assisted mitral valve repair. Femoral cannulation for cardiopulmonary bypass has been completed (*top*). The primary surgical incision and working ports are also shown (*bottom*). (From Kaplan JA, Reich JA, Savino JS. *Kaplan's Cardiac Anesthesia: The Echo Era*. 6th ed. Philadelphia: Saunders; 2011.)

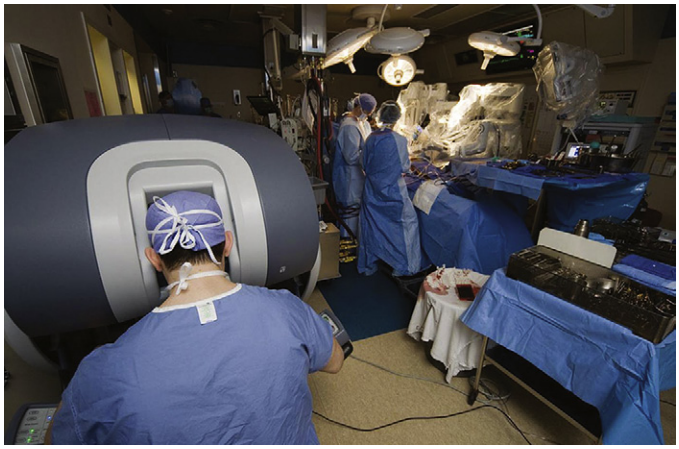


FIGURE **24-18** Robotic-assisted mitral valve repair. The surgeon (*lower left*) controls the robotic arms while seated at a console remote from the patient. (From Kaplan JA, Reich JA, Savino JS. *Kaplan's Cardiac Anesthesia: The Echo Era*. 6th ed. Philadelphia: Saunders; 2011.)

keeping in mind that if the patient is not extubated in the OR, the double-lumen endotracheal tube will need to be exchanged for a single-lumen endotracheal tube at the end of the procedure. If the double-lumen endotracheal tube is required, then placement and lung isolation confirmation is necessary after final patient positioning because access to the patient's chest and airway is extremely limited once the robotic arms are placed inside the chest. The anesthetist must not only consider management strategies for one-lung ventilation (if required) but also be prepared to treat and manage the untoward hemodynamic effects of carbon dioxide insufflation that may be used to create a capnothorax.

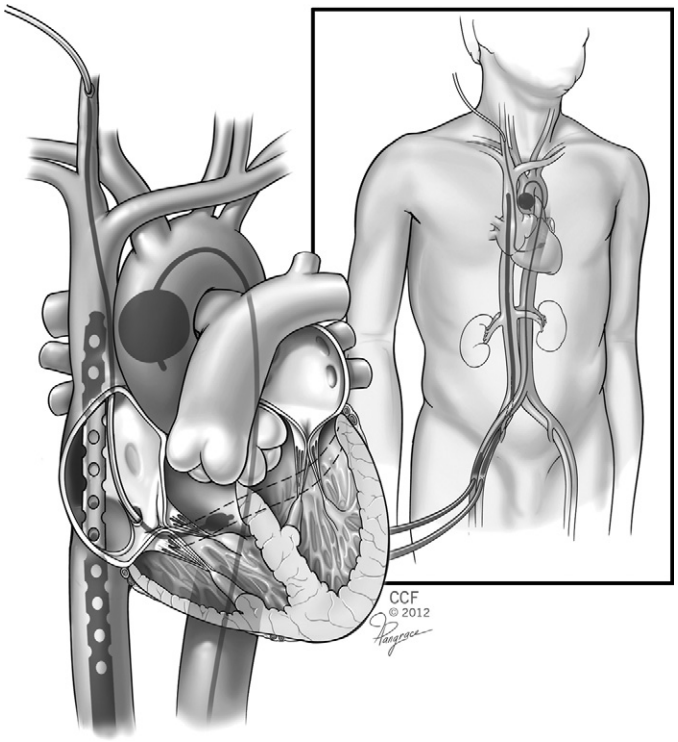


FIGURE **24-19** Overview of cannulation showing femoral venous and arterial cannulas, retrograde coronary sinus catheter, and endoballoon. (Reprinted with permission from Cleveland Clinic Center for Medical Art & Photography © 2006-2012. All rights reserved.)

CPB Cannulation and Cardioplegia. Minimally invasive mitral valve surgery employs the use of CPB. CPB cannulation is usually obtained from the femoral artery and vein under TEE guidance to confirm placement. Complications of femoral CPB cannulation include retrograde aortic dissection, limb ischemia, and chest wall hemorrhage.[156] If additional venous drainage is needed, the surgeon can perform superior vena cava (SVC) cannulation by passing a wire through a 16-gauge right internal jugular catheter using the Seldinger technique. The 16-gauge catheter is often placed by anesthesia after induction and then later prepped into the surgical field. An alternative is cannulating the SVC directly from the surgical field. The anesthetist may also access the right internal jugular vein for placement of a specialized catheter that allows delivery of percutaneous retrograde cardioplegia into the coronary sinus (Figure 24-19). Before placement of the percutaneous coronary sinus catheter, 70 to 100 units/kg of heparin is usually administered to avoid coronary sinus thrombus. Placement of these specialized catheters by the anesthetist is performed under fluoroscopy and/or TEE guidance, or they may be placed directly by the surgeon through the surgical incision. Proper positioning of the retrograde cannula in the coronary sinus can occasionally be quite challenging. If right internal jugular access is obtained for surgical CPB purposes, the left internal jugular vein will have to be accessed by the anesthetist for the administration of central intravenous medication.

Antegrade cardioplegia may be delivered to the aortic root by an aortic cannula inserted into the ascending aorta by the surgeon through a stab or thoracotomy incision.[149] Administration of antegrade cardioplegia also can be delivered by an endoaortic occlusion cannula that is advanced through a second opening (side arm) of a larger arterial femoral cannula (see Figure 24-19). The endoaortic catheter is advanced into the aorta and positioned at

the sinotubular junction using TEE guidance.[154] The baloon on the catheter not only allows for endoaortic occlusion, but also for administration of antegrade cardioplegia via an orifice on the end of the endoaortic baloon. Aortic occlusion also can be achieved by direct transthoracic cross-clamping to avoid potential complications associated with the endoaortic baloon system, such as endoaortic baloon rupture or migration. If the end-clamp system is used for aortic occlusion, correct positioning is confirmed with either TEE or fluoroscopy, and continuous monitoring for endoaortic baloon migration during CPB is necessary. In some centers for percutaneous CPB, the anesthetist places a specialized pulmonary artery catheter (PAC) for venting the PA. Bilateral radial arterial catheters are often placed to detect baloon migration. Migration of the baloon is suspected if a significant discrepancy in pressure readings occurs between bilateral arterial radial catheters.[149,155] Obstruction of the coronary arteries can occur if the baloon migrates toward the aortic valve because of overventing, high systemic flow, or high CPB flow.[149,152,154] Distal migration of the endoaortic baloon can cause neurologic injury due to obstruction of the innominate artery and may result in cerebral hypoperfusion. Distal migration of the endoaortic baloon and obstruction of the innominate artery should be suspected if there is a loss of the right arterial radial pulse.

As mentioned earlier, there are several minimally invasive surgical methods and techniques that are used to repair the mitral valve. Long-shafted instruments and a thorascopic-televised view of the surgical field may be used to repair the mitral valve when the video-assistance approach is selected. If the robotic system is used to repair the mitral valve, the surgeon will sit at a remote console away from the patient and surgical field. From the remote console the surgeon directs the extensors of the robot to perform the desired surgical maneuvers to repair the mitral valve (see Figure 24-18). A surgical assistant is usually present at the surgical field, and he or she guides the robotic arms and moves the robot whenever necessary. Higher cost, increased complexity, and in some reports (due to a learning curve) longer cross-clamp times are reported as disadvantages of robotic use.[149,152,154] Reported advantages of the robotic system over the thorascopic video-assisted approach to mitral valve repair include reduction in surgeon tremor, increased mobility with instrumentation, and three-dimensional vision.[149,150,154]

Minimally Invasive Aortic Valve Replacement

The surgical approach for aortic valve surgery has been traditionally through a full median sternotomy incision extending from the sternal notch to the xiphoid process, allowing complete exposure of the heart and ascending aorta. The alternative surgical approaches to the aortic valve that are in use today were not developed until the mid-1990s. The hemisternotomy (ministernotomy) and right minithoracotomy approaches are the two minimally invasive surgical approaches used today for isolated aortic valve surgery. Minimally invasive aortic valve surgery has demonstrated several advantages over traditional sternotomy. These include not only improved cosmesis but also decreases in length of stay in the ICU and hospital, blood transfusions, and postoperative ventilatory support. The approach is also selected in reoperations to avoid a sternotomy that could potentially disrupt patent bypass grafts. Reported disadvantages include limited surgical exposure, greater difficulty with ventricular de-airing, potential difficulty in placing a coronary sinus catheter for retrograde cardioplegia, and the potential for postoperative femoral wound infections.[157-160]

Both surgical mini-AVR approaches employ CPB. An arterial cannula may be placed directly into the aorta, or arterial access may be obtained from the femoral artery or subclavian artery. Venous cannulation may be accessed directly from the right atrium. If direct venous cannulation limits surgical exposure, then venous access to the right atrium may be obtained from either the internal jugular or femoral vein. If femoral access is obtained for either venous or arterial cannulation, TEE is necessary to guide and confirm placement of the femoral arterial and venous cannulae. TEE is also required to guide and confirm placement of the retrograde cardioplegia catheter into the coronary sinus. Anesthetic management for minimally invasive aortic surgery is comparable to anesthetic management for aortic valve surgery with a traditional sternotomy incision, but with some additional considerations. A fast-track approach may be incorporated into the anesthetic plan, including modalities that maintain normothermia to facilitate early extubation. Internal defibrillation paddles may be difficult to use in a mini-AVR approach; therefore it is necessary to ensure that external defibrillator/pacing pads are placed on the patient before incision. A brief period of hypotension and bradycardia should be anticipated by the anesthetist when the surgeon lifts the pericardium to facilitate maximal surgical exposure prior to cannulation. A preemptive bolus of phenylephrine may be administered prior to lifting the pericardium to maintain vascular tone and successful return to baseline MAP. Direct observation of the myocardium is limited with various mini-AVR surgical incisions. The anesthetist will have to rely on TEE and hemodynamic monitoring to assess adequacy of myocardial contractility and ventricular filling. The anesthetist should always be prepared to convert to a full sternotomy incision if surgical complications arise, such as difficulty in removal of intracardiac air, mediastinal bleeding, and cardiac tamponade.

Minimally Invasive Myocardial Revascularization

The quest to develop less invasive surgical techniques than the traditional median sternotomy for coronary revascularization has been in progress since the first minimally invasive coronary bypass revascularization was reported in 1967. In addition to improved cosmetics, the goals driving development include the desire to lower sternal wound infection rates, brachial plexus injury, cost, and length of stay.[154,161] Several different minimally invasive techniques for single LAD bypass grafting have emerged over the last 40 years. These employ surgical methods already mentioned in this chapter. Total endoscopic coronary artery bypass (TECAB), minimally invasive direct coronary artery bypass (MIDCAB), and port-access coronary artery bypass (PA-CABG) are the most common approaches for minimally invasive coronary revascularization. TECAB is a minimally invasive coronary revascularization approach that uses robotic instrumentation for assistance with anastomosis, and it is performed either on or off pump. The MIDCAB approach is performed through a small left anterolateral thoracotomy incision, usually off pump, and anastomoses are hand sewn (Figure 24-20). A right anterior thoracotomy may be performed for access to the right coronary artery (RCA) or posterior descending artery (PDA). PA-CABG uses video assistance for left internal thoracic artery (LITA) harvesting; CPB is employed, and anastomoses are often hand sewn. Regardless of which minimally invasive technique is selected, the anesthetist should have a detailed discussion with the surgical team beforehand. Topics that should be discussed include the surgical approach, incision, need for one-lung ventilation (OLV), use of CPB, and method of cannulation. Principles governing anesthetic management for CPB and off-pump coronary revascularization (mentioned earlier in the chapter), along with a fast-track approach, are all applicable to the patient selected for minimally invasive coronary revascularization. Additional considerations regarding the

surgical use of robotics or video assistance, OLV, femoral cannulation, and use of the endoaortic catheter system also may need to be incorporated into the anesthetic plan.

Transcatheter Aortic Valve Implantation

Transcatheter aortic valve implantation (TAVI) is an innovative, minimally invasive percutaneous procedure for the correction of severe aortic stenosis. It does not require sternotomy or CPB. A retrograde approach (transfemoral) via the femoral artery or an antegrade (transapical) approach via the left ventricular apex is used to implant a bioprosthetic valve into the native calcified valve. Approximately 30% of patients with critical aortic stenosis are not considered candidates for traditional sternotomy and CPB because advanced age and the presence of comorbidities make the risk prohibitively high.[162-164] On November 2, 2011, the Food and Drug Administration (FDA) announced approval of the SAPIEN Transcatheter Heart Valve for this population.[165] Trials in both Europe and the United States have shown the superiority of this technology over standard medical therapy in reducing the 1-year death rate by 20% as well as improving the quality of life.[166-169] In Europe, where the device has been approved since November 2007, the procedure now represents a significant portion of aortic valve replacement procedures. Now that the United States has approved the valve, the trend is expected to be repeated here.

Surgical Approach. The two types of valves currently in use are the baloon-expandable valve (Cribier-Edwards and Edwards SAPIEN), used for both the transfemoral and transapical approaches, and the self-expanding valve (CoreValveRevalving System), used only with the transfemoral approach. The bioprosthetic valve is delivered over a catheter system into the diseased stenotic valve via a transfemoral or transapical approach. Access is reached by an interventional cardiologist through the right and left femoral arteries and vein for deployment of the device and delivery of rapid ventricular pacing.[162] The femoral arterial and venous access also may be used for rapid CPB cannulation if emergent bypass becomes necessary. To prevent distal movement of the catheter and ensure proper placement of the device, both valvuloplasty and deployment of the valve are performed while ventilation is held (apnea) and a low cardiac output state is induced by rapidly pacing the ventricle at a rate of 200 bpm.[162,170] The lack of ventricular ejection prevents migration of the baloon or stent-valve that the stroke volume from the beating heart may cause during valvuloplasty and actual device deployment.[171] Fluoroscopy and TEE are used throughout the procedure to achieve accurate positioning of the valve and for continuous assessment of cardiac function. The transfemoral approach may be selected if there has been a previous left thoracotomy, chest radiation, or pathology in or near the LV apex.[170,171] The transfemoral approach delivers the bioprosthetic aortic valve in a retrograde fashion through the abdominal and thoracic aorta into the aortic valve (AV) annulus[172] (see Figure 24-20). Contraindications to the transfemoral approach include the presence of an ascending aortic aneurysm and femoral-iliac arteries that have a small diameter, contain great calcification, and are extremely tortuous.[170,173]

In addition to achieving femoral venous and femoral arterial access for the transapical approach, a left anterior minithoracotomy incision is made through the fifth or sixth intercostal space over the LV apex[172] (Figure 24-21). The surgeon opens the pericardium and places purse-string sutures at the LV apex. A puncture at the LV apex is then made to allow the bioprosthetic valve to be delivered (under TEE and fluoroscopy guidance) through the left ventricle into the AV annulus in an antegrade fashion. An antegrade approach is often selected for patients with severe aortic calcification or peripheral vascular disease, or if better surgical control is required over the baloon valvuloplasty and actual device implantation (due to the shorter distance between the LV apex and AV annulus).[162,171,172]

Anesthetic Considerations. Preoperative considerations for the high-risk aortic stenosis (AS) patient who is undergoing a TAVI are similar to those that apply to patients with severe AS, mentioned earlier in the chapter. The anesthetist must be aware of additional considerations that are inherent in a TAVI procedure to facilitate a safe and favorable surgical outcome. They begin with understanding the details of the surgical procedure, the unique set-up of a hybrid operating room, and the hemodynamic challenges that arise during the procedure. Figure 24-22 shows an example of the hybrid OR setup. It must also be recognized that a TAVI procedure is a

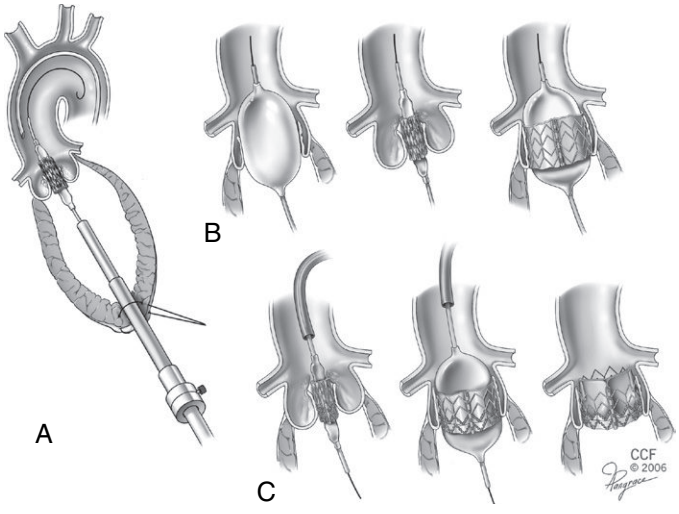


FIGURE **24-20** Transcatheter aortic valve implantation (TAVI). **A** and **B,** Antegrade, transapical approach. A baloon is first used to compress the diseased native valve. Then a compressed tissue heart valve is placed on the baloon catheter, inserted through the ribs into the apex of the left ventricle, and positioned directly inside the diseased aortic valve. Once in position, the baloon is inflated to secure the valve in place. **C,** Retrograde, transfemoral approach. Implantation process is similar, but baloon and catheter are positioned retrograde from the femoral artery. (Reprinted with permission from Cleveland Clinic Center for Medical Art & Photography © 2006-2012. All rights reserved.)

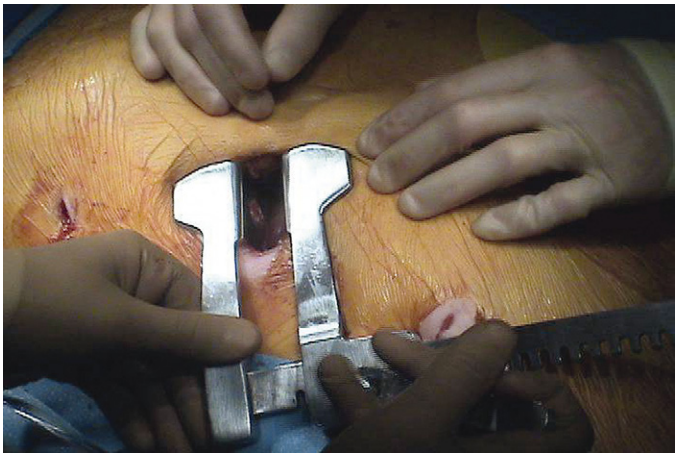


FIGURE **24-21** Left anterior thoracotomy for minimally invasive direct coronary artery bypass (MIDCAB). (From Miller RD, et al. *Miller's Anesthesia*. 7th ed. Philadelphia: Churchill Livingstone; 2009.)

collaborative effort among many disciplines including cardiology, anesthesia, and cardiothoracic surgery and that all team members must clearly communicate with one another. Because fluoroscopy is used throughout a TAVI procedure, protective radiation safety equipment must be worn. Noninvasive and invasive monitoring for TAVI procedures is similar to that of a standard cardiac case, including the use of a radial arterial catheter and pulmonary arterial catheter. All intravenous lines should have the appropriate amount of extension to facilitate safe use of any fluoroscopic device. Patients are positioned supine, with a slight tilt to the right for surgical exposure of the left chest if the transapical approach is selected.

Recent literature has reported the use of local anesthesia with sedation as an anesthetic technique for transfemoral catheter aortic implantation.[162,174] Continuous neurologic assessment, avoidance of complications associated with general anesthesia in high-risk patients who have severe aortic stenosis, and quicker recovery times are reported advantages of using local anesthesia with sedation.[162] To date, however, the majority of procedures are performed using general anesthesia with endotracheal intubation.[162] Advantages of having a protected airway include the ability to use TEE, control ventilation during valve deployment, and urgently institute CPB if needed. A balanced general anesthesia technique is usually selected with the goal of early emergence and extubation. Because the slightest patient movement (even ventilation) can be disastrous during valve deployment, muscle relaxants are used. Minimal doses of narcotics are needed for postoperative pain control. The use of OLV for the transapical approach is based on surgical preference.[171]

Vasoactive medications, such as phenylephrine, norepinephrine, and epinephrine, must be immediately available for administration to promptly treat hemodynamic instability. Although rapid ventricular pacing is usually limited to 10 to 15 seconds for valvuloplasty and stent deployment, preemptive boluses of a vasopressor may be administered to maintain vascular tone, coronary perfusion, and successful return to baseline rhythm and MAP.[162,171,172] Administration of crystalloid or colloid is usually sufficient to meet a patient's intraoperative intravascular fluid requirement during a TAVI procedure. However, typed and cross-matched blood, large-bore peripheral and central access, a fluid warming system, and a CPB team and pump should all be set up and available, in case a major complication develops, such as aortic dissection or pericardial tamponade. Most blood loss is associated with the initial placement and final removal of the deployment device sheath from either the femoral artery and/or LV apex.[171] AV block requiring permanent pacemaker placement has been a repeatedly reported complication after the TAVI procedure.[162,163,170,173,175] The anesthetist must be prepared to treat the sudden onset of any intraoperative dysrhythmias including AV block. The surgical suite should be equipped with a defibrillator and pacemaker. Radiolucent defibrillator pads should be placed on the patient before induction. Significant perivalvular leak, stent malpositioning, coronary obstruction, and stroke caused from atheromatous embolization are all additional perioperative complications that have been reported to occur during transcatheter aortic valve implantation.[163,173,175-177]

FIGURE **24-22** View of hybrid cardiovascular operating room. The cardiopulmonary bypass circuit is on the far right with its own boom. The operating table is in the middle of the picture, with a floor-mounted, fixed biplanar C-arm to the left. (From Kaplan JA, Reich DL, Savino JS. *Kaplan's Cardiac Anesthesia: The Echo Era*. 6th ed. Philadelphia: Saunders: 2011.)

Percutaneous Mitral Valve Repair

Although still under development, the Alfieri edge-to-edge repair using the MitraClip device is the most common percutaneous mitral valve repair technique today.[150,170,178] Alfieri first performed the procedure in 1991. So far, the majority of percutaneous mitral valve repairs in the United States have been performed in selected institutions under the EVEREST trial and in Europe under the ACCESS trial.[170,178,179] Patient eligibility and selection for repair of the mitral valve using a percutaneous approach is still evolving but has so far been based on severity of mitral regurgitation and specific mitral valve anatomic characteristics.[170,178]

The Alfieri edge-to-edge repair is a transcatheter valve procedure intended to reduce the degree of mitral regurgitation by delivering a clip to help secure and suture the free edge of the anterior mitral leaflet to the free edge of the posterior leaflet at the site of regurgitation. The technique results in the creation of a double-orifice mitral valve from a central suture that connects the opposing leaflets.[170,178] A femoral venous or transseptal approach is used, the procedure is performed under the guidance of TEE, and fluoroscopy A general anesthetic is usually administered for the MitraClip procedure because continuous TEE assessment is required; however, the use of conscious sedation has also been reported.[170,180] Results thus far for the MitraClip procedure have shown a reduction in mitral regurgitation (less than 2+) in the majority of patients, low rates of morbidity and mortality, and reduced hospital length of stay compared with traditional mitral valve surgical repairs.[170,178]

Devices and Procedures Developed to Manage Heart Failure

Mechanical Circulatory Assist Devices

Intra-Aortic Baloon Pump. An intra-aortic baloon pump (IABP) is a mechanical circulatory-assist device that reduces afterload and increases diastolic coronary perfusion to the heart. The IABP was first introduced in 1968. Since then its role as a key component of left ventricular support has grown in both medical and surgical settings. Medical uses include the management of cardiogenic shock, MI, intractable angina, and arrhythmias. In the perioperative setting, it is used to stabilize patients preoperatively and/or to help wean a patient who is having difficulty separating from CPB. The IABP is also used to help support coronary perfusion to high-risk patients during OPCAB procedures. Sepsis, descending aortic disease, severe peripheral vascular disease, and severe aortic regurgitation are contraindications to IABP placement.[181,182]

The IABP consists of a flexible catheter attached at one end to a drive console that contains computerized circuitry to determine

proper timing for inflation and deflation. At the other end of the catheter is an inflatable, cylindrical, polyethylene baloon that comes in various sizes between 25 and 50 mL. The baloon can be filled with helium or carbon dioxide. It is usually placed percutaneous through the femoral artery using the Seldinger technique and positioned 2 cm distal to the origin of the left subclavian artery so that the tip of the baloon is situated at the junction of the aortic arch and descending aorta.[181,183] Proper sizing and positioning are important considerations to prevent complications such as inadvertent vascular damage or vessel occlusion. Fluoroscopy, echocardiography, or chest x-rays are used to confirm IABP placement.

The IABP should be timed with the dicrotic notch of the arterial waveform so that the baloon inflates once the aortic valve closes and diastole begins. The inflated baloon (during diastole) will act as a seal within the proximal descending aorta, increasing pressure and displacing blood flow antegrade toward the coronary arteries. Consequently, coronary artery perfusion is enhanced and ultimately myocardial oxygen delivery improves. Deflation of the baloon is timed immediately before the onset of systole at the beginning of the R wave of the ECG. The deflation creates a vacuum effect that lowers the aortic pressure to reduce afterload, facilitates ventricular ejection, relieves ventricular workload, and reduces myocardial oxygen demand. Proper timing of the IABP is essential to prevent further strain on the myocardium and to achieve a maximal counter-pulsation benefit. Figure 24-23 shows arterial waveforms with correct timing and placement, and Figure 24-24 demonstrates arterial waveforms associated with incorrect IABP timing.

The IABP is synchronized with either the ECG or the arterial pressure waveform. More modern consoles are unaffected by electrical noise caused by electrocautery, and they can also differentiate pacer spikes from the QRS complex when pacing is used. Timing can be difficult with irregular rhythms such as atrial fibrillation and faster heart rates. IABP is usually timed to inflate with each heartbeat (1:1) or every other beat (1:2) until ventricular function improves. Then the counter pulsation ratio can be gradually weaned. To avoid the risk of thrombus, anticoagulation is needed for long-term IABP use; and except during CPB, an IABP is never completely turned off while it remains in the aorta. Vascular injury, infection at the IABP insertion site, and thrombocytopenia are the most common complications of IABP use.[184,185]

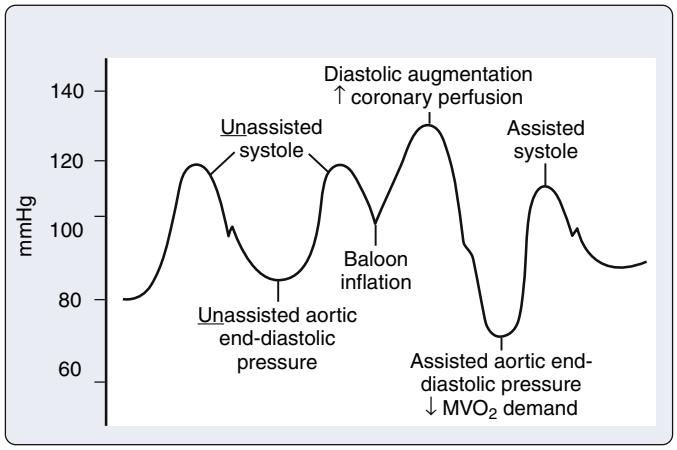


FIGURE **24-23** Arterial waveforms seen during intra-aortic baloon pump (IABP) assist. The first two waveforms are unassisted, and the last is assisted. Notice the decreased end-systolic and end-diastolic pressures and augmented diastolic pressures caused by IABP augmentation and the (correct) point at which baloon inflation occurs. These are waveforms generated by a correctly positioned and timed baloon. (Courtesy Datascope Corporation.)

Extracorporeal Membrane Oxygenation. Extracorporeal membrane oxygenation (ECMO) is a mechanical circulatory-assist device that can provide both pulmonary and systemic arterial perfusion support. It is a temporary (up to 30 days), closed circuit device that allows the heart and/or the lungs to recover from injury or trauma while maintaining oxygenation and perfusion. The primary conditions that call for use of ECMO are cardiogenic shock, failure to wean from CPB, right heart failure, heart failure that cannot be treated with a VAD, and (as a last resort) resuscitation of patients requiring cardiopulmonary resuscitation (CPR).[182,184] ECMO is also used to support patients with severe respiratory failure and ARDS that have failed to respond to standard treatments and advanced modes of mechanical ventilation.

There are two types of ECMO, and their goals and cannulae placement are somewhat different. Venovenous ECMO is the preferred method of treatment for respiratory failure.[184,186] It supports the lungs by improving gas exchange and allowing lung protective ventilation modes. In venovenous ECMO, the femoral and internal jugular veins are often selected as cannulation sites. If left ventricular support is required in addition to pulmonary support, venoarterial ECMO is selected. In contrast to venovenous ECMO, venoarterial ECMO bypasses pulmonary circulation altogether and a higher arterial oxygenation is achieved. The carotid artery and jugular vein or femoral artery and vein are common sites for venoarterial ECMO cannulation. In either case, blood drains through the venous cannula to a centrifugal or roller pump that then circulates the blood at a rate of 3 to 6 L/min through a membrane oxygenator (artificial lung), where carbon dioxide is removed and oxygen is added. Before the blood is returned to the patient, a heat exchanger rewarms the blood that has cooled. The oxygenated blood is then returned either through an arterial or venous cannula, depending on whether venoarterial or venovenous ECMO isused. The process is similar to CPB.

Anticoagulation with heparin administration is necessary with ECMO to prevent clot and thrombus formation. Because heparinization is required, bleeding becomes a major risk factor for patients supported with ECMO. The risk of stroke caused by bleeding or emboli, risk of infection, and hemolysis all contribute to the limited duration of support that ECMO may provide patients who are in cardiac or respiratory failure.

Ventricular Assist Devices

General Considerations. Heart transplantation is the only definitive treatment for end-stage heart failure. It is estimated that close to 40,000 patients would benefit from a transplant; but over the past several years, because of the lack of donors, only about 2000 heart transplants are performed each year. Additionally, the prevalence of heart failure increases with age and patients over 65 years of age are often not eligible transplant candidates.[187,188] Ventricular assist devices (VADs) are bringing new hope to this population.

Today VADs are used to assume the function of the failing ventricle or ventricles as a bridge to recovery, bridge to transplant, or as destination therapy. Heart failure patients considered for long-term VAD support typically have become refractory to standard medical therapy. They are often symptomatic at rest and are receiving intravenous inotropic support.[189] It is not uncommon for these patients to develop end-organ dysfunction caused by decreased perfusion pressure and a low cardiac output. Cardiogenic shock from an acute MI, viral cardiomyopathies, or post CPB can all be indications for short-term VAD support (lasting days or weeks) and bridge to recovery.[190] In this situation, the myocardium is granted time to rest while the VAD maintains circulation and decompression of the ventricle. Studies show that the decreased wall tension and myocardial oxygen demand that occur as a result

of the ventricular unloading allow remodeling and recovery of the ventricle.[191,192] Careful patient selection is key to achieving a successful outcome with VAD placement. Contraindications to VAD insertion include active infection or sepsis, irreversible renal or hepatic dysfunction, severe pulmonary hypertension unrelated to cardiac disease, metastatic cancer, and major coagulation disorders such as hemophilia and von Willebrand disease.[193] Since the first successful VAD implant performed in 1966 by Dr. Michael DeBakey for post-cardiotomy cardiogenic shock, ventricular assist devices and their management have greatly evolved. Several studies have shown that VAD support is effective in stabilizing multiorgan failure in end-stage heart failure patients who are awaiting transplant.[194,195] The REMATCH trial compared long-term left ventricular assist device (LVAD) support to medical management for patients with end-stage heart disease who were not eligible transplant candidates. Patients who received an LVAD showed a 48% reduction in the risk of death, fewer adverse events, shorter hospital stays, lower prescription cost, and improved quality of life.[190,196] Improved outcomes have also been demonstrated in early institution of VAD support with the use of a CentriMag assist device for cardiogenic shock after cardiotomy.[197]

Components, Types, and Heart Mate II. The VAD is a mechanical circulatory assist device that is attached to the heart through cannulae. An LVAD collects oxygenated blood that is returned to the left atrium from an inflow cannula usually placed at the apex of the left ventricle. From the inflow cannula blood enters a pumping chamber. The pumping chamber then ejects blood into the systemic circulation through an outflow cannula that is usually attached to the aorta. A right ventricular assist device (RVAD) is similarly constructed, except that it receives deoxygenated blood from the right atrium and pumps blood into the pulmonary circulation. The RVAD inflow cannula is anastomosed to either the right atria or right ventricle, and the RVAD outflow cannula is anastomosed to the pulmonary artery.

VADS are categorized according to type of blood flow (continuous or pulsatile), length of time the device can be used for support (short, intermediate, long-term), location of device (intra-, extra-, or paracorporeal), and their source of driving power (pneumatic or electric). Two generations of VADS are currently in clinical use and more generations are under development. A complete discussion of VADs is beyond the scope of this chapter, but Tables 24-16 and 24-17[187] list some of the important characteristics of devices

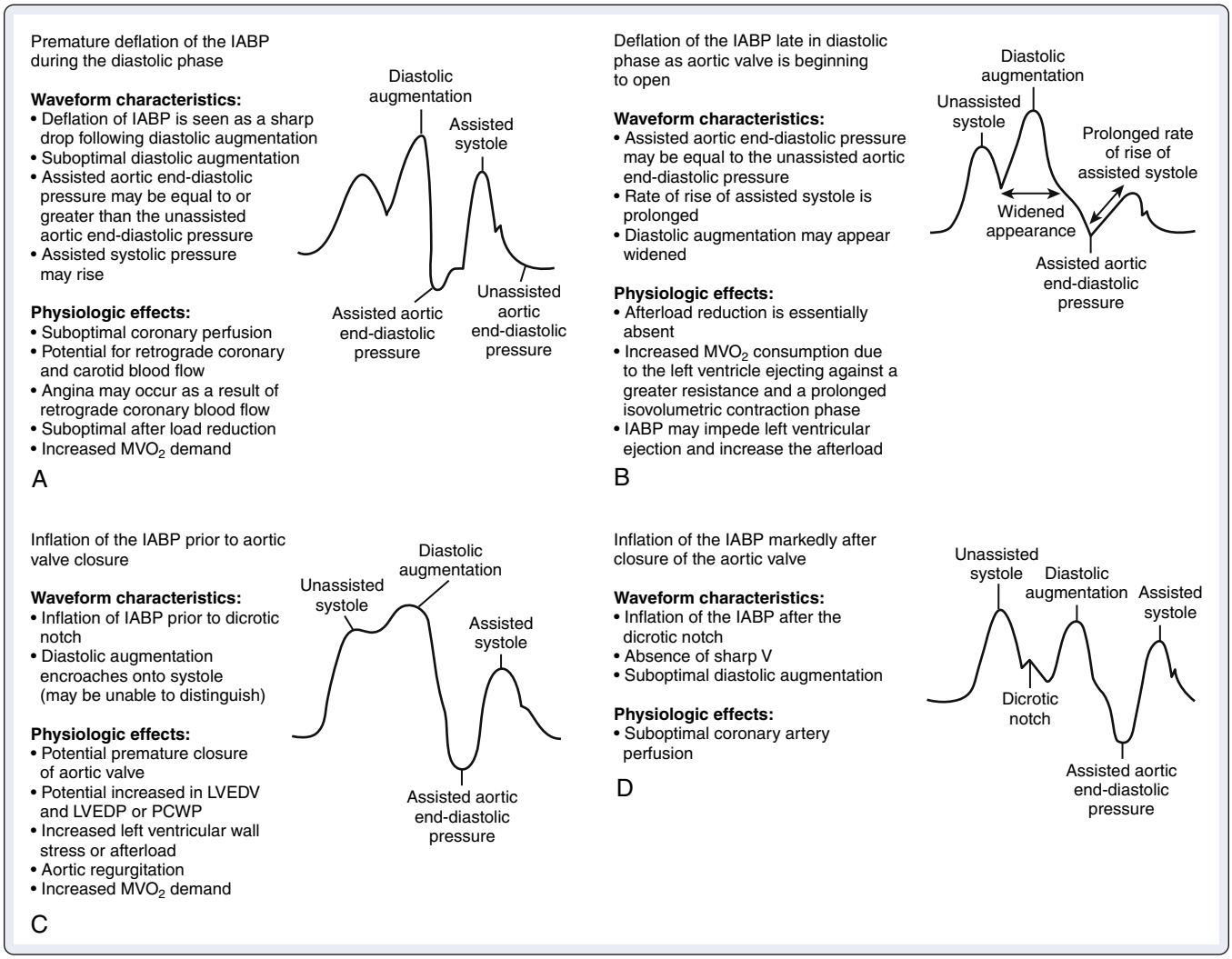


FIGURE **24-24** Alterations in waveform tracings caused by errors in timing of intra-aortic baloon pump (IABP). **A,** The baloon was deflated too early. **B,** The baloon was deflated too late. **C,** The baloon was inflated too early. **D,** The baloon was inflated too late. *LVEDP,* Left ventricular end-diastolic pressure; *LVEDV,* left ventricular end-diastolic volume; MVO_2; mixed venous oxygen saturation; *PCWP,* pulmonary capillary wedge pressure. (Courtesy Datascope Corporation.)

used for short-term and long-term support. HeartMate II is currently the only second-generation LVAD approved for intermediate- to long-term support or destination therapy (Figure 24-25).

HeartMate II is an intracorporeal and nonpulsatile continuous flow device. An electrically powered axial-flow pump can generate up to 10 liters per minute of continuous blood flow. It can also operate at lower speeds, allowing the ventricle to assist with the workload. The HeartMate II is 60% smaller (weight 400 g) than the HeartMate I and is more durable.[193] Common complications from VAD support such as stroke, postoperative bleeding, RV failure, and percutaneous lead infection have been shown to be far fewer with HeartMate II than with HeartMate I.[142] Anticoagulation is required with the HeartMate II.

Anesthetic Management. Anesthetic management of the LVAD candidate begins with preoperative assessment of the end-stage heart failure patient. Neurologic deficits, hepatic and renal dysfunction, and current cardiac function should be noted. Hepatic congestion from right heart failure, preoperative use of anticoagulation drugs, and exposure of the patient's blood to nonbiologic surfaces of the LVAD device can all contribute to potentially substantial blood loss and coagulopathy that may develop after placement. Blood products (platelets, fresh frozen plasma [FFP]) and red blood cells should be available, and large-bore central and peripheral intravenous access should be secured before incision, in case rapid transfusion becomes necessary. Antifibrinolytic agents such as aminocaproic acid may be administered perioperatively to minimize blood loss. Placement of a radial or brachial arterial catheter and pulmonary arterial catheter in addition to standard ASA monitors prior to induction is recommended to assist the anesthesia provider in achieving hemodynamic stability during induction. Decreases in preload and increases in afterload are poorly tolerated in end-stage heart failure patients. These patients are extremely dependent on heart rate and considered to have a relatively fixed cardiac output, with an inability to increase stroke volume. Rapid deterioration and cardiovascular collapse can occur on induction if the patient becomes bradycardic or loses

TABLE 24-16 Basic Characteristics of the Devices Currently Used for Short-Term Support*

Device	Type of Support	Fill Mechanism	Drive Mechanism	System Control and Output
Abiomed BVS5000	Pulsatile	Gravity drainage	Pneumatic compression of blood chamber	Automatically adjusts rate of pumping to provide up to 5 L/min of outflow (output depends on intravascular volume status and downstream vascular resistances)
Thoratec	Pulsatile	Vacuum assisted	Pneumatic compression of blood chamber	Depending on the mode of operation, user-defined settings determine the output (intravascular volume status is important)
Abiomed AB5000 ventricle	Pulsatile	Vacuum assisted	Pneumatic compression of blood chamber	Automatically adjusts rate of pumping to provide up to 6 L/min of outflow (output depends on intravascular volume status and downstream vascular resistances)
Centrifugal pumps	Nonpulsatile	Gravity drainage assisted by vortex	Centrifugal force drives blood	Output is dependent on user-defined speed of impeller rotation and afterload
CentriMag	Nonpulsatile	Gravity drainage assisted by vortex	Centrifugal force drives blood	Output is dependent on user-defined speed of impeller rotation and afterload

From Stone ME, et al. New approaches to the surgical management of end-stage heart failure. In: Kaplan JA, Reich DL, Savino JS. *Kaplan's Cardiac Anesthesia: The Echo Era*. 6th ed. Philadelphia: Saunders; 2011.
*For example, bridge to recovery.

TABLE 24-17 Basic Characteristics of the Devices Currently Used for Long-Term Support

Device	Type of Support	Fill Mechanism	Drive Mechanism	System Control and Output
HeartMate XVE	Pulsatile; LVAD only	Gravity drainage	Electrically powered compression of blood chamber	Fixed-rate and automatic modes available; 85-mL blood chamber; maximum flow
Thoratec	Pulsatile; BiVAD possible	Vacuum assisted	Pneumatic compression of blood chamber	Depending on the mode of operation, user-defined settings determine the output (intravascular volume status is important)
IVAD	Pulsatile; BiVAD possible	Vacuum assisted	Pneumatic compression of blood chamber	Depending on the mode of operation, user-defined settings determine the output (intravascular volume status is important)
HeartMate II	Nonpulsatile flow; axial device; LVAD only	Gravity drainage assisted by vortex	Continuous rotation of axial pump impels blood forward	Output is dependent on user-defined speed of impeller rotation, available volume in ventricle, and afterload
CardioWest TAH	Pulsatile; replaces natural heart	All venous and pulmonary arterial blood returns to device	Pneumatic compression of blood chambers	Maximum stroke volume 70 mL; can deliver more than 9 L/min of output

From Stone ME, et al. New approaches to the surgical management of end-stage heart failure. In: Kaplan JA, Reich JA, Savino JS. *Kaplan's Cardiac Anesthesia: The Echo Era*. 6th ed. Philadelphia: Saunders; 2011.
BiVAD, Biventricular assist device; *IVAD*, implanted vascular assist device; *LVAD*, left ventricular assist device; *TAH*, total artificial heart.

sympathetic tone. Judicious use of etomidate and a neuromuscular blocker, or a high-dose narcotic with a neuromuscular blocker such as pancuronium, may be selected to minimize hemodynamic instability. Because sepsis is the leading cause of mortality in LVAD recipients, attention should be given to the antibiotic regimen and strict sterile technique should be maintained.[185,187,198]

A complete TEE examination assists with placement and detection of anatomic problems that can potentially complicate proper functioning of the device. Aortic insufficiency, intracardiac shunts (PFO), mitral stenosis, tricuspid insufficiency, presence of thrombus, right ventricle function, and adequacy of VAD inflow and outflow function can all be determined from the TEE.[199] Many concerns, such as AI, tricuspid regurgitation, or a patent foramen ovale will require surgical correction before LVAD placement for the device to function properly.[187] TEE also serves as a monitor of right and left ventricular function, thereby helping to guide the anesthetist with fluid and hemodynamic management.

Before separation from CPB, ventilation is reestablished, the device is de-aired, and its function is evaluated to confirm that it will support circulation. The right ventricle is assessed closely because it is needed to fill the left ventricle. Unfortunately, 30% of LVAD recipients do develop right ventricular dysfunction after LVAD implantation, most likely because of a combination of factors, including left ventricular decompression, myocardial stunning from CPB, fixed pulmonary hypertension, and right ventricular overload from LVAD activation.[142] The TEE and filling pressures are closely monitored to avoid overloading the right ventricle. Inotropes, such as epinephrine, or a phosphodiesterase III inhibitor, such as milrinone, help support function and decrease right ventricular afterload. Inhaled nitric oxide may be used to dilate the pulmonary vasculature. If right ventricular dysfunction ensues despite pharmacologic support, biventricular support should be considered.

LVAD flow is very dependent on volume. The anesthetist should be prepared to administer volume (mainly blood and blood products) rapidly if massive bleeding and a coagulopathy develop. Patients who are potential future transplant recipients should receive blood that has been leukocyte-reduced. Vasoplegic syndrome can also develop and is best managed with vasopressin, because it causes less pulmonary vasoconstriction than norepinephrine or phenylephrine and will help prevent increases in right heart afterload. Hypertension should be treated with a vasodilator such as sodium nitroprusside to avoid causing stress and malfunction of the LVAD.[187]

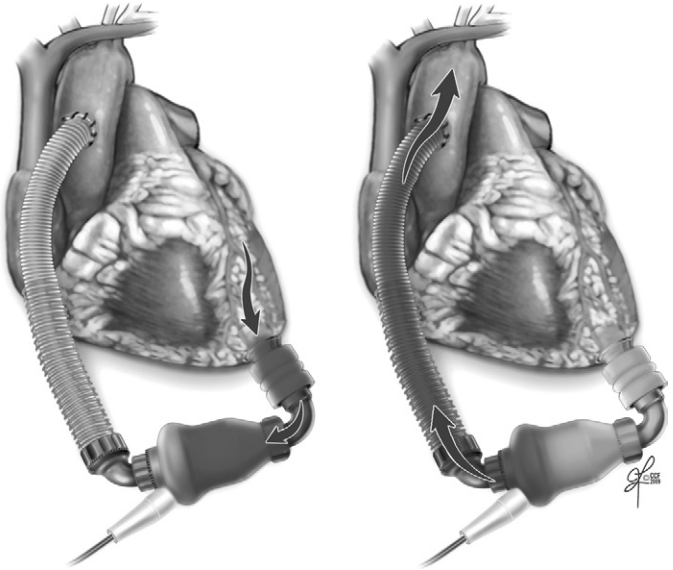


FIGURE **24-25** HeartMate II is an intracorporeal electrically powered axial-flow pump. Blood is drawn from the apex and pumped continuously to the ascending aorta. (Reprinted with permission from Cleveland Clinic Center for Medical Art & Photography © 2006-2012. All rights reserved.)

Cardiac Transplantation

General Considerations. The first human heart transplant was performed in South Africa in 1967 by Christiaan Barnard,[200] but it was not until the introduction of cyclosporine in the 1980s that there was significant long-term survival.[188,201-204] Today heart transplantation is the only definitive treatment for end-stage heart failure, and survival rates (adjusted for diagnosis, sex, race/ethnicity, and age) approach 90% at 1 year and 55% at 10 years.[188] The United Network for Organ Sharing (UNOS) is the organization in the United States that is responsible for coordinating organ procurement and allocation. An extensive multidisciplinary evaluation is required to prioritize placement on the donor list, but generally candidates must have New York Heart Association Class IV heart failure, an EF less than 20%, and a diagnosis of end-stage heart disease that is terminal in 1 to 2 years if transplant does not occur. Once on the list, patients are assigned a priority status of 1A, 1B, or 2. Status 1A is the highest priority and usually indicates that the patient is hemodynamically deteriorating, requiring vasopressor and/or mechanical circulatory assist support and mechanical ventilation.[51,205] Ischemic or idiopathic cardiomyopathy is the most common diagnosis of heart transplant candidates, but failure can arise from many other causes.[73] Organ donation comes from a relatively healthy patient who has been declared brain-dead. The donor heart is extensively examined before being deemed suitable. Allocation of the heart is based on the UNOS priority status, ABO blood type compatibility match, and weight ratio (within 20%). The donor and recipient must be close enough geographically to assure that the ischemic time of the heart is not prolonged.

Right ventricular failure is the major cause of short-term morbidity after transplantation. Fixed pulmonary hypertension in the recipient causes acute right heart failure in the donor heart. The pulmonary vasculature is examined closely to determine whether it responds to vasodilator therapy. A larger donor heart, heterotopic heart transplant, or a heart-lung transplant may be considered if the recipient has fixed pulmonary hypertension (transpulmonary gradient greater than 15 mmHg or PVR greater than 5 dynes/second/cm^5).[73,203-205]

Anesthetic Management. The preoperative period has important time constraints. Close communication is imperative among all members of the transplant center's surgical/anesthetic team and the organ procurement team to avoid prolonged donor heart ischemic time (ischemic time should be less than 4 hours).[206] The recipient will have had an extensive evaluation so that all information necessary for a quick assessment is readily available for review. Preoperative evaluation should follow an approach similar to that of any routine urgent preanesthetic evaluation, taking particular note of any recent deterioration. Chronic systemic hypoperfusion, venous congestion, hepatic dysfunction, and abnormal coagulation profiles are common. IABP settings and timing, VAD flow rates and settings, and all inotropic drug infusions should be noted. Patients with ICDs will need them deactivated before use of electrocautery. Because most heart transplantations are usually scheduled on short notice, most recipients will be considered full stomachs, and last oral intake and the need for a rapid sequence or modified rapid sequence induction should be assessed.

Induction of anesthesia for a heart transplant recipient follows many of the same principles for any traditional cardiac surgery on a patient with poor left ventricular function, with some noted

exceptions. All medications must be administered cautiously because severe heart failure patients are extremely sensitive to any alterations in myocardial preload and afterload. Obtaining rapid control of the airway to prevent aspiration during induction is often indicated. It is imperative to maintain the patient's heart rate, intravascular volume, and to avoid decreases in systemic vascular resistance to prevent cardiovascular collapse on induction. This can often be achieved with a short-acting hypnotic agent such as etomidate, which produces minimal myocardial depression; a small- to moderate-dose narcotic such as fentanyl to blunt sympathetic response to laryngoscopy and intubation; and a fast-onset muscle relaxant such as succinylcholine or rocuronium. Longer circulation times due to low ejection fractions in transplant candidates should be anticipated.

Once surgery begins, cross-matched, irradiated blood should be available. A repeat sternotomy may warrant cannulation of the femoral arterial and venous sites or axillary cannulation, to avoid trauma to the great vessels or preexisting coronary artery bypass grafts. Otherwise, the distal ascending aorta is cannulated and the inferior vena cava (IVC) and superior vena cava (SVC) are individually cannulated via the high right atrium.[203] Before venous cannulation, the pulmonary arterial catheter should be withdrawn from the right atrium and left in the sterile protective sheath so that it can be refloated into the pulmonary artery after CPB.

Ninety-eight percent of heart transplantation is orthotopic.[205] The biatrial techniques can be seen in Figures 24-26, *A* and *B*. If the size mismatch between donor and recipient hearts is gross, or if significant irreversible pulmonary hypertension exists, heterotopic heart transplant may be indicated. In heterotopic heart transplantation, the recipient's heart is not excised. Instead the donor's heart is placed in the right anterior thorax and anastomosed to the recipient's native heart, which creates a parallel circulation. Acute right ventricular failure in the donor heart may be avoided with heterotopic placement because the recipient's native right ventricle will provide most of the right-sided ventricular output against elevated pulmonary arterial pressures.

A high dose of glucocorticoid (methylprednisolone) is administered either preoperatively or before release of the aortic cross-clamp to decrease the chance of a hyperacute immune response. Pharmacologic inotropic support such as an isoproterenol and/or an epinephrine (direct acting) infusion may be initiated prior to CPB separation for both inotropy and chronotropy purposes. In addition to pharmacologic agents, temporary epicardial pacing may be needed due to the presence of slow junctional rhythms and loss of sinus node function.[207] Insertion of a permanent cardiac pacemaker is required in 5% to 25% of transplanted patients.[205,208] Proper oxygenation, ventilation, and acid/base balance is necessary to adequately manage right heart failure that may occur during separation from CPB. In addition, inhaled nitric oxide, prostaglandin, and/or a phosphodiesterase inhibitor such as milrinone may be used to promote pulmonary vasodilation. The transplanted heart becomes extremely preload dependent once it is denerved. Due to the loss of normal vagal tone, sympathetic and parasympathetic innervation, the denerved transplanted heart responds to hypovolemia and hypotension by initially increasing stroke volume (Frank-Starling mechanism). The administrations of ephedrine or anticholinergic drugs such as atropine are ineffective in increasing heart rate in the transplanted heart. Only pharmacologic agents such as epinephrine and isoproterenol that have direct-acting effects on catecholamines will be effective in increasing heart rate.

The anesthetist should anticipate potential post-CPB bleeding and coagulopathy, which can develop for many reasons including preoperative chronic anticoagulation, chronic hepatic congestion, extensive surgical suture lines, and CPB-induced platelet dysfunction. Anesthetic management and evaluation of ventricular function and pulmonary hypertension can be further guided by the TEE and hemodynamic measurements from the pulmonary arterial catheter.

Once hemostasis is achieved, the chest is closed in the usual fashion and the transplanted recipient, intubated, is transported to the ICU. Opportunistic infection, acute allograft rejection, and renal, pulmonary, and hepatic dysfunction are all possible postoperative complications of cardiac transplantation.[206,209]

Surgery on the Ascending Aorta and Aortic Arch

General Considerations

The cause of aortic disease is usually congenital (e.g., Marfan syndrome, Ehlers-Danlos syndrome, bicuspid AV) in patients who present at younger ages for surgery but acquired (e.g., hypertension, inflammation) in older ones.[9] A discussion of aortic disease, as well as the classification, etiology, diagnosis, and treatment of thoracic aneurysms (TA), can be found in Chapter 25. This chapter focuses on anesthetic management for surgeries on the ascending aorta and arch. Care of patients having aortic surgery requires close communication between the surgeon, perfusionist, and anesthesia provider. Management will vary markedly, depending on what segment(s) of the aorta are involved and whether the aortic valve can be preserved, repaired, or replaced. The plan for cannulation, invasive monitoring, and cerebral protection should be discussed prior to the case.

Surgery is generally indicated for ascending thoracic aneurysms that are dilated to 5.0 cm for congenital lesions or 5.5 cm for acquired lesions.[210] TAs generally grow slowly over a period of years, and are often found coincidentally after an x-ray in an

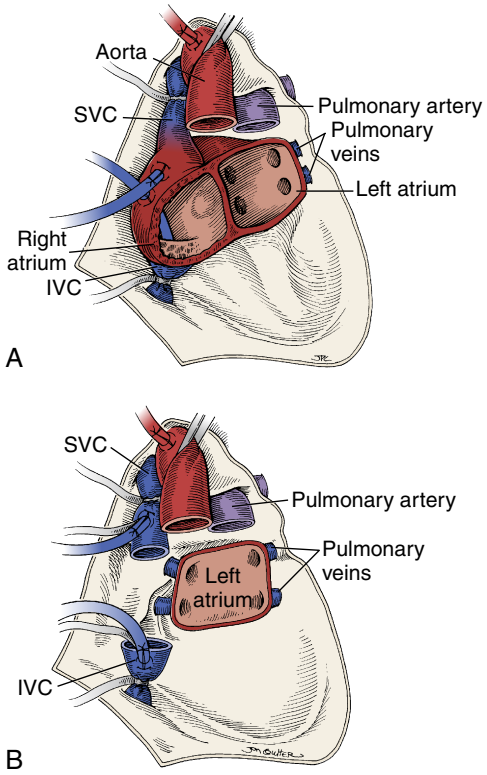


FIGURE **24-26** Mediastinum after excision of the heart but before allograft placement. Venous cannulas are present in the superior (SVC) and inferior vena cava (IVC), and the arterial cannula is present in the ascending aorta. **A,** Classic orthotopic technique. **B,** Bicaval anastomotic technique. (From Kaplan JA, Reich JA, Savino JS. *Kaplan's Cardiac Anesthesia: The Echo Era*. 6th ed. Philadelphia: Saunders; 2011.)

asymptomatic patient. Large TAs can cause a mass effect that leads to a variety of symptoms including cough, dysphasia, or hoarseness due to compression on the trachea, esophagus, or recurrent laryngeal nerve.[9] Sometimes, superior vena cava syndrome develops. TAs of the ascending aorta and arch are usually repaired using a median sternotomy. The type of procedure will vary depending on the extent of the aneurysm and the function of the aortic valve. TEE is an invaluable assessment tool for determining whether the valve can be spared or repaired and for measuring the aorta.

Ascending Aortic Aneurysms

When the aortic aneurysm involves only the root and proximal aorta, standard aortic cannulation and CPB can be used because the distal aorta can be cannulated and a clamp placed between the cannula and the aneurysm. The femoral artery may be used as an alternate arterial cannulation site when the aortic cannula cannot be placed without jeopardizing flow to the head vessels. In this case, arterial flow is retrograde from the femoral artery to the great vessels. Newer approaches also include cannulation of the right axillary or carotid artery, allowing antegrade perfusion of the innominate.[211] Usually a single, standard two-stage venous cannula suffices. A simple tube graft can be used to replace the aorta when the aortic root and valve are normal (Figure 24-27). If the aortic annulus or sinuses of Valsalva (where the coronary arteries attach) are involved, the options become more complicated and the selected technique may depend on the surgeon's expertise and preferences. When the sinuses of Valsalva are normal, the coronary arteries do not have to be reimplanted. The valve is repaired or replaced, the sinuses spared, and a tube graft is used to repair the aneurysm. If the aortic root is dilated, a technically difficult valve-sparing operation known as a modified David's reimplantation procedure can be used (Figure 24-28). A special instrument known as the Hegar's dilator is used to sew the native aortic valve (repaired if necessary) inside the graft used to repair the aneurysm. The coronary arteries are then reimplanted into the graft. When the valve cannot be spared, an alternative procedure is the Bentall procedure, in which the surgeon uses a composite valve-graft conduit. That is, a prosthetic AV (or pulmonary homograft) is sewn into one end of the conduit and the resulting composite valve-graft is used to replace both the aortic valve and ascending aorta. Again, the coronaries must be reimplanted or alternatively, an aortocoronary bypass graft can be used (Cabrol technique).[146]

Aortic Arch Aneurysms

Aneurysms that involve the arch are much more complicated. Because the vessels perfusing the brain are involved, the risk of neurologic injury is high from both the threat of global ischemia and embolization of atherosclerotic debris. CPB is used with a technique known as deep hypothermic circulatory arrest (DHCA) employed to protect the brain while the arch is replaced. DHCA is addressed under the discussion of anesthetic management. If only the proximal aortic arch is involved, a hemiarch or partial arch replacement can be done. The origins of the arch vessels are usually dissected *en bloc* so that the three vessels lie on an island of native aortic tissue that can be anastomosed to the synthetic graft. The surgeon completes the distal anastomosis to the descending aorta first and then sews on the island of tissue containing the arch vessels. Next the aortic clamp is moved proximal to the arch vessels so that CPB flow can be reestablished and the cerebral vessels perfused. Finally, the proximal aortic graft anastomosis is completed[211] (Figure 24-29). Aneurysms that involve the entire thoracic aorta are extremely complicated and are often repaired in stages combining both open and endovascular techniques.

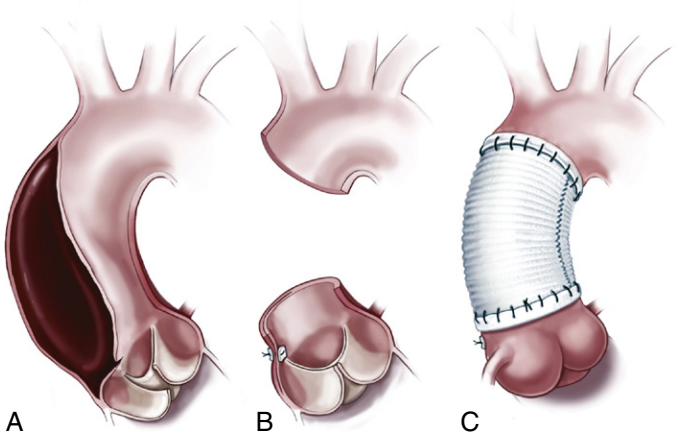


FIGURE **24-27** Ascending aortic disssection repair. **A,** The dissecting hematoma is seen and usually extends all the way to the iliac arteries. **B,** The compromised commissure of the valve is resuspended by a full-thickness pledgeted suture. **C,** The ascending aorta is replaced with a vascular graft, usually using strips of felt to reinforce the delicate adventitial tissues. (From Otto CM, Bonow RO. *Valvular Heart Disease: A Companion to Braunwald's Heart Disease*. 3rd ed. Philadelphia: Saunders; 2009.)

Anesthetic Management

Anesthesia implications are similar to those of other cardiac surgeries involving a median sternotomy with CPB, but there are several additional concerns. The anesthetist must prepare for the possibility of a difficult airway if the aneurysm is large and possibly causing a mass effect. Occasionally a reinforced endotracheal tube must be used and advanced beyond the point of compression. Caution is advised if there is resistance to passing the TEE probe or oral gastric tube as the aneurysm may be compressing the esophagus as well. An epi-aortic echocardiographic examination may be necessary. If AI is present, all the anesthetic management principles previously discussed regarding acute and chronic AI apply. In general, maintenance of a relatively high heart rate and low SVR will enhance forward flow. It is important to control the systolic pressure, keeping it less than 120 mmHg to minimize the chance of dissection.[9] Vasodilators are often indicated to control blood pressure and lower the SVR. Pulmonary artery catheters are usually indicated because large shifts in volume can be reasonably anticipated, especially if the arch is involved. Blood loss can be significant, so several units of red cells should be available. Fresh frozen plasma and platelets are transfused as needed based on coagulation studies and nonsurgical bleeding. A large-bore multilumen PAC introducer is helpful. Alternatively, several large-bore PIVs can be used with a standard introducer. The best location for the arterial line is determined by the plan for placement of the aortic cannula and aortic cross-clamp. For ascending aortic aneurysms, there is no consensus in the literature as to the best location for the arterial line; the left brachial artery as well as the left and right radial arteries have all been advocated.[138,146,211] When the arch is involved, two A-lines are placed one in either radial or brachial artery and one in a femoral artery. If the right axillary artery is to be cannulated for CPB, then the left radial or brachial is preferred. Some practitioners place three A-lines, one in each upper extremity as well as the femoral artery. The surgeon can then be alerted to pressure differences between the A-lines that most likely indicate inadequate flow and potential ischemia. Nasal or tympanic temperature is monitored as a reflection of brain temperature. The nasal probe should be placed before heparin is administered, to prevent bleeding in this fragile area.

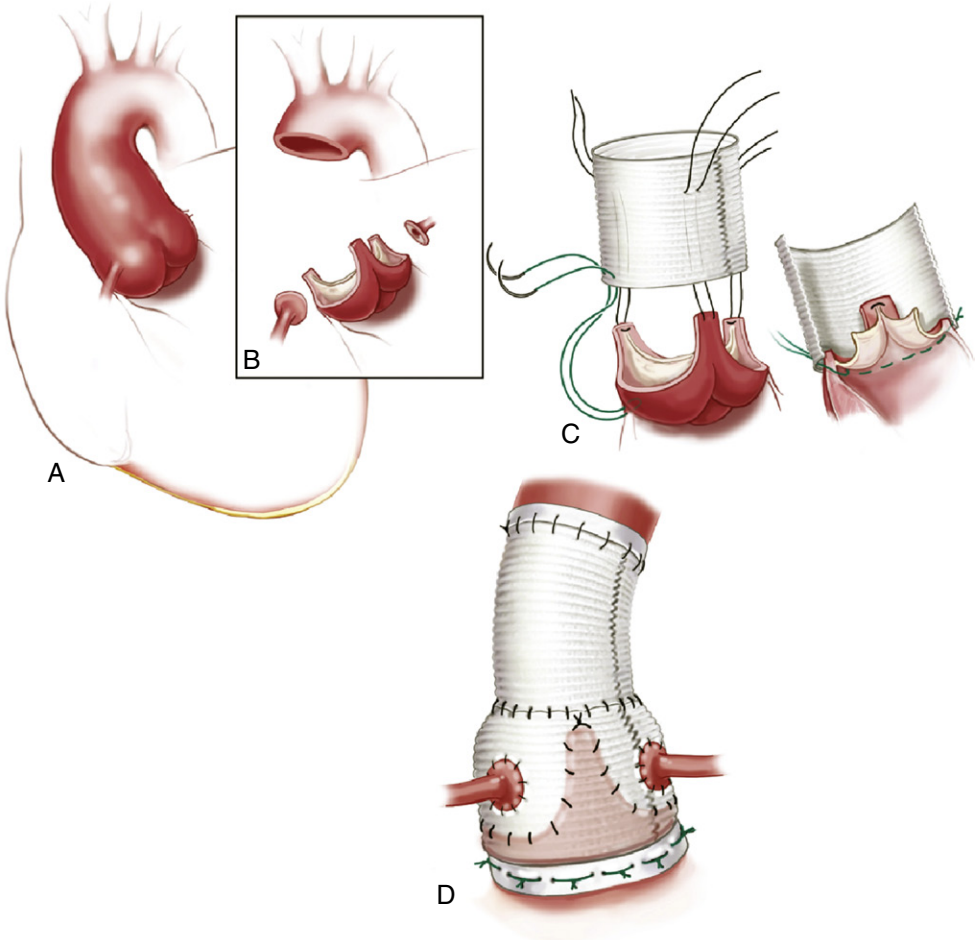


FIGURE **24-28** David procedure. Aneurysmal root (**A**) is resected (**B**) including sinuses of Valsalva with coronary "buttons" mobilized away. **C**, Subannular sutures (six to eight) are placed. Commissural posts are drawn up inside the valve and the annular sutures are passed through the proximal end of the graft. **D**, Annular sutures are tied gently. Then the valve is reimplanted with continuous 5-0 polypropylene suture inside the graft. Aortic continuity is reestablished with another graft of a size appropriate to the desired sinotubular junction and proximal arch. (From Otto CM, Bonow RO. *Valvular Heart Disease: A Companion to Braunwald's Heart Disease*. 3rd ed. Philadelphia: Saunders; 2009.)

Usually bladder and PA temperatures are also measured to help in the rewarming process.

Aortic Dissection

Acute ascending or aortic arch dissections are highly lethal, and timely surgical intervention correlates with survival.[9] The dissection begins from an intimal tear that can spread antegrade or retrograde throughout the aorta, possibly encompassing the great vessels and/or the aortic valve. Chapter 25 discusses in detail the pathophysiology of aortic dissection and the management of descending aneurysms. Patients usually present with sudden severe chest pain, but symptoms mimicking a stroke, myocardial infarction, or arterial embolization also can occur. Syncope is an ominous sign that cerebral or cardiac circulation is compromised. Diagnosis can be made with TEE, contrast-enhanced spiral computed tomography (CT) scan, or magnetic resonance imaging (MRI). Acute AI, tamponade, or limb ischemia can develop at any time. Initially, it is important to gain adequate vascular access to monitor and transfuse the patient. The arterial line site should be carefully selected, avoiding ischemic limbs and locations that will be impacted by surgical cannulation. The aim of hemodynamic management is to decrease sheer forces that can cause further dissection or rupture. The heart rate and blood pressure are most often controlled using a beta-blocker first to achieve a heart rate of about 60 bpm followed by cautious vasodilation to achieve a systolic blood pressure lower than 120 mmHg.[146] Coexisting myocardial depression can make medication titration challenging.[9,146,211] Some institutions have the patient prepped and draped prior to induction in case urgent CPB must be initiated because of rupture. All of the previously mentioned anesthetic considerations apply.

Deep Hypothermic Circulatory Arrest

Cerebral perfusion must be temporarily interrupted during repair of aneurysms involving the aortic arch. Deep hypothermia is the most important therapeutic intervention to prevent cerebral ischemia. The patient is cooled using CPB to maximally decrease the cerebral metabolic rate and oxygen consumption, thereby extending the period that the brain can tolerate circulatory arrest. As cooling on CPB is initiated, most institutions cool the brain topically by placing ice bags around the head. Care should be taken to protect the eyes and skin. The optimal temperature, the best site for temperature measurement, and a safe duration for deep hypothermic circulatory arrest (DHCA) remain matters of debate.[212] Generally, a nasopharyngeal temperature is measured and the patient is cooled to 15° to 22° C. Arrest periods of

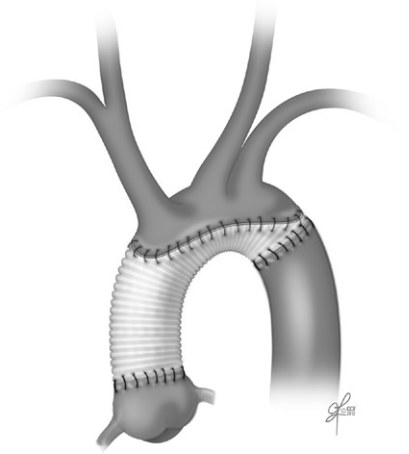


FIGURE **24-29** Repair of the ascending aorta and aortic arch. Note that the great vessels to the head are usually resected as an island of tissue that is anastomosed to the graft. (Reprinted with permission from Cleveland Clinic Center for Medical Art & Photography © 2006-2012. All rights reserved.)

less than 25 minutes are generally considered safe.[211] One study showed that at least 50 minutes of cooling or a nasopharyngeal temperature of 12.1° C was needed to produce electrical silence on the EEG in 95% of patients.[213] The traditional goal is to have a flat EEG, but the bispectral index (BIS) and cerebral oximeters also have been used to try to detect, and thus prevent, cerebral ischemia.[214] Other efforts to improve the safety of DHCA include reducing blood viscosity and hematocrit in an effort to counteract the increased blood viscosity that develops secondary to cooling. Pharmacologic attempts at neuroprotection include the administration of barbiturates or propofol to decrease cerebral oxygen demand. Steroids, lidocaine, and mannitol also have been used. However, because no pharmacologic intervention has proved effective, these are not considered a substitute for achieving adequate hypothermia.[215]

Retrograde Cerebral Perfusion. To further protect the brain during DHCA, the surgeon may choose to use retrograde cerebral perfusion (RCP). A snared cannula is introduced into the right atrium and advanced into the superior vena cava (SVC) for use during the period of arest.[146] When the patient is cooled to the desired temperature and the EEG shows burst suppression or the BIS is 0, the pump is turned off. During the period of arrest, cold oxygenated blood between 8° C and 14° C is infused at a rate of 220 to 600 mL/min through the SVC cannula. Ideally flow reaches the brain in a retrograde fashion through the venous system. The patient is kept in slight Trendelenburg position to prevent air embolism. High-pressure tubing used to measure the CVP pressure port of the PAC is disconnected (the port is capped) and reconnected to the side port introducer to measure SVC pressure. The SVC pressure should be maintained below 25 mmHg during RCP.[146] Alternatively, some surgeons attach the arterial cannula of the CPB circuit to the SVC cannula and direct low flows through the cannula to maintain an SVC pressure of about 20 mmHg.[211] Although there are no randomized controlled trials demonstrating the benefit of RCP, a recent large-scale, single-center study found a decrease in the rates of mortality and stroke.[216]

Antegrade Cerebral Protection. If DHCA is expected to last more than 30 minutes, selective antegrade cerebral protection (ACP) into the axillary, innominate, subclavian, or even internal carotid artery has been attempted.[217] The perfusionist controls antegrade flow with a roller pump. Rates between 400 and 1000 mL/min are typical, the goal being to maintain MAP at about 50 to 80 mmHg. Efficacy of the technique has been demonstrated with ACP times of 75 to 235 minutes.[218]

Rewarming. Once systemic perfusion is reestablished using CPB, a period of hypothermic reperfusion is recommended. When rewarming begins, it should be done gradually, maintaining a temperature gradient no greater than 10° C in the heat exchanger, and cerebral hyperthermia must be avoided.[210] Even slight hyperthermia in patients with cerebral ischemia or infarction may exacerbate any damage.[219] The optimal temperature for coming off bypass is a matter of debate. Some believe that a bladder temperature of 36.5° C should be achieved to decrease bleeding, while others hold that 35° C is cerebral protective and that bleeding is due to the procedure and to other causes.[146,220]

SUMMARY

As the population ages, coronary artery disease, valvular heart disease, and heart failure will continue to be major health burdens. The risk profile of the average cardiac surgical patient and the complexity of the procedures continue to rise. Technology and innovative surgical approaches to managing cardiovascular disease has changed the landscape of cardiac anesthesia. A clear understanding of the core physiologic and pathophysiologic principles that impact coronary blood flow and myocardial function will enable the anesthetist to adapt anesthetic management in this ever-evolving field. Each clinician is encouraged to stay abreast of the evidence-based outcome studies that have so greatly impacted our clinical practice. Enjoy the excitement and challenge of cardiac anesthesia and always remember to "take care of the pipes, the pump and the volume."

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Anesthesia for Vascular Surgery

CHAPTER 25

◆ *Sass Elisha*

PERIPHERAL VASCULAR DISEASE

Atherosclerosis is the most common cause of occlusive disease. This degenerative process involves the formation of atheromatous plaques that may obstruct the vessel lumen and thereby cause a reduction in distal blood flow. The pathophysiologic processes that affect the arteries include plaque formation, which obstructs the lumen (stenosis); thrombosis, which can result in acute ischemia; embolism from microthrombi or atheromatous debris, which decreases distal blood flow; and weakening of the arterial wall with aneurysm formation. The most common risk factors associated with atherosclerosis are shown in Box 25-1. Cigarette smoking and diabetes mellitus are major risk factors in the pathogenesis of atherosclerosis in the peripheral vascular system. Typical symptoms of peripheral occlusive disease include claudication, skin ulcerations, gangrene, and impotence.[1] The extent of disability is primarily influenced by the development of collateral blood flow. Initially, collateral blood flow sufficiently meets tissue oxygen demands. As the disease process progresses, supply is unable to meet demand, and limb ischemia becomes symptomatic, requiring therapeutic intervention. The mortality rate associated with patients with vascular disease is two- to sixfold higher than within the general population.[2] There is a relationship between inflammation and the development of atherosclerosis. Platelet interaction with leukocytes and other cells that modulate the immune response play a major role in the development of atherosclerosis.[3,4] Researchers have discovered heritable genetic factors that predispose patients to developing vascular disease.[5]

Treatment for peripheral occlusive disease may range from pharmacologic therapy to surgery. Surgical therapy includes transluminal angioplasty, endarterectomy, thrombectomies, endovascular stenting, and arterial bypass procedures. Some common surgical maneuvers used for bypassing occlusive lesions are aortofemoral, axillofemoral, femorofemoral, and femoropopliteal bypass techniques. Bypass techniques may be classified as *inflow* or *outflow* procedures, depending on the level of the obstruction, with the dividing axis being at the level of the groin. Temporary occlusion of the operative artery is mandatory when bypass procedures are used. The response to aortic cross-clamping in patients with aortoiliac occlusive disease produces less hemodynamic variability as compared to patients with aneurysmal disease. The development of collateral circulation provides alternative vascular blood flow in patients with occlusive disease.[6,7]

Preoperative Evaluation

The atherosclerotic process in occlusive disease is not limited to the peripheral arterial beds and should be expected to be present in the coronary, cerebral, and renal arteries. More than half the mortality associated with peripheral vascular disease results from adverse cardiac events.[8] It has been estimated that 42% of patients presenting for abdominal aortic aneurysm (AAA) repair have significant coronary artery disease (CAD).[9] The identification and management of cardiac pathology, which often occurs in this patient population, must be managed aggressively to optimize cardiac functioning and decrease morbidity and mortality from cardiac causes. For a complete discussion of a preoperative cardiac evaluation, refer to Chapter 19.

The advantages of β-blockade as relates to factors that affect myocardial oxygen supply and demand have been extensively studied in this patient population, and the judicious use of β-blockers is recommended in patients at high risk for myocardial ischemia and infarction.[10] For patients having AAA repairs, there is a 10-fold decrease in cardiac morbidity.[11] β-blockade therapy should be instituted days to weeks before surgery and titrated to a target heart rate between 50 and 60 beats per minute (bpm).[12] Vascular surgery patients with limited heart rate variability after receiving β-blocking medication exhibit less cardiac ischemia and troponin values postoperatively and have a decreased mortality from all causes 2 years postoperatively.[13] It has been suggested that because of their antiinflammatory effects, a statin drug should be instituted 30 days prior to the surgical procedure.[14]

The presence of concurrent pulmonary, renal, neurologic, and endocrine dysfunction should be identified, and measures should be taken to improve organ function before surgery. Preoperatively, the greater number of comorbidities that exist, the greater the risk of morbidity and mortality during the perioperative period.

Monitoring

The extent of perioperative monitoring should be based on the presence of coexisting disease and the type of surgery. Clearly the detection of myocardial ischemia should be a primary objective in patients with vascular disease. Methods for assessing cardiac function include electrocardiographic, pulmonary artery pressure, and transesophageal echocardiography (TEE) monitoring. The effectiveness of pulmonary artery catheters (PACs) in improving patient outcomes has been controversial for years. Many randomized controlled trials have been performed to assess whether they offer any benefit. It was determined that PAC monitoring had no effect on mortality or length of hospital stay. Additionally, there were higher rates of pulmonary embolism, pulmonary infarction, and hemorrhage in the PAC group.[15-17] Practice guidelines provided by the American Society of Anesthesiologists Task Force on Pulmonary Artery Catheterization states that the routine use of PACs is not warranted.[18]

Because of the global nature of atherosclerotic disease, some degree of systemic cardiovascular disease in patients with peripheral vascular disease should be assumed.[9] Patients with hypertension and/or angiopathology rely on increased mean arterial pressures to perfuse their vital organs. Thus cerebral and coronary autoregulation occurs at higher than normal pressures. Direct intraarterial blood pressure monitoring allows for near–real-time

determination of blood pressure values and is warranted because of dramatic fluctuations that can occur during anesthesia.

Anesthetic Selection

The anesthetic technique chosen for patients having vascular surgery depends on the type of surgical procedure to be performed and the presence of coexisting disease. In certain instances, infiltration of local anesthetic and intravenous sedation may be sufficient, whereas other situations may require the use of general anesthesia. Regional anesthesia for surgery on the lower extremities may decrease the overall morbidity and mortality associated with this patient population. Numerous studies have failed to yield demonstrative advantages for any single anesthetic technique. A comprehensive meta-analysis combining data from 141 studies involving 9559 patients suggested a 30% reduction in mortality for those patients who received a combined general anesthetic and epidural combination. A reduction in the rate of myocardial infarction stroke and respiratory failure was found when epidural anesthesia was used in patients undergoing aortic surgery.[19] Several major studies have been conducted evaluating various end points associated with major vascular surgery.[20] None of the studies have definitively concluded that superior outcomes depend on the anesthetic technique used.[21] The major advantages to using a epidural technique are most noted during the postoperative period. Specific physiologic benefits of an epidural used for major abdominal vascular surgery are summarized in Box 25-2. Some considerations include the findings that inhalation anesthetic agents induce cardioprotection in patients having noncardiac surgery.[22] In addition, many vascular patients are receiving anticoagulant therapy; therefore, neuraxial anesthetic techniques must be used with caution to avoid epidural hematoma formation.[23]

BOX 25-1

Risk Factors Related to the Development of Atherosclerotic Lesions

- Hypercholesterolemia
- Elevated triglycerides
- Cigarette smoking
- Hypertension
- Diabetes mellitus
- Obesity
- Genetic predisposition
- Sedentary lifestyle
- Sex (male at greater risk than female)
- Impaired long-term glucose regulation
- Homocysteine
- C-reactive protein

Postoperative Considerations

Postoperative pain management is an important issue related to peripheral vascular surgery. Most clinicians agree that postoperative administration of narcotics not only provides patient comfort but also contributes to cardiac stability. The use of epidural opioid and local anesthetics in patients recovering from vascular surgery is an important component of postoperative care because pain can greatly enhance sympathetic nervous system stimulation. Despite a decrease in discomfort during the postoperative course, these patients must be monitored in an appropriate surgical unit that is capable of detecting possible adverse events, such as myocardial infarction or respiratory depression, which could be attributed to the administration of epidural opioids and local anesthetics. Presently data are insufficient to confirm that adequate analgesic techniques decrease morbidity and mortality from postoperative complications.[24]

ABDOMINAL AORTIC ANEURYSMS

Incidence

The incidence of abdominal aortic aneurysm (AAA) is estimated to range between 3% and 10% for patients older than 50 years of age who reside in the western world.[25] Improved detection of AAAs is the result of increased screening of asymptomatic aneurysms by noninvasive diagnostic modalities, such as computed tomography (CT), magnetic resonance imaging (MRI), and ultrasonography. The occurrence of AAAs has increased because of the increased age of the general population and the vascular changes that occur as a result of aging.[26]

BOX 25-2

Benefits of the Epidural Technique in Vascular Surgery

Endocrine
- Inhibits surgical stress response
- Inhibits epinephrine and cortisol release
- Inhibits hyperglycemia
- Inhibits lymphopenia and granulocytosis
- Causes nitrogen sparing
- Blocks sympathetic tone
- Inhibits inflammatory mediator release

Cardiovascular
- Decreases myocardial oxygen demand and afterload
- Increases endocardial perfusion at ischemic zone
- Increases hemodynamic stability
- Decreased blood loss
- Decreases general anesthetic medication requirements
- Redistributes blood to lower extremities

Pulmonary
- Decreased effect on FVC, FEV_1, and PEFR
- Decreases ventilation perfusion mismatch
- Improves atrioventricular oxygen differentiation
- Decreases pulmonary postoperative complications
- Decreased incidence of thromboembolism

Renal
- Increases blood flow in the renal cortex
- Decreases renovascular constriction

Geriatric
- Inhibits physiologic stress
- Improves postoperative mental status

Miscellaneous
- Allows earlier extubation, ambulation, and discharge
- Improves postoperative pain control

FEV_1, Forced expiratory volume in 1 second; *FVC*, forced vital capacity; *PEFR*, peak expiratory flow rate.

Risk Factors

The incidence of AAAs in a given population depends on the presence of risk factors (Box 25-3). Independent risk factors thought to be causes rather than markers for the development of a AAA include age, gender, and smoking. Smoking is the risk factor that is most highly correlated with AAA. In cigarette smokers, the incidence of AAAs increases fivefold.[25]

Mortality

Elective AAA repair is one of the most frequent vascular surgical procedures, with approximately 40,000 operations performed in the United States annually.[27,28] Mortality rates for elective abdominal aortic aneurysmectomies have decreased since the 1970s. The present mortality rate ranges from 1% to 11%, although it is most commonly estimated at 5%. This is compared with mortality rates of 18% to 30% in the 1950s.[25,29-35] Advanced detection capabilities, earlier surgical intervention, extensive preoperative preparation, refined surgical techniques, better hemodynamic monitoring, improved anesthetic techniques, and aggressive postoperative management have all contributed to this improvement in surgical outcomes. Data suggest that risk of rupture is very low for AAAs less than 4 cm in diameter, but the risk dramatically increases for AAAs with a 5-cm or greater diameter. Surgical intervention is recommended for AAAs 5.5 cm or greater in diameter.[36] Unfortunately, mortality rates for those with undetected or untreated ruptured aortic aneurysms have not followed the trend of those who have surgical intervention. Estimates of mortality resulting from ruptured AAAs vary from 35% to 94%.[28,37-40] Combining prehospital with operative mortality, the overall mortality for AAA rupture is 80% to 90%. The 5-year mortality rate for individuals with untreated AAAs is 81%, and the 10-year mortality rate is 100%.[33] Other criteria for surgical intervention for AAA include ruptured AAA, 4- to 5-cm AAA with greater than 0.5 cm enlargement in less than 6 months, patients who are symptomatic for AAA, and 5.0-cm AAA or greater for elective repair for patients with a reasonable life expectancy. Early detection and elective surgical intervention can be lifesaving because elective surgical mortality is less than 5% in most series.[41]

Diagnosis

Frequently, asymptomatic aneurysms are detected incidentally during routine examination or abdominal radiography. Smaller aneurysms are often undetected on routine physical examination. Diagnostic techniques, such as ultrasonography, CT scan, and MRI, may identify vascular abnormalities in these patients. Such noninvasive techniques not only reveal the presence of aneurysms but also provide information about aneurysm size, vessel wall integrity, and adjacent anatomic definition.[42] Invasive techniques, including contrast-enhanced CT scan, contrast angiography, and digital subtraction angiography, can provide additional information and more detailed representations of arterial anatomy.

BOX 25-3

Conditions and Traits Associated with Development of Abdominal Aortic Aneurysm

- Smoking
- Older age
- Gender, male more often than female
- Family history
- Coronary artery disease
- High cholesterol
- Chronic obstructive pulmonary disease (COPD)
- Height (per 7 cm interval)
- Hypertension
- Peripheral vascular occlusive disease
- Caucasian

ABDOMINAL AORTIC RECONSTRUCTION

Patient Selection

As a result of recent advances in surgical and anesthetic techniques, the mortality associated with elective repair of AAAs is fairly low compared with nonsurgical management. Most patients with abdominal aneurysms, including the elderly, are considered surgical candidates. Although advancing age contributes to an increased incidence of morbidity and mortality, age alone is not a contraindication to elective aneurysmectomy.[43] However, physiologic age is more indicative of increased surgical risk than chronologic age. Contraindications to elective repair include intractable angina pectoris, recent myocardial infarction, severe pulmonary dysfunction, and chronic renal insufficiency.[6] Patients with stable CAD and coronary artery stenosis of greater than 70% who require nonemergent AAA repair do not benefit from revascularization if β-blockade has been established.[44] Table 25-1 lists characteristics that define high-risk patients; however, in most cases the presence of an AAA warrants surgical intervention.[33]

The dimensions of an aneurysm can change over time. Abdominal aortic aneurysms grow approximately 4 mm/yr.[45] Aneurysmal vessel dimensions correspond to the law of Laplace:

$$T = P \times r$$

where T = wall tension, P = transmural pressure, and r = vessel radius.

TABLE 25-1 Criteria for High Risk in Abdominal Aortic Aneurysm Repair

Parameter	Criterion
Age	Older than 70 years
Gender	Female
Cardiac	History of myocardial infarction Angina pectoris Myocardial disease Q waves on electrocardiogram (ECG) ST/T wave changes on ECG Ventricular ectopy Hypertension with left ventricular hypertrophy Congestive heart failure
Endocrine	Diabetes
Neurologic	Stroke
Renal	Chronic or acute renal failure
Pulmonary	Chronic obstructive pulmonary disease Emphysema Dyspnea Previous pulmonary surgery

Modified from Pairolero PC. Repair of abdominal aortic aneurysms in high-risk patients. *Surg Clin North Am.* 1989;69:765-774; Fillinger MF. Abdominal aortic aneurysms: evaluation and decision making. In: Cronenwett JL, Johnston W, eds. *Rutherford's Vascular Surgery.* 7th ed. Vol. 2. Philadelphia: Saunders; 2010; Rubin BG, Sicard GA. Abdominal aortic aneurysms: open surgical treatment. In: Cronenwett JL, Johnston W, eds. *Rutherford's Vascular Surgery.* 7th ed. Vol. 2. Philadelphia: Saunders; 2010.

TABLE 25-2 Range of Potential Rupture Rates for a Given Size of Abdominal Aortic Aneurysm

AAA Diameter (cm)	Rupture Risk (%/yr)
<4	0
4-5	0.5-5
5-6	3-15
6-7	10-20
7-8	20-40
>8	30-50

From Brewster DC, Cronenwett JL, Hallett JW Jr, et al. Guidelines for the treatment of abdominal aortic aneurysms: report of a subcommittee of the Joint Council of the American Association for Vascular Surgery and Society for Vascular Surgery. *J Vasc Surg*. 2003;37:1106-1117.
AAA, Abdominal aortic aneurysm.

As the radius of a vessel increases, the wall tension increases. Therefore the larger the aneurysm, the more likely the risk of spontaneous rupture. As stated, aneurysms measuring more than 4 to 5 cm in diameter generally require surgical intervention,[29] but aneurysms measuring less than 4 to 5 cm should not be considered benign. An aneurysm has the potential to rupture regardless of its size. As the diameter of the aneurysm increases in size, the risk of rupture increases, as shown in Table 25-2.

Patient Preparation

Perioperative myocardial infarction is the most common reason for poor outcomes in noncardiac surgery. Optimization of myocardial oxygen supply and demand and modification of cardiac risk factors is the major goal of preoperative risk reduction. β-blockers, statins, and aspirin are the hallmark pharmacologic treatments for medical management. Prophylactic coronary revascularization is recommended only as per the same indications as the nonoperative setting. Preoperative cardiac testing is recommended only if interpretation of the results will change anesthetic management.[46-48]

Preoperative fluid loading and restoration of intravascular volume are perhaps the most important techniques used to enhance cardiac function during abdominal aortic aneurysmectomies. Reliable venous access must be secured if volume replacement is to be accomplished. Large-bore intravenous lines and central lines can be used to infuse fluids or blood. Massive hemorrhage is an ever-present threat; therefore, the availability of blood and blood products should be ensured. Provisions for rapid transfusion and intraoperative blood salvage should be confirmed.

Routine Monitoring

Standard monitoring methods include electrocardiography (with display of lead II for detection of dysrhythmias and the precordial V_5 lead for analysis of ischemic ST-segment changes), pulse oximetry, and capnography. An esophageal stethoscope allows for continuous auscultation of heart and breath sounds, as well as temperature monitoring. Placement of an indwelling urinary catheter is necessary for continuous measurement of urinary output and renal function. Neuromuscular function is also routinely monitored.

Invasive Monitoring

Maintaining cardiac function is crucial for a successful surgical outcome; cardiac function should be closely monitored during abdominal aortic reconstruction. Invasive blood pressure monitoring permits beat-to-beat analysis of the blood pressure, immediate identification of hemodynamic alterations related to aortic clamping, and access for blood sampling. However, information obtained from pulmonary artery catheters has been shown to have low sensitivity and low specificity in detecting myocardial ischemia when compared with electrocardiographic and transesophageal echocardiography (TEE). As previously discussed, pulmonary artery catheters are not routinely used unless a specific indication is warranted in these procedures.[18,49]

By detecting changes in ventricular wall motion, two-dimensional TEE provides a sensitive method for assessing regional myocardial perfusion. TEE is a primary method of intraoperative cardiac assessment in patients undergoing surgery on the heart and the aorta.[46,50,51] Wall motion abnormalities also occur much sooner than electrocardiographic changes during periods of reduced coronary blood flow.[52] Myocardial ischemia poses the greatest risk of mortality after abdominal aortic reconstruction. Intraoperative monitoring may enable earlier detection and intervention during ischemic cardiac events.

Aortic Cross-Clamping

Abdominal aortic reconstruction may be one of the most challenging situations for the anesthetist. Patients with AAAs tend to be elderly and have varying degrees of coexisting disease. In addition to the risks associated with any major surgical procedure, these patients also experience physiologic changes that are specific to abdominal aortic aneurysmectomies. Perhaps the most dramatic physiologic change occurs with the application of an aortic cross-clamp. Temporary aortic occlusion produces various hemodynamic and metabolic alterations.

Hemodynamic Alterations

The hemodynamic effects of aortic cross-clamping depend on the application site along the aorta, the patient's preoperative cardiac reserve, and the patient's intravascular volume. The most common site for cross-clamping is infrarenal, because most aneurysms appear below the level of the renal arteries. Less common sites of aneurysm development are the juxtarenal and suprarenal areas.

During aortic cross-clamping, *hypertension* occurs *above* the cross-clamp and *hypotension* occurs *below* the cross-clamp. Aortic cross-clamping results in a series of complex metabolic and humoral responses involving the sympathetic and renin-angiotensin-aldosterone systems. There is an absence of blood flow distal to the clamp in the pelvis and lower extremities.[6] Increases in afterload cause myocardial wall tension to increase. Mean arterial pressure (MAP) and systemic vascular resistance (SVR) also increase. Cardiac output may decrease or remain unchanged. Pulmonary artery occlusion pressure (PAOP) may increase or display no change. Table 25-3 summarizes the physiologic changes associated with aortic cross-clamping.

Patients with adequate cardiac reserve commonly adjust to sudden increases in afterload without the occurrence of adverse cardiac events. However, patients with ischemic heart disease or ventricular dysfunction are unable to fully compensate, as a result of the hemodynamic alterations. The increased wall stress attributed to aortic cross-clamp application may contribute to decreased global ventricular function and myocardial ischemia. Clinically, these patients experience increases in PAOP in response to aortic cross-clamping. Aggressive pharmacologic intervention is required for restoration of cardiac function during this time. An algorithm that depicts the systemic hemodynamic responses to aortic cross-clamping is shown in Figure 25-1.

TABLE 25-3 The Physiologic Changes Associated with Aortic Cross-Clamping

Hemodynamic Changes	Metabolic Changes	Intraoperative Interventions
Increased arterial blood pressure above the clamp	Decreased total body oxygen consumption	*Reduce Afterload* Sodium nitroprusside Inhalation anesthetics Milrinone Shunts and aorta to femoral bypass
Decreased arterial blood pressure below the clamp	Decreased total body carbon dioxide production	*Reduce Preload* Nitroglycerin Atrial to femoral bypass
Increased wall motion abnormalities and left ventricular wall tension	Increased mixed venous oxygen saturation	*Renal Protection* Fluid administration Mannitol Furosemide Dopamine N-acetylcysteine Renal cold perfusion
Decreased ejection fraction and cardiac output	Decreased total body oxygen extraction	*Miscellaneous* Hypothermia Decrease minute ventilation Sodium bicarbonate
Decreased renal blood flow	Increased catecholamine release	
Increased pulmonary occlusion pressure	Respiratory alkalosis	
Increased central venous pressure	Metabolic acidosis	
Increased coronary blood flow		

Adapted from Norris EJ. Anesthesia for vascular surgery. In: Miller RD, et al, eds. *Miller's Anesthesia*. 7th ed. Philadelphia: Churchill Livingstone; 2010; Fillinger MF. Abdominal aortic aneurysms: evaluation and decision making. In: Cronenwett JL, Johnston W, eds. *Rutherford's Vascular Surgery*. 7th ed. Vol. 2. Philadelphia: Saunders; 2010.

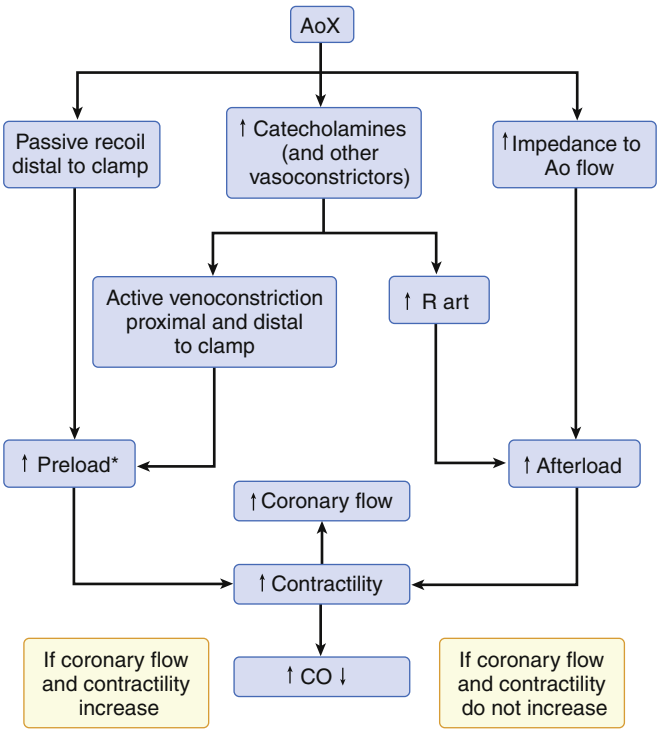

FIGURE 25-1 Systemic hemodynamic response to aortic cross-clamping. Preload *(asterisk)* does not necessarily increase with infrarenal clamping. Depending on splanchnic vascular tone, blood volume can be shifted into the splanchnic circulation, and preload will not increase. *Ao*, Aortic; *AoX*, aortic cross-clamping; *R art*, arterial resistance. (Adapted from Gelman S. The pathophysiology of aortic cross-clamping. *Anesthesiology*. 1995;82:1026-1060.)

Metabolic Alterations

After the application of an aortic cross-clamp, the lack of blood flow to distal structures makes these tissues prone to developing hypoxia. In response to hypoxia, metabolites such as lactate accumulate. Both epinephrine and norepinephrine stimulate myocardial β_1-receptors that can increase heart rate and myocardial oxygen demand.

The release of arachidonic acid derivatives also may contribute to the cardiac instability observed during aortic cross-clamping. Thromboxane A_2 synthesis, which is accelerated by the application of an aortic cross-clamp, may be responsible for the decrease in myocardial contractility and cardiac output that occurs. Numerous studies have attempted to determine whether cyclooxygenase inhibition caused by the administration of aspirin or ibuprofen before elective aneurysmectomies can preserve myocardial function.

Traction on the mesentery is a surgical maneuver used for exposing the aorta. Mesenteric traction syndrome is associated with this procedure. Decreases in blood pressure and SVR, tachycardia, increased cardiac output, and facial flushing are common responses to mesenteric traction. Although the cause of this syndrome is unknown, it has been associated with high concentrations of 6-keto-prostaglandin F_1, the stable metabolite of prostacyclin at the time of mesenteric traction.[53] The 6-ketoprostaglandin F_1 levels and hemodynamic stability return to preclamp values as reperfusion occurs.

The neuroendocrine response to major surgical stress is believed to be mediated by cytokines such as interleukin (IL)-1B, IL-6, and tumor necrosis factor, as well as plasma catecholamines and cortisol.[54] These mediators are thought to be responsible for triggering the inflammatory response that results in increased body temperature, leukocytosis, tachycardia, tachypnea, and fluid sequestration. Patients who have an exaggerated plasma stress mediator release had longer operative and cross-clamp times and required a greater number of blood transfusions.

TABLE 25-4 Hemodynamic Responses to Aortic Declamping and Therapeutic Interventions

Hemodynamic Changes	Metabolic Changes	Intraoperative Interventions
Decreased arterial blood pressure	Increased lactate	Decrease anesthetic depth
Decreased myocardial contractility	Increased total body oxygen consumption	Decrease vasodilators
Decreased systemic vascular resistance	Decreased mixed venous oxygen saturation	Increase fluids
Decreased central venous pressure	Increased prostaglandins	Increase vasoconstrictor drugs
Decreased preload	Increased activated complement	Reapply cross-clamp for severe hypotension
Decreased cardiac output	Increased myocardial depressant factors	Consider administration of mannitol and sodium bicarbonate
Increased pulmonary artery pressure	Decreased temperature	
	Metabolic acidosis	

Adapted from Norris EJ. Anesthesia for vascular surgery. In: Miller RD, et al, eds. *Miller's Anesthesia*. 7th ed. Philadelphia: Churchill Livingstone; 2010; Fillinger MF. Abdominal aortic aneurysms: evaluation and decision making. In: Cronenwett JL, Johnston W, eds. *Rutherford's Vascular Surgery*. 7th ed. Vol. 2. Philadelphia: Saunders; 2010.

Effects on Regional Circulation

Structures distal to the aortic clamp are underperfused during aortic cross-clamping. Renal insufficiency and renal failure have been reported to occur after abdominal aortic reconstruction. Suprarenal and juxtarenal cross-clamping may be associated with a higher incidence of altered renal dynamics; however, reductions in renal blood flow occur even when aortic cross-clamping occurs below the renal arteries. Infrarenal aortic cross-clamping is associated with a 40% decrease in renal blood flow.[55] Renal insufficiency more commonly occurs with suprarenal than infrarenal cross-clamping. Suprarenal clamp time longer than 30 minutes increases the risk of postoperative renal failure. These effects may lead to acute renal failure, which is fatal in 50% to 90% of patients who have undergone aneurysmectomies.[56] Neither renal dose dopamine nor mannitol has been definitively proven to preserve or improve renal function postoperatively. Preoperative evaluation of renal function is the best method to assess and anticipate which patients may develop postoperative renal dysfunction. A complete evaluation of renal function is required during the preoperative period.

Spinal cord damage is associated with aortic occlusion. Interruption of blood flow to the greater radicular artery (artery of Adamkiewicz) in the absence of collateral blood flow has been identified as a factor that causes paraplegia in patients having AAA repair. The incidence of neurologic complications increases as the aortic cross-clamp is positioned in a higher or more proximal area. Somatosensory evoked potential (SSEP) monitoring has been advocated as a method of identifying spinal cord ischemia. However, SSEP monitoring reflects dorsal (sensory) spinal cord function and does not provide information regarding the integrity of the anterior (motor) spinal cord.[6] Motor evoked potential (MEP) monitoring is capable of determining anterior cord function. This monitoring modality relies on intact neuromuscular functioning for analysis, which limits its use in abdominal aortic aneurysmectomies because neuromuscular blocking drugs are routinely used. Alternative methods for reliable evaluation of spinal cord ischemia are still under investigation.[57]

Ischemic colon injury is a well-documented complication associated with abdominal aortic resections. Ischemia of the colon is most often attributed to manipulation of the inferior mesenteric artery, which supplies the primary blood supply to the left colon. This vessel is often sacrificed during surgery, and blood flow to the descending and sigmoid colon depends on the presence and adequacy of the collateral vessels. Mucosal ischemia occurs in 10% of patients who undergo AAA repair. In less than 1% of these patients, infarction of the left colon necessitates surgical intervention.[56]

Aortic Cross-Clamp Release

While the aorta is occluded, metabolites that are liberated as a result of anaerobic metabolism, such as serum lactate, accumulate below the aortic cross-clamp and induce vasodilation and vasomotor paralysis. As the cross-clamp is released, SVR decreases, and blood is sequestered into previously dilated veins, which decreases venous return. Reactive hyperemia causes transient vasodilation secondary to the presence of tissue hypoxia, release of adenine nucleotides,[56] and liberation of an unnamed vasodepressor substance, which may act as a myocardial depressant and peripheral vasodilator. This combination of events results in decreased preload and afterload. The hemodynamic instability that may ensue after the release of an aortic cross-clamp is called *declamping shock syndrome*.[58] Evidence demonstrates that venous endothelin (ET)-1 may be partially responsible for the hemodynamic alterations that accompany declamping shock syndrome. Venous ET-1 has a positive inotropic effect on the heart and a vasoconstricting and vasodilating action on blood vessels. Table 25-4 summarizes the most commonly observed hemodynamic responses to aortic declamping and therapeutic interventions.

The magnitude of the response to unclamping the aorta may be manipulated. Although SVR and MAP decrease, intravascular volume may influence the direction and magnitude of change in cardiac output. Restoration of circulating blood volume is paramount in providing circulatory stability before release of the aortic clamp.[7,56,58-60] The site and duration of cross-clamp application, as well as the gradual release of the clamp, influence the magnitude of circulatory instability. For this reason, it is vital that communication between the anesthetist and the surgical team occurs. Partial release of the aortic cross-clamp over time often results in less severe hypotension. An algorithm depicting the systemic hemodynamic response to aortic unclamping is shown in Figure 25-2.

Surgical Approach

The standard approach for elective abdominal aortic reconstruction is the transperitoneal incision. The advantages of this route include exposure of infrarenal and iliac vessels, ability to inspect intraabdominal organs, and rapid closure.[61] Unfavorable consequences associated with this approach include increased fluid losses, prolonged ileus, postoperative incisional pain, and pulmonary complications.

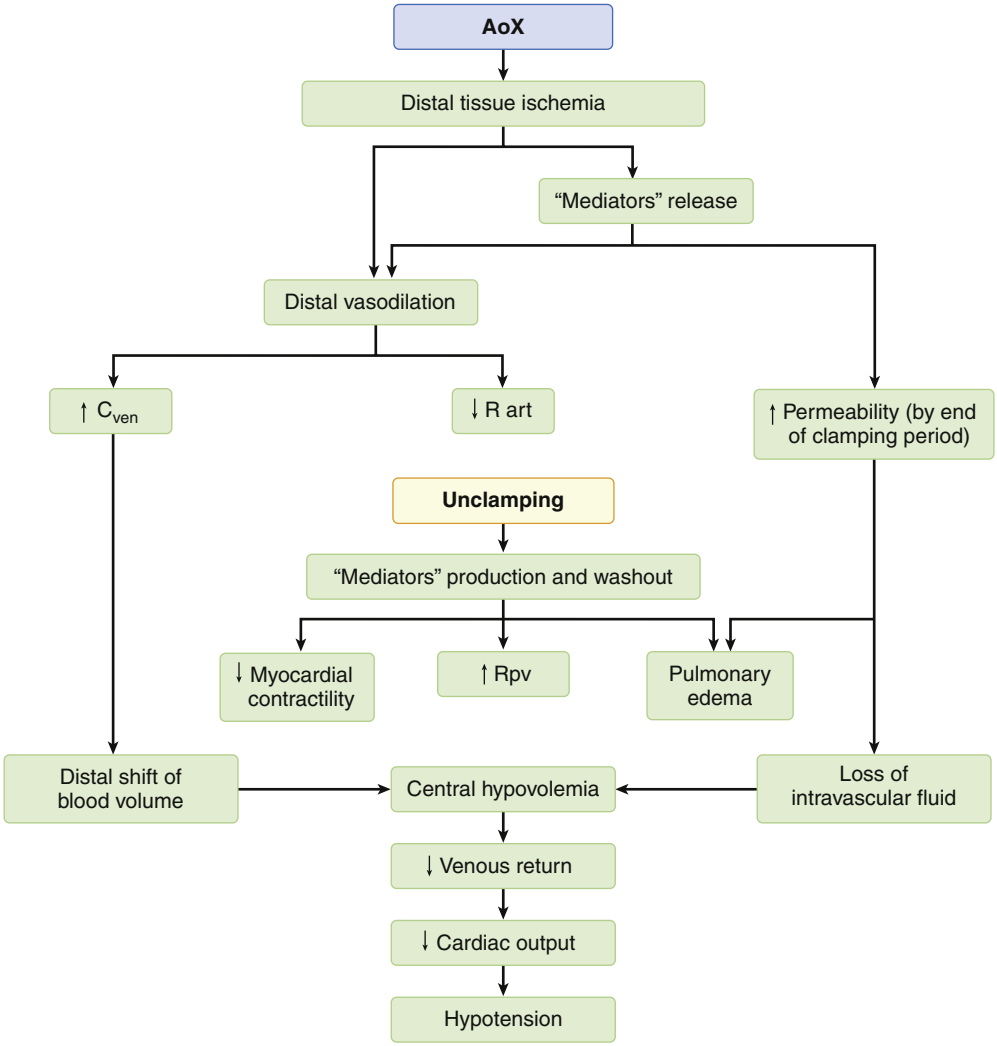

FIGURE **25-2** Systemic hemodynamic response to aortic unclamping. *AoX,* Aortic cross-clamping; C_{ven}, venous capacitance; *R art,* arterial resistance; *Rpv,* pulmonary vascular resistance. (From Gelman S. The pathophysiology of aortic cross-clamping and unclamping. *Anesthesiology.* 1995;82:1026-1060.)

The retroperitoneal approach is an alternative to the standard route. Its advantages include excellent exposure (especially for juxtarenal and suprarenal aneurysms and in obese patients), decreased fluid losses, less incisional pain, and fewer postoperative pulmonary and intestinal complications. After implantation with a synthetic graft, the aortic adventitia is closed (Figure 25-3). In addition, the retroperitoneal approach does not elicit mesenteric traction syndrome.[61] The reported limitations of this approach are unfamiliarity of surgeons with this technique, poor right distal renal artery exposure, and inability to inspect the integrity of the abdominal contents. Table 25-5 compares the standard and retroperitoneal surgical approaches.

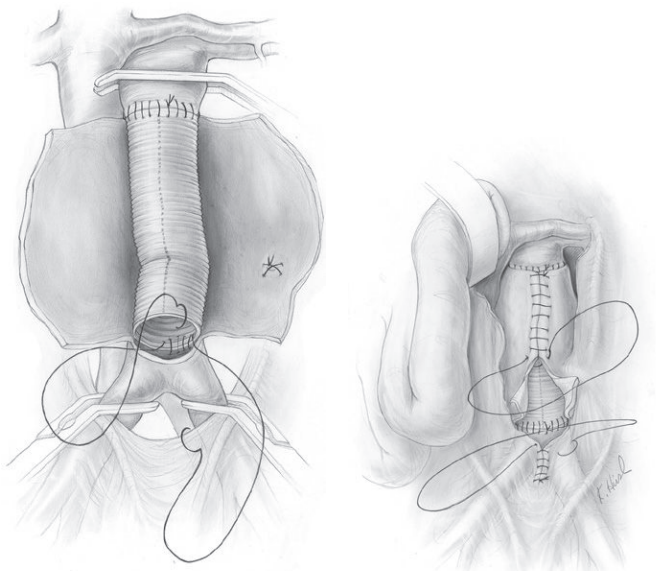

FIGURE **25-3** Dacron graft used to repair aneurysm. (From Zarins CK, Gewertz BL. *Atlas of Vascular Surgery.* 2nd ed. Philadelphia: Churchill Livingstone; 2009.)

Management of Fluid and Blood Loss

Extreme loss of extracellular fluid and blood should be expected with abdominal aortic aneurysmectomies. The degree of surgical and evaporative losses and third spacing will determine the magnitude of the patient's fluid volume deficit. Furthermore, the surgical approach, duration of the surgery, and the experience of the surgeon affects the total blood loss. Most blood loss occurs because of back bleeding from the lumbar and inferior mesenteric arteries after the vessels have been clamped and the aneurysm is opened.[56,62] The use of heparin also contributes to blood loss. Excessive bleeding, however, can occur at any point during

surgery, and blood replacement is commonly administered during abdominal aortic resections.

Owing to the heightened awareness of transfusion-related morbidity, the use of autologous blood via a cell saver system is a standard procedure. Presently, three options are available for administering autologous transfusions: preoperative deposit, intraoperative phlebotomy and hemodilution, and intraoperative blood salvage. Preoperative deposit is becoming more feasible because asymptomatic aneurysms are being detected with greater frequency. Ideally, patients donate their own blood to minimize the intraoperative use of homologous blood products and the subsequent risk of transfusion-related viruses. With anemia and decreased hemoglobin, oxygen transport is decreased, thus making the patient with systemic vascular disease at increased risk for myocardial infarction and stroke. Autotransfusion systems may be used for replacing intraoperative blood loss. In a study at the Mayo Clinic in which intraoperative autologous red-cell salvage was used, 75% less banked blood was transfused. In a prospective study of 100 patients who underwent elective abdominal aortic resections, 80% of the patients received only their own blood.[62]

TABLE 25-5 Comparison of Transperitoneal and Retroperitoneal Approaches

Transperitoneal	Retroperitoneal
Advantages	
Familiarity	Exposure for juxtarenal and suprarenal aneurysms
Access to infrarenal aorta and iliac vessels	Decreased fluid loss
Visualization of intraabdominal viscera	Improved postoperative respiratory function
Rapid opening and closure	Better-tolerated incisional pain avoids formation of intraabdominal adhesions
Versatility	Mesenteric traction syndrome, nonelicited
Disadvantages	
Increased fluid losses	Inaccessibility to distal right renal artery complications
Less postoperative ileus	
More frequent postoperative respiratory complications	
Increased postoperative incisional pain	

Modified from Sicard GA, et al. Retroperitoneal versus transperitoneal approach of repair of abdominal aortic aneurysms. *Surg Clin North Am*. 1989;69:795-806; Rubin BG, Sicard GA. Abdominal aortic aneurysms: open surgical treatment. In: Cronenwett JL, Johnston W, eds. *Rutherford's Vascular Surgery*. 7th ed. Vol. 2. Philadelphia: Saunders; 2010.

Presence of Concurrent Disease

Preoperative Management

The presence of underlying CAD in patients with vascular disease has been well documented. Reports suggest that CAD exists in more than 50% of patients who require abdominal aortic reconstruction and is the single most significant risk factor influencing long-term survivability.[7,8,63-65] Myocardial infarctions are responsible for 40% to 70% of all fatalities that occur after aneurysm reconstruction.[6,7,32,65] Preoperative cardiac evaluation begins with the identification of risk factors that may contribute to adverse cardiac events and subsequent death. When preoperative CAD exists, an increased incidence of postoperative adverse cardiac complications has been demonstrated.[66]

The end-point of any method of preoperative cardiac evaluation for aneurysmectomy is identification of functional cardiac limitations. Depending on the degree of cardiac dysfunction, preoperative optimization of cardiac function may range from simple pharmacologic manipulation to surgical intervention. The American College of Cardiology and the American Hospital Association guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery are generally followed when preparing patients for these procedures. Optimizing patient preoperative pathophysiologic states as described in Box 25-4 minimizes the overall rate of morbidity and mortality.

BOX 25-4

Optimization of Body Systems Prior to Abdominal Aortic Aneurysm Repair

Cardiac Evaluation
- Quantify risk factors and optimize cardiac function
- Institute appropriate β-blocker therapy
- Control hypertension
- Institute appropriate anticoagulation therapy

Pulmonary Evaluation
- Smoking cessation
- Radiologic tests and pulmonary function testing as indicated
- Pharmacologic therapy may include corticosteroids and bronchodilators

Renal Evaluation
- Assess electrolytes, creatinine, and glomerular filtration rate

Adrenal Evaluation
- Steroid supplementation for patients at risk for acute adrenal crises

Deep Vein Thrombosis Prophylaxis
- Pharmacologic prophylaxis
- Graduated compression stockings
- Intermittent pneumatic compression
- Venous foot pumps

Musculoskeletal Evaluation
- Assess neck range of motion prior to airway management
- Assess functional limitations for positioning to avoid postoperative paresthesia

Endocrine Evaluation
- Because of the high incidence of diabetes, short- and long-term glycemic control is mandatory

Miscellaneous Considerations
- Laboratory assessment—complete blood count (CBC), coagulation panel, electrolyte panel, blood urea nitrogen, creatinine, albumin, blood sugar, liver function tests, type and crossmatch 6 units packed red blood cells

Intraoperative Management

Anesthetic Selection

Several anesthetic techniques are available for abdominal aortic resections. Although each technique has its advantages and disadvantages, a superior technique has not been identified. Anesthetic selection should be based on the following objectives: providing optimum analgesia and amnesia, facilitating relaxation, maintaining hemodynamic stability, preserving renal blood flow, and minimizing morbidity and mortality.

General Anesthesia. Circulatory stability is desirable for patients undergoing AAA reconstruction, especially for those with CAD. All inhalation anesthetics may depress the myocardium and cause hemodynamic instability. Therefore, high concentrations of inhalation agents in patients with moderate to severe decreased ejection fraction should not be used. Because the degree of myocardial depression is dose dependent, it is acceptable to administer inhalation agents at lower inhaled concentrations. Beneficial effects attributed to inhalation agents include the ability to alter autonomic responses, reversibility, rapid emergence, potentially earlier extubation, and neurologic- and cardioprotection.[22] Cardiovascular stability provided by opioids has been well documented, and this feature is especially attractive for patients with ischemic heart disease and ventricular dysfunction. Provision of intense analgesia for the initial postoperative period after major abdominal vascular surgery (via the administration of neuraxial opioid) does not alter the combined incidence of major cardiovascular, respiratory, and renal complications.[67] Despite the absence of direct myocardial depression, the sympathetic nervous system inhibition that ensues may decrease systemic vascular resistance and heart rate. Therefore, especially in an individual with a moderate to severely decreased ejection fraction, narcotics should be carefully titrated to the patient's hemodynamic response.

Regional Anesthesia. The use of epidural anesthesia for abdominal aneurysmectomies is commonly considered. The benefits of epidural use include decreased preload and afterload, preserved myocardial oxygenation, reduced stress response, excellent muscle relaxation, decreased incidence of postoperative thromboembolism, increased graft flow to the lower extremities, decreased pulmonary complications, and improved postoperative analgesia. Potential disadvantages include anticoagulation and the possibility of epidural hematoma, and if local anesthesia is employed intraoperatively, severe hypotension during blood loss or declamping.[23,68]

Combination Techniques. Combining anesthetic techniques for major vascular surgery is more popular than using them alone; the advantages of each technique contribute to a smoother anesthetic. Epidural anesthesia combined with light general anesthesia provides the benefits of epidural anesthesia and the ability to provide amnesia and controlled ventilation.

In summary, all the aforementioned anesthetic techniques can be used safely and can demonstrate positive outcomes. Even more important than anesthetic selection is the clinical management of each patient. Observation, accurate interpretation, and immediate intervention during the anesthetic process reduce morbidity and mortality to a much larger extent than does selection of the superior anesthetic technique.

Fluid Management

Maintaining intravascular volume may be an extreme challenge during abdominal aortic resections. Controversy exists regarding whether the administration of crystalloids or colloids affects the overall incidence of morbidity and mortality. Crystalloids may be used for replacing basal and third-space losses at an approximate rate of 10 mL/kg/hr.[60] Blood losses initially can be replaced with crystalloids at a ratio of 3:1. The combination of crystalloid and colloid administration is also acceptable. Regardless of the choice of fluid, volume replacement must be dictated by physiologic parameters. Fluid replacement should be sufficient to maintain normal cardiac filling pressures, cardiac output, and urine output of at least 1 mL/kg/hr.[7] Patients with limited cardiac reserve can develop congestive heart failure if hypervolemia occurs. As mentioned previously, cell saver blood retrieval is commonly used, and two large-bore intravenous lines in addition to a central venous catheter is warranted.

Hemodynamic Alterations

Hemodynamic changes are likely to occur throughout the procedure. Adequate preoperative sedation should be given before placement of invasive monitoring equipment. Momentary fluctuations in heart rate and blood pressure should be anticipated during induction and intubation. Preoperative replacement of fluid deficits prevents exaggerated responses to vasodilating induction agents. For patients with adequate left ventricular function, hemodynamic stability can be preserved with a "slow" induction using opioids and β-adrenergic blocking agents. Etomidate has minimal myocardial depressant effects and may be most suitable for patients with limited cardiac reserve. The response to mesenteric traction (discussed previously) is also associated with momentary hemodynamic changes.

Renal Preservation

Mortality is four to five times greater in patients who develop acute kidney injury postoperatively. Mechanisms for preserving renal function during aortic cross-clamping include maintaining adequate hydration, avoiding severe and prolonged hypotension, and using renal protection agents such as mannitol, dopamine, furosemide, and N-acetylcysteine. With suprarenal clamp placement, the use of renal cold perfusion at 5° C of hypoosmolar crystalloid solution instilled into the kidney may be an effective renal protection strategy. The theorized mechanism is a decrease in renal metabolic rate resulting in a 7% reduction in oxygen consumption for each degree Celsius drop in temperature.[55] However, the best predictor of postoperative renal dysfunction is based on the patient's preoperative renal function.

Postoperative Considerations

Cardiac, respiratory, and renal failure are the most common complications observed postoperatively in patients recovering from abdominal aortic reconstruction. Cardiovascular function must be closely monitored in the intensive care unit (ICU) for at least 24 hours after surgery. Maintaining adequate blood pressure, intravascular fluid volume, and myocardial oxygenation is paramount during this period. Myocardial infarction frequently contributes to postoperative morbidity and mortality; serial cardiac enzyme analysis may be justified. Pharmacologic agents used in the treatment of hypertension must also be available.

Most patients require ventilatory assistance during the postoperative period. Vigilant monitoring of respiratory function is mandatory, especially when epidural catheters are used for postoperative analgesia. To address the significant number of serious postoperative complications, which are noted in Box 25-5, intensive and continuous assessment of the patient condition is vital. Patients are admitted to the ICU for high-acuity care.

Juxtarenal and Suprarenal Aortic Aneurysms

Although most AAAs occur below the level of the renal arteries, 2% extend proximally and involve the renal or visceral arteries.[60,70]

Juxtarenal aneurysms are located at the level of the renal arteries, but they spare the renal artery orifice. More proximal suprarenal aneurysms include at least one of the renal arteries and may involve visceral vessels. The effects of aortic cross-clamping for juxtarenal or suprarenal aneurysms are similar to those for infrarenal aortic occlusions; however, the magnitude of hemodynamic alterations increases as the aorta is clamped more proximally.

Renal failure, although possible during infrarenal aortic cross-clamping, occurs more often because of suprarenal aortic occlusion. Maintaining adequate intravascular volume and administering osmotic and loop diuretics may minimize renal ischemia and dysfunction.

Paraplegia is possible when the blood supply to the spinal cord is interrupted by aortic cross-clamping at or above the level of the diaphragm. Increasing the MAP or decreasing cerebrospinal fluid (CSF) pressure by placing a catheter in the subarachnoid space to drain CSF may be used as a means to increase spinal cord perfusion pressure.[7,69,70] Total body hypothermia and multimodal neurological monitoring including somatosensory and motor evoked potentials can be used to decrease the incidence of paraplegia. Neurologic deficits can become evident weeks after surgery. Box 25-6 summarizes the complications that may result from juxtarenal or suprarenal aortic occlusion.

Ruptured Abdominal Aortic Aneurysm

A high mortality rate of 80% to 90% is associated with a ruptured AAA, whereas postoperative mortality is estimated to range from 40% to 50%.[71] Endovascular aortic repair is being used to treat ruptured AAAs and may decrease the overall mortality. The most common symptoms of ruptured AAAs include a triad of severe abdominal discomfort or back pain, hypotension, and a pulsatile mass.[72] Other common symptoms include syncope, groin or flank pain, hematuria, and groin hernia. Risk factors associated with an increase in mortality in patients with a ruptured AAA are noted in Box 25-7.

Hypotension and a history of cardiac disease are two factors associated with the poorest prognosis.[37,39] Patients with these symptoms should be immediately transferred to the operating room for surgical exploration. When hypotension is absent, more time is available for a comprehensive preoperative assessment and testing.

Once the patient arrives in the operative suite, a brief preoperative evaluation, establishing venous access, and provisions for fluid and blood product administration can be completed. Hemodynamic stability must be the primary objective, and anesthetic induction and maintenance agents must be selected on a case-by-case basis.

Cardiovascular stability is the primary focus until blood loss from the proximal aorta is controlled by surgical intervention. Fluid resuscitation can begin with crystalloids; colloids and blood products can be administered as they become available. Intraoperative blood salvage provisions should be available. Coagulation studies and other laboratory tests including hemoglobin, hematocrit, and ionized calcium values should be obtained. Calcium is a positive inotrope, and it is necessary for normal myocardial excitation contractile coupling. Large amounts of citrate used as a preservative in banked blood bind calcium ions and result in relative hypocalcemia. Decreased myocardial contractility as evidenced by hypotension, increased left ventricular end-diastolic pressure, and increased central venous pressure can be caused by hypocalcemia. If hypocalcemia occurs, calcium chloride can be administered as an intravenous drip to reestablish normocalcemia. Dilutional thrombocytopenia is the most common reason for coagulopathy to develop after massive intravenous fluid and blood administration. The use of fresh frozen plasma has been shown to decrease the total transfusion requirements and the incidence of coagulopathies.[37] The ability to administer platelets also may be necessary.

After initial fluid resuscitation has been performed and hemodynamic stability has been ensured, direct arterial blood pressure monitoring must be instituted. A central venous or pulmonary artery catheter may be inserted. The hemodynamic effects of aortic cross-clamping and release are similar to those for elective surgery; however, responses may be extreme, especially if hypotension exists when the clamp is released. Because most patients

BOX 25-5

Postoperative Considerations for Patients Having Abdominal Aortic Aneurysm Repair

- Continue invasive hemodynamic monitoring
- Treat acute blood pressure extremes, arrhythmias (atrial fibrillation)
- Assess for postoperative myocardial infarction
- Ventilatory management with weaning and extubation
- Assess for abdominal compartment syndrome
- Evaluate hemoglobin, hematocrit, coagulation status, and adequacy of volume replacement
- Assess blood urea nitrogen/creatinine and urine output
- Institute deep vein thrombosis prophylaxis per protocol

BOX 25-6

Potential Complications of Juxtarenal or Suprarenal Aortic Occlusion

- Renal failure
- Hemorrhage
- Distal arterial occlusion
- Infarction
- Pulmonary or cardiac dysfunction
- Impotence
- Paraplegia
- Thrombosis
- Pseudoaneurysm formation
- Aortoenteric fistula

BOX 25-7

Risk Factors Associated with an Increased Risk of Mortality in Patients with Abdominal Aortic Aneurysm Rupture

- Increasing age
- Women
- Nonwhite race
- Insurance status (higher for those who self-pay or are on Medicaid in the United States)
- Comorbid conditions
- Congestive heart failure
- Renal failure
- Valvular heart disease

(From Cronenwett JL, Johnston W. *Rutherford's Vascular Surgery*. 7th ed. Vol. 2. Philadelphia: Saunders; 2010.)

require large amounts of fluid and blood replacement, postoperative mechanical ventilation is recommended.

THORACIC AORTIC ANEURYSMS

The mortality associated with elective thoracic aneurysms is 22%, and if rupture occurs, this figure increases to 54%.[73] Patients with aortic dissections have only a 3-month survival if they do not undergo surgical repair, because the incidence of rupture is high.[74] Aneurysms have been described for hundreds of years, but not until 1951 did the development of the arterial prosthesis lead to successful bypass options.[75] The refinement of synthetic grafts, surgical and perfusion techniques, and intraoperative management has contributed to improved surgical outcomes. Improved outcomes are associated with those medical centers that treat a high volume of patients with thoracic aortic aneurysms.

TABLE 25-6 Classification Schemes of Acute Aortic Dissection

Classification	Site of Origin and Extent of Aortic Involvement
DeBakey	
Type I	Originates in the ascending aorta and extends at least to the aortic arch and often to the descending aorta (and beyond)
Type II	Originates in the ascending aorta; confined to this segment
Type III	Originates in the descending aorta, usually just distal to the left subclavian artery, and extends distally
Stanford	
Type A	Dissections that involve the ascending aorta (with or without extension into the descending aorta)
Type B	Dissections that do not involve the ascending aorta

Braverman AC, et al. Diseases of the aorta. In: Bonow RO, et al, eds. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*. 9th ed. Vol. 2. Philadelphia, Saunders; 2012:1320.

Classification

Aneurysms of the thoracic aorta may be classified with respect to type, shape, and location. Typically, aneurysms involving all three layers of the arterial wall—tunica adventitia, tunica media, and tunica intima—are considered to be *true aneurysms*. In comparison, aneurysms that solely involve the adventitia are termed *false aneurysms*. The shape of the lesion also can serve as a means of characterizing aneurysms. Fusiform aneurysms have a spindle shape and result in dilation of the aorta. Saccular aneurysms are spherical dilations and are generally limited to only one segment of the vessel wall. Aortic dissection is the result of a spontaneous tear within the intima that permits the flow of blood through a false passage along the longitudinal axis of the aorta. There are two major classification schemes of aortic dissection based on the location. They are the DeBakey and Stanford classifications. (Table 25-6). Thoracoabdominal aortic aneurysms (TAAA) are classified using the Crawford classification as shown in (Figure 25-4).

Etiology

Atherosclerosis is the most common cause of aneurysmal pathology. Atherosclerotic lesions occur most often in the descending and distal thoracic aorta and are most often classified as fusiform. Less common causes include aortic dissection and various mechanical, inflammatory, and infectious processes. The various causes of aortic aneurysms are classified in Box 25-8.

Diagnosis

The symptomatology of thoracic aneurysms is often related to the site of the lesion and its compression on adjacent structures. Pain, stridor, and cough may result from compression of thoracic structures. Symptoms related to aortic insufficiency may be observed in aneurysms of the ascending aorta. An upper mediastinal mass

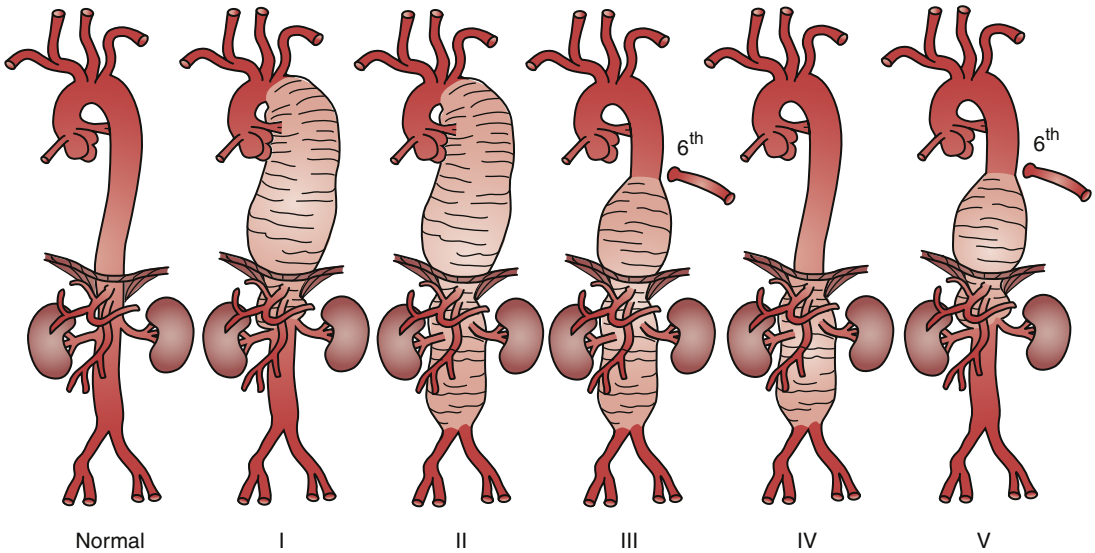

FIGURE 25-4 Crawford classification of thoracoabdominal aortic aneurysms. *Type I*, distal to the left subclavian artery to above the renal arteries. *Type II*, distal to the left subclavian artery to below the renal arteries. *Type III*, from the sixth intercostal space to the renal arteries. *Type IV*, from the 13th intercostal space to the iliac bifurcation (entire abdominal aorta). *Type V*, below the sixth intercostal space to just above the renal arteries. (From Cronenwett JL, Johnston KW. *Rutherford's Vascular Surgery*. 7th ed. Vol. 2. Philadelphia: Saunders; 2010:2021.)

may be an incidental finding on conventional chest radiography in an asymptomatic patient. Further investigation with noninvasive methods such as CT scan and MRI can describe the configuration and location of the aneurysm.

Treatment

As previously described, a high mortality rate is associated with rupture of thoracic aneurysms. Therefore early detection and surgical intervention make a significant contribution to long-term survival. Surgical approach and the method of aneurysm resection vary according to the location of the lesion within the thoracic aorta. Resection of the ascending aorta and graft replacement necessitate the use of cardiopulmonary bypass. The aortic valve also may require replacement. Surgical resection of lesions in the transverse arch compromises cerebral perfusion, although various bypass techniques combined with profound hypothermia and circulatory arrest have been used.[76] Aneurysms of the descending aorta may be resected by application of an aortic cross-clamp. However, perfusion to distal organs can be compromised during this procedure.

AORTIC DISSECTION

Aortic dissection is characterized by a spontaneous tear of the vessel wall intima, permitting the passage of blood along a false lumen. Although the cause of the dissection is unclear, lesions that were thought to be related to cystic necrotic processes may actually be caused by variations in wall integrity. Hypertension is the most common factor that contributes to the progression of the lesion. Manipulation of the ascending aorta during cardiac surgery may be associated with aortic dissection.[77] The symptoms of aortic dissection are the result of interruption of blood supply to vital organs. The most serious complication is aneurysm rupture. Diagnosis can be accomplished by the previously mentioned noninvasive techniques.

Treatment of dissecting aortic lesions depends on their location within the thoracic aorta (Figure 25-5). Type A lesions have the highest incidence of rupture and require immediate surgical intervention. Type B lesions may initially be managed medically, with the administration of arterial dilating and β-adrenergic blocking agents.

In summary, surgical resection of thoracic aortic lesions enhances long-term survival. Refinement of surgical techniques and improvement in perfusion technology have reduced the overall mortality rate. The surgical method used is dependent on the location of the aortic lesion. Anesthesia for aneurysms of the ascending and transverse aorta requires cardiopulmonary bypass.

DESCENDING THORACIC AND THORACOABDOMINAL ANEURYSMS

Preoperative Assessment

Patients who undergo major vascular surgery often are elderly and have varying degrees of concurrent disease. Most patients who develop a descending thoracic aortic aneurysm (DTAA) are asymptomatic. Operative surgical decisions are based on the size, extent, and rate of expansion of the aneurysm. For patients with degenerative aortic disease, surgical repair is advised for aneurysms 6 cm or larger. Independent risk factors for DTAA include pain,

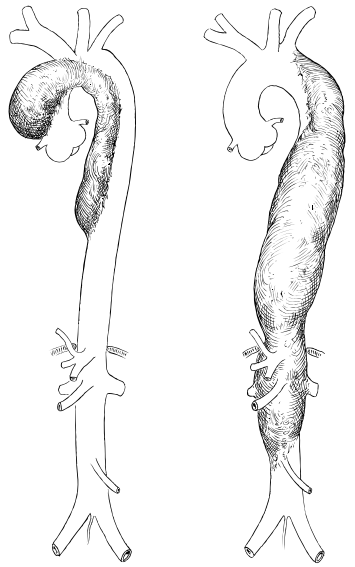

FIGURE **25-5** Types of aortic dissection. *Type A* involves the ascending aorta and may extend into the aortic arch. *Type B* starts at the proximal descending aorta and extends distally.

BOX **25-8**

Etiology of Thoracoabdominal Aortic Aneurysms

Degenerative
- Nonspecific (commonly considered arteriosclerotic), dysplastic (80%)

Mechanical (Hemodynamic)
- Dissections (15%-20%)
- Poststenotic
- Arteriovenous fistula
- Blunt or penetrating trauma

Connective Tissue
- Ehlers-Danlos syndrome
- Marfan syndrome

Inflammatory (Noninfectious)
- Takayasu's disease
- Behçet's syndrome
- Reiter's syndrome
- Kawasaki disease
- Microvascular disorder (e.g., polyarteritis)
- Ankylosing spondylitis
- Rheumatoid aortitis
- Periarterial inflammatory disease (e.g., pancreatitis)

Infectious
- Tuberculosis
- Bacterial
- Fungal
- Spirochetal (syphilis)

Anastomosis
- Postarteriotomy
- Postoperative pseudoaneurysm

increased age, chronic obstructive pulmonary disease (COPD), renal insufficiency, aneurysm size, and aneurysm expansion rate.[78]

The importance of a thorough preoperative evaluation cannot be overemphasized. Special attention should be directed toward cardiac, renal, and neurologic function. Although most fatalities related to thoracic aortic surgery are cardiac in origin, renal and neurologic dysfunction contribute to poor surgical outcomes.[79] Preoperative renal dysfunction is directly related to postoperative renal failure and is thought to be one of the strongest contributors to renal deterioration after surgery.[79,80] Neurologic function should be carefully assessed in the preoperative phase. Because paraplegia is one of the most devastating consequences of thoracic aortic surgery, any alteration in lower-extremity function should be noted. Hoarseness related to compression of the recurrent laryngeal nerve should be assessed and documented. The left recurrent laryngeal nerve is most susceptible to damage because of its close proximity to the aortic arch. Bilateral recurrent laryngeal nerve compression or damage can result in respiratory compromise.

Intraoperative Management

Monitoring

Intraoperative monitoring devices used for thoracoabdominal aneurysm resection are the same as for those used for abdominal aneurysmectomies. Direct intraarterial blood pressure and pulmonary artery pressure monitoring is standard during extracorporeal circulation. If the aneurysm involves the thoracic region or the distal aortic arch, right radial arterial line monitoring is preferred because left subclavian arterial blood flow may be compromised during surgery. Use of TEE is suggested for cardiac monitoring in patients with myocardial dysfunction. An indwelling urinary catheter is used for assessing renal function. To facilitate exposing the descending thoracic aorta, a double-lumen endotracheal tube is inserted to allow for one-lung ventilation. As a result, careful monitoring of oxygenation is mandatory. Routine use of pulse oximetry may be limited if the left subclavian artery is manipulated; therefore, the right hand, the ear, or the nasal passages should be used for monitoring oxygen saturation. Finally, a lumbar intrathecal catheter is inserted to access CSF. Somatosensory evoked potentials or MEPs are often used to monitor and detect neurologic dysfunction.

Spinal Cord Ischemia

Neurologic dysfunction is a serious complication of thoracic aortic reconstruction. Spinal cord injury is categorized into immediate and delayed paraplegia. The incidence of immediate paraplegia with DTAA ranges from 0% to 3% if surgery is performed with adjunctive procedures or clamp times are less than 10 minutes. However, for patients having TAAA, postoperative neurologic injuries vary from 2% to 20% depending on the type of aneurysm, surgical technique, cross-clamp time, and use of spinal cord protection interventions.[81-83] The exact incidence of delayed paraplegia is unknown, but it is believed that 25% of all spinal cord injuries are delayed. The primary preoperative risk factors for delayed paraplegia include type 2 aneurysms, emergency procedures, number of sacrificed segmental segments, and renal failure. The main postoperative factors include hemodynamic instability caused by atrial fibrillation, bleeding, multiorgan failure, and sepsis.[78]

Neurologic deficits are the result of hypoperfusion to the spinal cord during thoracic aortic reconstruction. The artery of Adamkiewicz, also known as the *greater radicular artery*, originates from an intercostal branch between T8 and L2 and provides the majority of blood flow to the anterior spinal artery. The anterior spinal artery perfuses the ventral aspect of the spinal cord, which is responsible for motor control.[80] Although attempts are made to reimplant the intercostal branches that contribute blood flow to the spinal cord, these efforts do not always decrease the incidence of paraplegia.[80,84]

Several techniques have been successful in an effort to decrease the incidence of neurologic dysfunction after thoracic aortic surgery. These include SSEP and MEP monitoring, CSF drainage, hypothermia, reattachment of intercostal arteries, and distal aortic perfusion. Systemic hypothermia and selective cooling of the spinal cord may lengthen ischemic time intervals; however, the clinical benefits of these hypothermia methods are unclear.[85,86] The use of various bypass mechanisms and distal shunts may minimize the length of aortic occlusion time.

Spinal cord perfusion pressure can be estimated by calculating the arterial blood pressure minus the CSF pressure. During aortic clamping, CSF pressure increases while arterial pressure decreases distal to the clamp. The spinal cord perfusion pressure can therefore be manipulated by altering arterial blood pressure and draining CSF through the intrathecal catheter.[86,87] Postoperative CSF drainage for as long as 72 hours is believed to decrease the incidence of late paraplegia. Avoiding prolonged periods of hypotension is vital to avoid spinal cord deficits.

Methods for detecting spinal cord ischemia were previously discussed. The intraoperative use of SSEPs and MEPs can provide early identification of neurologic dysfunction, but these monitoring modalities do not ensure spinal cord integrity. Factors that contribute to the development of neurologic deficit include level of aortic clamp application, ischemic time, embolization or thrombosis of a critical intercostal artery, failure to revascularize intercostal arteries, and urgency of surgical intervention.[86,87] Delayed paraplegia also may be the result of reperfusion injury, although the exact mechanism of injury has not been proven.[78,88-90]

Renal Dysfunction

The incidence of renal dysfunction after thoracoabdominal aortic resection is estimated to be between 10% and 20%.[78,91,92] The major causes of renal insufficiency is type and size of aneurysmal disease, ischemic time, and the degree of preoperative renal dysfunction. Kidney protection during TAAA repair includes distal aortic perfusion, cold crystalloid perfusion, and normothermic blood perfusion. Intraoperative hypotension has been identified as an independent predictor of postoperative renal dysfunction, and a MAP of 60 mmHg is warranted.[78] Maintenance of intravascular volume and stable circulatory status appears to be the most reliable method of minimizing renal dysfunction. Preoperatively, volume status should be corrected with non–glucose-containing crystalloid solutions. Intraoperative volume replacement should be guided by invasive monitoring.

In summary, neurologic and renal dysfunction are devastating consequences of thoracic and thoracoabdominal aortic resections. A complete preoperative evaluation, identification of risk, optimization of organ function, and use of the suggested methods to minimize the consequences of ischemia all contribute to optimal surgical outcomes. Additional complications of thoracoabdominal aortic reconstruction are listed in Box 25-9.

Anesthetic Management

The principles of perioperative management of thoracic or thoracoabdominal aneurysms are similar to those previously discussed for abdominal aortic aneurysmectomies. Anesthetic selection should be based on the presence of concomitant disease processes, with the objective of maintaining cardiovascular stability and minimizing morbidity and mortality. Intraoperative monitoring should

BOX **25-9**

Complications After Thoracoabdominal Aortic Aneurysm Repair

Early Complications
- Respiratory failure (most common complication)
- Hemorrhage
- Myocardial infarction
- Congestive heart failure
- Early paraplegia
- Embolization/thrombosis
- Distal artery occlusion
- Bowel ischemia
- Sexual dysfunction
- Infection
- Renal failure
- Cerebrovascular accident

Late Complications
- Delayed paraplegia
- Graft thrombosis
- Fistula formation
- False aneurysm
- Graft infection

focus on detection of myocardial, neurologic, and renal ischemia. The hemodynamic consequences of aortic cross-clamping should be attenuated by the use of pharmacologic adjuncts. Restoration of circulating blood volume minimizes the hemodynamic alterations caused by the release of the aortic clamp.

Unique to thoracic aortic surgery is the use of one-lung ventilation. To detect potential inadequacies in ventilation and oxygenation with this approach, the highest degree of vigilance must be used. Extreme blood loss should be anticipated. Venous access and blood product availability should be confirmed during the preoperative phase. Methods of minimizing the use of homologous blood products (e.g., perioperative blood salvage) are commonly used. Coagulopathy is a constant threat with the administration of blood products. Close monitoring of coagulation parameters and administration of fresh frozen plasma, platelets, or specific coagulation factors can minimize the incidence and severity of coagulopathies.

Postoperative Considerations

After surgery is completed, if a double-lumen endotracheal tube was used, it should be replaced with a standard endotracheal tube to provide a secure airway since postoperative ventilatory assistance is usually required. Airway anatomy may become edematous during surgery, causing difficulty with ventilation and reintubation. Under these circumstances, the double-lumen endotracheal tube may be left in place. Replacement can proceed in the postoperative period after the airway edema has dissipated.

Close observation of neurologic, circulatory, pulmonary, and renal status is warranted in the postoperative phase. Hemodynamic control is vital to maintaining perfusion to vital organs without creating excessive demands on the heart or the aortic graft. Careful monitoring of respiratory status aided by arterial blood gas analysis is important. Epidural analgesia using local anesthetics, narcotics, or both can be administered for pain relief.

ENDOVASCULAR AORTIC ANEURYSM REPAIR

In 1991, the first endovascular stent was performed to repair an infrarenal aortic aneurysm. The development of this technique has created a less invasive approach to aortic aneurysm repair. Studies suggest that severe cardiac and respiratory pathology make as many as 30% of patients with aortic aneurysms poor surgical candidates.[93] Endovascular aortic aneurysm repair (EVAR) was initially developed to help patients with severe coexisting disease who were not considered to be surgical candidates. The popularity of EVAR has increased as the success of the procedure has improved. It is estimated that 90% of all AAA repairs will be accomplished using the EVAR technique within the next 10 years.[94] Schermerhorn et al.[95] suggested that the patient population who may benefit most from EVAR are high-risk patients.

The largest source of data is EUROSTAR (*EURO*pean collaborators on Stent/graft *T*echniques for aortic *A*neurysm *R*epair), a registry that provides insight on the potential advantages and shortcomings of EVAR. The registry contains data from patients who were treated in over 135 European medical centers. The patient population included patients with infrarenal aortic aneurysms. Results suggest that the larger the diameter of the AAA (greater than 5.5 cm), the greater the 30-day mortality rate. Cumulatively, the 30-day operative mortality was 2.5%. There were no statistically significant differences in the AAA-related death rate at 1 year comparing EVAR with open surgical treatment (98.2% versus 98.6%).[96] Five years after EVAR, the patient survival rate was 76%. There was a low incidence of intraoperative AAA rupture occurring in only 32 patients. The cumulative rate of rupture was estimated to be approximately 1% per year. *Endoleak* (defined as persistent blood flow and pressure ["endotension"] between the endovascular graft and the aortic aneurysm), graft migration, and kinking were determined to be significant risk factors for late open conversion. The overall risk of late failure was approximately 3% per year.[95,97]

The results comparing EVAR with traditional open AAA repair for abdominal aortic aneurysm assessing short-term success are promising. Two large randomized controlled studies have compared the effects of EVAR to open AAA repair—the Endovascular Aneurysm Repair Trial 1 (EVAR 1) and the Dutch Randomized Endovascular Aneurysm Management (DREAM). A national audit of the effectiveness of EVAR by the Canadian Institute for Health Information database provides information that supports the endovascular technique.

The purpose of the EVAR 1 trial was to determine which surgical intervention—endovascular or open aneurysmectomy—was superior in patients who were deemed fit for open AAA repair. Patients were randomized to either the EVAR group (n = 543) or the open AAA repair group (n = 539). The 30-day mortality rate was 1.7% in the EVAR group versus 4.7% in the open AAA repair group. Secondary interventions were more common in the EVAR group (9.8% versus 5.8%).[98] However, there was no significant difference between the groups with respect to 2-year survival.

The DREAM study was a multicenter randomized controlled trial comparing short-term results (30 days) of conventional and endovascular repair of AAAs in 345 patients whose aneurysms were a minimum of 5 cm in diameter. For the open repair group, the operative mortality was 4.6%, and severe complications occurred in 9.8% of patients. In the EVAR group, operative mortality was 1.2%, and severe complications occurred in 4.7% of patients. The conclusion was that EVAR was superior to open repair in this patient population. However, it was also determined that 2-year moderate and severe adverse patient events were nearly identical for both groups. The researchers stated that long-term follow-up studies were needed to determine whether the advantages of EVAR would be sustained.[99]

The Canadian National Audit included results from 1996 patients with nonruptured AAAs. A comparison of EVAR

BOX 25-10

Coexisting Diseases for Patients Who Are Prone to Aortic Aneurysm Development

- Hypertension
- Male gender
- Heart disease
- Smoking
- Chronic obstructive pulmonary disease
- Diabetes mellitus
- Renal impairment
- Carotid artery disease
- Peripheral arterial disease
- Family history

Data from Townsend CM, et al. *Sabiston Textbook of Surgery*. 19th ed. Philadelphia: Saunders; 2012.

(n = 178) versus open aneurysm repair (n = 1818) was completed. The findings indicated that in-hospital mortality was 0.6% and mean length of stay (LOS) was 5.8 days for EVAR, whereas in-hospital mortality for open procedures was 4.6% and LOS 11.9 days. The conclusion was that EVAR was presently being underused in Canada.[100]

Endovascular aortic aneurysm repair is also being used to treat patients with thoracic aortic aneurysms. The mortality rate for EVAR for elective descending thoracic aneurysm repairs range from 3.5% to 12.5%, as compared with an open approach, where mortality is approximately 10%.[101] Reports also show that EVAR has a low incidence (0% to 6%) of spinal cord ischemia and paraplegia.[102] Potential explanations for the absence of spinal cord complications are (1) no thoracic aortic cross-clamping and (2) no prolonged periods of extreme hypotension. Perioperative hypotension (MAP less than 70 mmHg) was a significant predictor of spinal cord ischemia in patients having EVAR for thoracic aneurysm repair.[103] Endograft therapy has also been used with success and may eventually become the treatment of choice for thoracic aneurysm repair in patients older than 75 years of age.[104]

The mortality rate for patients with a ruptured AAA who are alive when diagnosed in emergency departments is 40% to 70%.[105] Since the 1950s, mortality from ruptured AAAs has only decreased 3.5% per decade.[106] The EVAR approach has been used successfully to repair ruptured AAAs, but the number of patients treated and the quality of randomized controlled data on this subject are limited. However, 30-day mortality rates were 10% to 45%.[107] Medical centers that consider EVAR for ruptured AAA repair must have emergent CT imaging capabilities, trained endovascular teams, adequate endovascular supplies available, and a specially arranged surgical suite.

From the data presented above, it would appear that EVAR has specific advantages as compared with the traditional open AAA repair.[108,109] However, there are questions about the procedure that have yet to be answered, most importantly, Is there a long-term survival benefit to EVAR? As described in EVAR 1, reinterventions due to endoleak were required in three times as many patients who had EVAR. Of these, 7% of endoleaks were discovered within 1 month of implantation and another 13% occurred within 4 years postoperatively.[110] Problems with graft migration and durability are the primary determinants of this complication. However, the majority of this data was collected while physicians were implanting first- and second-generation endografts. Newer-generation endografts and superior surgical techniques may decrease this adverse effect in the future.

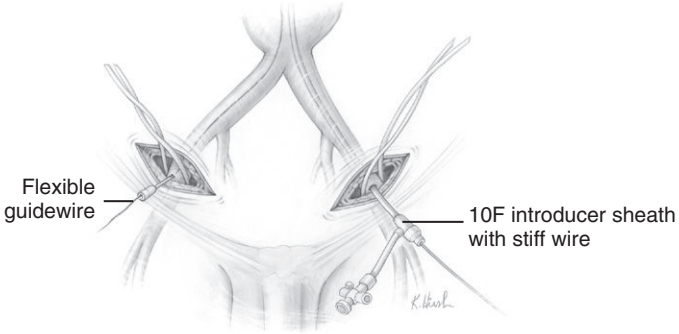

FIGURE **25-6** Femoral cutdown and insertion of introducer sheath. (From Zarins CK, Gewertz BL. *Atlas of Vascular Surgery*. 2nd ed. Philadelphia: Churchill Livingstone; 2009.)

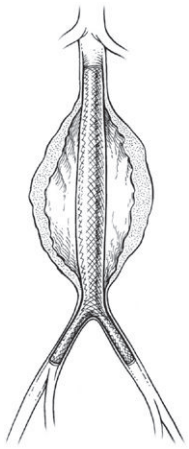

FIGURE **25-7** Aortic endovascular graft.

A comparison of outcomes evaluating EVAR and open AAA repair in nearly 23,000 patients was reported.[108] The conclusion was that EVAR was associated with lower short-term morbidity and mortality. Three-year survival rates were similar for both surgical approaches. Further randomized controlled studies must be done on the long-term effects of EVAR. Patients who are prone to aortic aneurysm development commonly have coexisting diseases as listed in Box 25-10.

Procedure

Endovascular aortic aneurysm repair involves deployment of an endovascular stent graft within the aortic lumen. The graft restricts blood flow to the portion of the aorta where the aneurysm exists. This procedure can be performed for patients who have descending thoracic aortic aneurysms or AAAs. Cannulation of both femoral arteries is performed. As seen in Figure 25-6, a guide wire is threaded through the iliac artery to the level of the aneurysm. Next, a sheath is inserted over the guide wire and positioned at the aneurysm location through use of fluoroscopy. The proximal end of the sheath must extend beyond the aneurysm. Once the sheath is deployed, radial force or fixation mechanisms such as hooks or barbs on the stent become embedded into the aortic wall to prevent stent migration (Figure 25-7).

The procedure frequently takes place in an interventional radiology suite. Compared with the conventional surgical method, advantages of the endovascular approach include no aortic cross-clamping, improved hemodynamic stability, decreased incidence of embolic events, decreased blood loss, reduced stress response,

BOX **25-11**

Potential Complications Associated with EVAR

Graft and Deployment Complications
- Failed deployment
- Microembolization
- Migration/occlusion of major branch arteries (i.e., renal, mesenteric)
- Aortic perforation/aneurysm rupture
- Aortic dissection
- Hematoma formation
- Endoleak
- Stenosis/kink/thrombosis
- Graft tear
- Damage to access arteries (femoral → iliac)
- Infection

Radiologic Implications
- Radiation exposure
- Allergy to contrast dye
- Renal insufficiency from contrast dye

Systemic Complications
- Neurologic (CVA, paraplegia)
- Cardiac morbidity/mortality
- Pulmonary insufficiency
- Renal insufficiency
- Postimplant syndrome

EVAR, Endovascular aneurysm repair; *CVA*, cardiovascular accident.

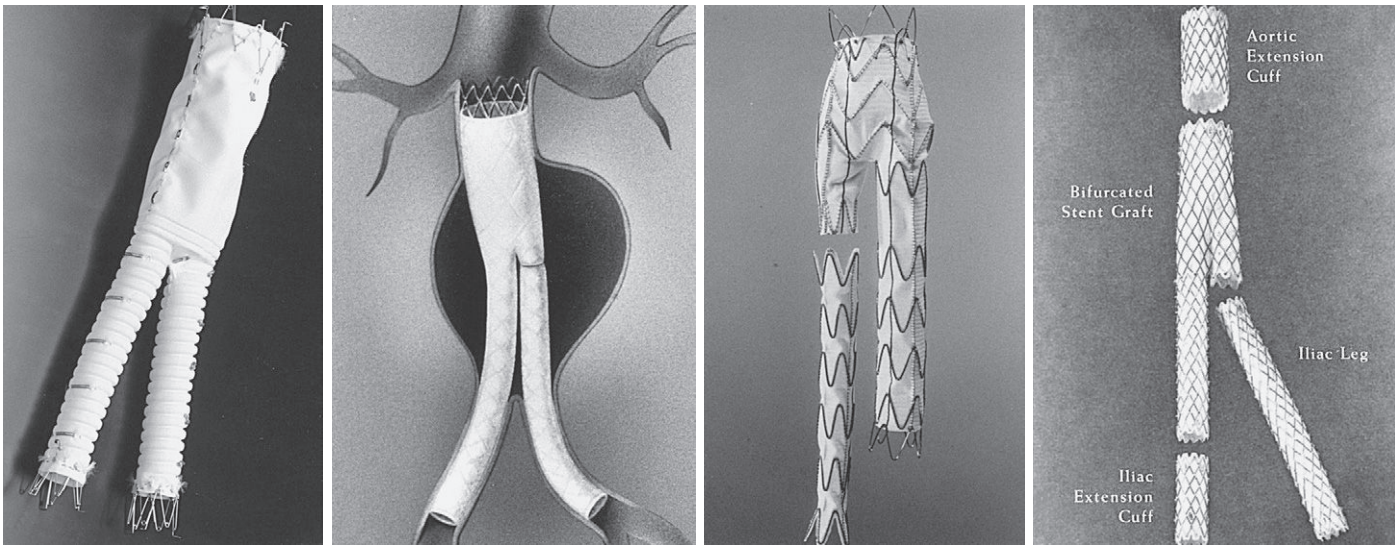

FIGURE **25-8** Various types of endovascular grafts. (Adapted from Cronenwett JL, Johnston KW. *Rutherford's Vascular Surgery*. 7th ed. Vol. 2. Philadelphia: Saunders; 2010:1363-1383.)

decreased incidence of renal dysfunction, and decreased postoperative discomfort.[111,112] Systemic anticoagulation with heparin, 50 to 100 units/kg, is administered prior to catheter manipulation.[113] Antibiotic coverage is recommended at the beginning of surgery. The anesthetic techniques that can be used for EVAR include general anesthesia, neuraxial blockade, or local anesthesia with sedation.[114] There is presently a lack of data suggesting that one anesthetic technique is clearly superior for patients having EVAR. Local anesthesia with sedation, as compared with general anesthesia, is associated with a decrease in nonfatal cardiac morbidity, respiratory complications, renal failure, and overall mortality.[115,116] There is also a decreased pulmonary morbidity as compared with general anesthesia, and local anesthesia with sedation is associated with a shorter length of stay as compared with general and neuraxial anesthesia.[117] The goals for intraoperative management for EVAR include maintaining hemodynamic stability, providing analgesia and anxiolysis, and being prepared to rapidly convert to an open procedure.

With infrarenal or suprarenal EVAR, creatinine clearance values decreased by 10% in the first year.[118] However, proximal endovascular graft migration can occur, causing renal artery occlusion and postoperative renal failure.[119] Further randomized controlled trials are needed to substantiate these results. Plasma catecholamine concentrations and mediators of the systemic immune response were decreased in patients who underwent the endovascular approach as compared with patients who underwent conventional repair.[120,121] Pearson et al.[122] determined that plasma cortisol release was lower in patients having EVAR than in those having traditional open AAA repair. The EVAR group also developed significantly less sepsis and systemic immune response syndrome. Complications that can arise from the EVAR approach include endograft thrombosis, migration or rupture, graft infection, iliac artery rupture, and lower extremity ischemia.[123] Fatal cerebral embolism resulting in sudden respiratory arrest has occurred during EVAR.[124] Box 25-11 lists potential complications associated with EVAR.

Endovascular graft design and durability continue to improve. Graft devices are either unibody (comes in one piece) or modular (comes in multiple pieces). The endograft fabric is either woven polyester (Dacron) or polytetrafluoroethylene. There is no significant difference in biologic response when comparing these two materials.[125] The graft skeleton is constructed of stainless steel, Nitinol, or Elgiloy (Figure 25-8). Nitinol stents are popular because they exhibit minimal shortening after deployment. There is considerable interest and research involving drug-eluting stents.

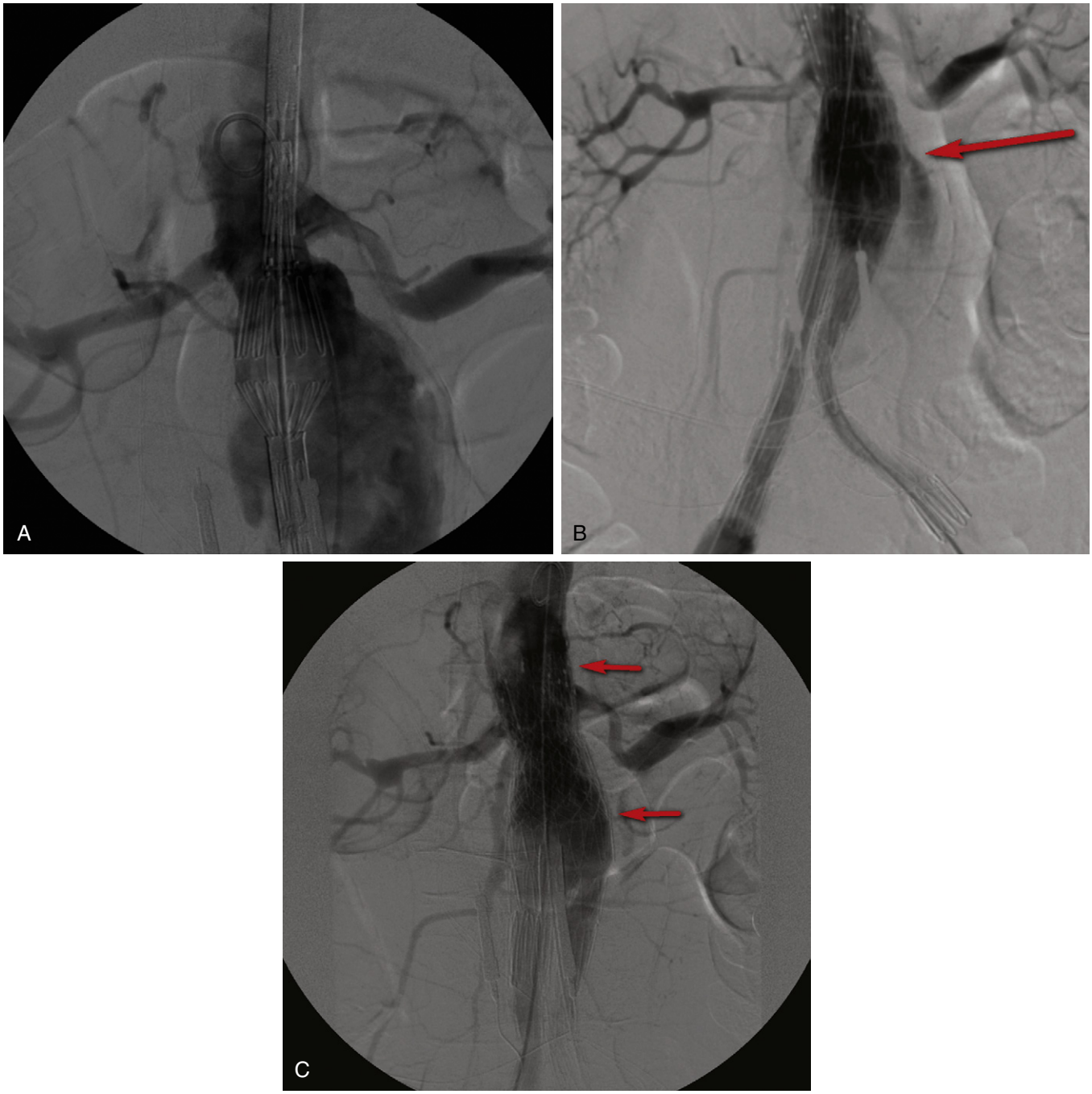

FIGURE **25-9** **A,** Short aortic neck immediately before endovascular aneurysm repair. **B,** Type IA endoleak (arrow) after initial endograft placement and molding balloon angioplasty. **C,** Resolution of the type IA endoleak after placement of a 5010 "giant" Palmaz stent (*arrows* show proximal and distal extent). (From Cronenwett JL, Johnston W. *Rutherford's Vascular Surgery*. 7th ed. Vol. 2. Philadelphia: Saunders; 2010:1306.)

Drugs being tested are immunomodulators, antiinflammatories, and antiproliferative drugs. Researchers have shown in initial clinical trials that restenosis rates are improved with the newer-generation endovascular stents.[126,127]

Endoleak, shown in Figure 25-9 and noted earlier as persistent blood flow and pressure (endotension) between the endovascular graft and the aortic aneurysm, is a serious complication of this procedure. Types of endoleaks are listed in Table 25-7. Endoleak diagnosed by postoperative CT scan has been reported to occur in 15% to 52% of patients.[128] Most are type II, and 70% spontaneously close within the first month after implantation.[129] Type II endoleaks are caused by collateral retrograde perfusion. Type I and type III endoleaks are caused by device-related problems. The most frequent interventions used to correct these complications include implantation of a second endograft or open repair.[130] Long-term results of endovascular aortic aneurysm repair have demonstrated that this procedure yields good results, but the overall durability of conventional surgical techniques is superior.[131]

Postoperative follow-up care for patients who have undergone EVAR is vital because long-term outcomes have not been quantitatively established. Physical examination and contrast-enhanced CT scan are recommended at 1, 6, 12, and 18 months

TABLE 25-7 Classification of Types of Endoleak

Classification	Description	Treatment
Type I endoleak	Attachment site leaks Perigraft channel	Proximal or distal graft extension Secondary endograft Open repair
Type II endoleak	Branch leaks (i.e., lumbar artery, renal artery, internal iliac artery, inferior mesenteric artery)	Conservative Laparoscopic clip application Embolization
Type III endoleak	Graft defect (fabric tear, modular disconnection)	Secondary endograft Open repair
Type IV endoleak	Graft wall fabric porosity/suture holes	Observation Open repair
Endotension	Systemic pressure in aneurysm sac despite no evidence of endoleaks	Secondary endograft Open repair

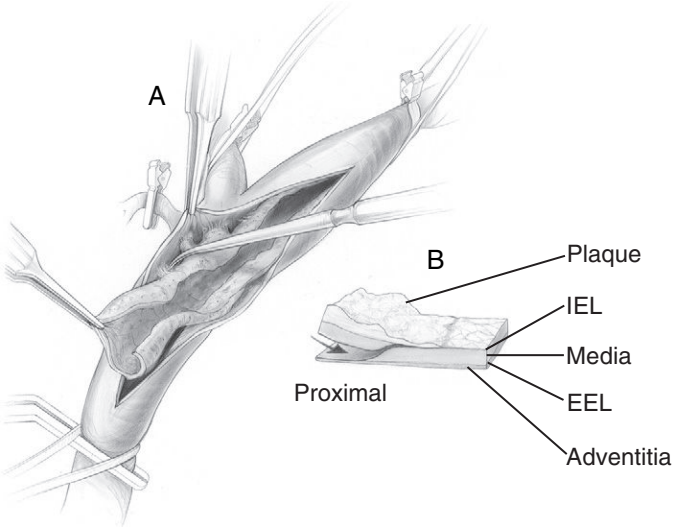

FIGURE **25-10** **A,** Removal of plaque from carotid artery, **B,** Formulation of plaque on the intima of carotid artery. *IEL,* Internal elastic lamina; *EEL,* external elastic lamina (From Zarins CK, Gewertz BL. *Atlas of Vascular Surgery*. 2nd ed. Philadelphia: Churchill Livingstone; 2009.)

postoperatively and then annually.[132] Additionally, abdominal x-rays should be obtained on a regular basis. Lifelong radiographic evaluation and surveillance is necessary to monitor aneurysm size, graft migration, and endoleak. Intensive follow-up care, the need for reinterventions, and the cost of the endograft make EVAR more expensive than open repair.[133]

In the future, minimally invasive aortic aneurysm surgery will continue to be used. Improvements in surgical techniques, imaging, and graft devices will allow a greater number of patients to experience the technical and physiologic advantages of EVAR.

CEREBROVASCULAR INSUFFICIENCY AND CAROTID ENDARTERECTOMY

Carotid endarterectomy is the second most common vascular operation performed in the United States per year (the first being coronary revascularization). Cerebrovascular accidents, or strokes, are the third leading cause of death in the United States.[134,135] Most strokes are caused by cerebral ischemia as compared with intracranial hemorrhage. In carotid atherosclerotic disease, subintimal fatty plaques can increase in size over time and incrementally occlude the vascular lumen, which results in decreased cerebral blood flow. The plaque may rupture and release fibrin, calcium, cholesterol, and inflammatory cells. This phenomenon can lead to abrupt occlusion of the lumen from thrombosis due to platelet activation, or an embolus may form and decrease cerebral blood flow distal to the carotid artery. In each scenario, an abrupt decrease in cerebral blood flow (CBF) leads to transient ischemic attacks (TIAs) or strokes. Note the anatomic details of the plaque removal as seen in Figure 25-10.

More than half of all strokes are preceded by a TIA. The Framingham study reported that the risk of a stroke was 30% 2 years after a TIA and approximately 55% 12 years after a TIA had occurred.[136] It is this increased risk of stroke associated with TIA that provides the rationale for use of carotid endarterectomy (CEA), the surgical procedure in which the internal carotid artery is incised and the plaque within the carotid arterial lumen removed to improve cerebral blood flow.

Indications

Since 1954, specific indications for and expected outcomes of CEA have been the subject of heated debate. Ischemic stroke accounts for approximately 80% of first-time strokes and is primarily caused by atheromatous plaques. The initial indication for CEA was symptomatic stenosis but not complete occlusive carotid disease. This presentation occurs in most patients who undergo carotid surgery. Some centers have extended the indications to include evolved ("nondense"), nonhemorrhagic strokes and asymptomatic severe stenosis or lesser stenosis associated with contralateral occlusive disease.[134] The North American Symptomatic CEA Trial concluded that CEA for patients with recent hemispheric TIAs and high-grade stenosis (70% to 99%) had a risk reduction of 65% for the development of an ipsilateral stroke 2 years after surgery, compared with patients whose condition was medically managed.[137] The Executive Committee for Asymptomatic Carotid Atherosclerosis Study demonstrated that asymptomatic patients with carotid artery stenosis of at least 60% who underwent CEA had a 53% lower 5-year risk of ipsilateral stroke than patients who were treated medically.[138] Other widely reported large-scale studies including the Asymptomatic Carotid Atherosclerosis Study (ACAS) and the European Asymptomatic Carotid Surgery Trial (EACST) demonstrated a benefit of CEA with medical therapy (aspirin and atherosclerotic risk factor reduction) over medical therapy alone for patients with carotid stenosis in the 60% to 99% range.[139,140] These trials showed a similar absolute and relative reduction in risk for stroke of approximately 5% and 50%, respectively, at 5 years for CEA over medical therapy. Symptomatic patients are at a higher risk than asymptomatic patients for perioperative adverse events. The benefit, however, of CEA in patients with recent ipsilateral carotid territory symptoms and moderate to severe carotid stenosis is much greater than the benefit of CEA in asymptomatic patients.[141]

Morbidity and Mortality

The surgical outcomes reported for CEA vary because of differences in patient populations and varying degrees of surgical expertise. Other variables that cannot be stratified in studies but may affect patient outcomes include the state of collateral flow through the circle of Willis, the presence of concurrent atherosclerotic disease in the cerebral vasculature, the size and morphology of the

BOX 25-12

Factors Contributing to Morbidity During Carotid Endarterectomy

- History of stroke
- Operative timing
- Hyperglycemia
- Multiple comorbidities
- Age
- Contralateral carotid artery disease
- Progressing stroke
- Ulcerative lesion
- Intraoperative hemodynamic instability
- Surgery with shunt
- Surgery without shunt

BOX 25-13

Preoperative Risk Factors for Patients Scheduled for CEA

- Neurologic (cerebrovascular accident)
- Coronary artery disease
- Hypertension
- Diabetes
- Renal disease
- Thromboembolism

CEA, Carotid endarterectomy.

offending plaque, the specific presenting symptoms, and the presence of concurrent cardiovascular disease.[142] Carotid artery stenosis is the primary cause of approximately 20% of all strokes.[143] The recommended acceptable perioperative stroke rates should be limited to less than 3% in asymptomatic patients, less than 5% in symptomatic patients, and 10% or less in patients with recurrent disease or existing strokes.[144] Morbidity rates related to CEA have been reported to be at or below these recommended limits.[144,145] The perioperative myocardial infarction rate of 2% to 5% illustrates the global nature of atherosclerotic disease and represents the greatest contribution to overall morbidity. The perioperative mortality rate for CEA is approximately 0.5% to 2.5%,[146,147] and the long-term postoperative stroke incidence ranges from 1% to 3% per year.[134,148,149]

Patient Selection

The risks associated with having surgery and the possibility of a stroke must be measured against the risks associated with not having surgery and undergoing medical management. Those patients who have the greatest benefit from CEA are those with stenosis of greater than 70%, and it is of lesser benefit in symptomatic patients with 50% to 69% stenosis.[143] Surgical intervention was most beneficial in men who are older than 75 years of age and within 2 weeks of their last ischemic event.[150] As mentioned previously, the Framingham study identified the incidence of stroke after TIAs and demonstrated an increased risk of stroke in untreated disease. Preoperative neurologic dysfunction was found to be the most significant factor for predicting postoperative stroke incidence (4%). Several conditions that can increase the risk of perioperative complications include severe preoperative hypertension, CEA performed in preparation for coronary artery bypass, angina, internal carotid artery stenosis near the carotid siphon, age older than 75 years, and diabetes mellitis.[151,152] Box 25-12 identifies various factors that contribute to morbidity during CEA.

Diagnosis

The neurologic symptoms associated with cerebral vascular dysfunction such as TIAs and strokes are most often related to decreased CBF. Asymptomatic carotid bruits may be a sign of the possibility of carotid artery disease. Amaurosis fugax, or monocular blindness, occurs in 25% of patients with high-grade carotid artery stenosis. This syndrome is believed to be caused by microthrombi that travel into the internal carotid artery and decrease the blood supply of the optic nerve via the ophthalmic artery. Standard diagnostic imaging techniques used to assess the extent of carotid disease include duplex ultrasonography, digital subtraction angiography, computed tomographic angiography, and magnetic resonance angiography (MRA).[153]

Preoperative Assessment

The presence of concurrent CAD and carotid stenosis is well documented. Although stroke is a devastating consequence of CEA, myocardial infarction contributes more often to poor surgical outcomes than stroke. Although coronary angiography may not be justified in all patients undergoing CEA, a systematic approach for identifying CAD and its subsequent risks should be performed before elective surgery.

Patients with no significant medical history, normal physical examination, and normal electrocardiography should proceed directly to surgery; these patients have low surgical risks. When abnormal cardiac information is obtained, further evaluation should be performed. The presence of significant comorbidities will determine the extent to which further preoperative testing is appropriate. Box 25-13 lists some preoperative risk factors in patients having carotid endarterectomy.

Intraoperative Considerations

Cerebral Physiology

Cerebral blood flow (CBF) can remain relatively constant at different cerebral perfusion pressures as a result of cerebrovascular autoregulation. Cerebral perfusion pressure can be expressed as the difference between MAP and intracranial pressure. During CEA, intracranial pressure is usually not elevated; therefore, MAP plays the predominant role in determining cerebral perfusion pressure. When MAP is maintained between 60 and 160 mmHg, CBF remains constant. However, the adverse effects of chronic systemic hypertension shift the patient's cerebral autoregulatory curve to the right, and therefore a higher than normal MAP may be required to ensure adequate cerebral perfusion. Cerebral blood flow is also influenced by arterial carbon dioxide and oxygen concentrations, as well as by inhalation agents.

Normal CBF is approximately 50 mL/100 g/min. Neuronal function is generally maintained at levels greater than 25 mL/100 g/min. Levels less than this critical value jeopardize cellular function. Decreased perfusion and ischemia can be reflected in changes in consciousness. Cellular death occurs at levels less than 6 mL/100 g/min, as evidenced by flattening seen on an electroencephalogram.

Carotid occlusive disease jeopardizes the cerebral perfusion pressure in the ipsilateral artery. Ischemia leads to the disruption of autoregulation and compensatory vasodilation, and thus blood flow becomes pressure dependent. During CEA the anesthetic goals must focus on improvement and protection of CBF and diligent monitoring of brain function.

Cerebral Monitoring

In addition to standard monitoring, direct intraarterial pressure must be continuously assessed via arterial line placement. During CEA, blood pressure fluctuation commonly occurs. Owing to the high incidence of CAD and neurovascular disease in this patient population, prompt tight control of blood pressure is imperative. Pulmonary artery catheterization is not warranted in most individuals unless the presence of concurrent cardiac disease justifies its use. Carbon dioxide has a potent effect on cerebrovascular tone. Hypocapnia decreases and hypercapnia increases CBF; therefore, maintenance of normocapnia is paramount.

During repair, the carotid artery cross-clamp is applied. Various monitoring techniques have been proposed for assessing the adequacy of CBF during this maneuver. A summary of select cerebral monitoring techniques is presented in Box 25-14. Each of these monitoring modalities has limitations; the most sensitive and specific measure of adequate cerebral blood flow is responsiveness in an awake patient. Electroencephalographic monitoring constitutes the gold standard in identifying neurologic deficits related to carotid artery cross-clamping.[143,154] Electroencephalogram has demonstrated reliability in monitoring cortical electrical function.[155] Loss of β-wave activity, loss of amplitude, and emergence of slow-wave activity all are indicative of neurologic dysfunction.

Carotid stump pressure has been used as a means of assessing collateral flow.[156] After the carotid cross-clamp is placed, distal pressure in the operative internal carotid artery is measured. A carotid stump pressure of less than 40 to 50 mmHg reflects neurologic hypoperfusion and is a criterion for shunt placement. However, there is no correlation between stump pressures and electroencephalographic changes.[145] In a study by Harada et al.,[157] a carotid stump pressure of less than 50 mmHg had a positive predictive value for only 36% of patients who exhibited ischemic electrocardiogram (EEG) changes during carotid artery cross-clamping.

SSEP monitoring can be used to identify inadequate CBF during cross-clamping; however, false-positive results can occur. In addition, SSEPs are a measure of the integrity of the dorsal or sensory portion of the spinal cord. Therefore, a motor deficit can occur despite a normal SSEP waveform. Additionally, there are no values for decreased amplitude and increased latency that correlate with cerebral ischemia.

Transcranial Doppler velocity monitoring has been used as a method of detecting adverse cerebral events during CEA. McDowell et al.[158] used intraoperative transcranial Doppler monitoring during 238 carotid endarterectomies. They concluded that this method was more reliable than EEG for assessing interior integrity of the cerebral hemispheres.

The use of cerebral oximetry using near-infrared spectroscopy to determine the adequacy of cerebral perfusion has been shown to be useful.[159] The reduction of critical oxygen saturation during clamping of greater than 25% or 20% if persistent for longer than 4 minutes indicates the potential for deficits. As compared with stump pressure monitoring, cerebral oximetry more accurately predicts cerebral oxygenation.[160] Box 25-14 outlines the cerebral monitoring modalities during general anesthesia for CEA.

Cerebral Protection

The major objective during carotid artery revascularization is to maintain CBF and decrease cerebral ischemia. Prevention of cerebral ischemia can be accomplished in one of two ways: by increasing collateral flow (placement of intraluminal shunt) or by decreasing cerebral metabolic requirements (pharmacologic adjunct). Multiple interventions are available for cerebral protection including avoiding hyperglycemia, hemodilution, maintenance of normocarbia, and tight control of arterial blood pressure.

BOX 25-14

Cerebral Monitoring Modalities During General Anesthesia for CEA

- *Electroencephalogram (EEG)*: Assesses cortical electrical function
- *Somatosensory evoked potential (SSEP)*: Assesses sensory evoked potentials
- *Carotid stump pressure (CSP)*: Assesses perfusion pressure in the operative carotid artery
- *Transcranial Doppler (TCD)*: Assesses blood flow velocity in the middle cerebral artery
- *Cerebral oximetry*: Assesses cerebral regional oxygen saturation (near-infrared spectroscopy)

CEA, Carotid endarterectomy.

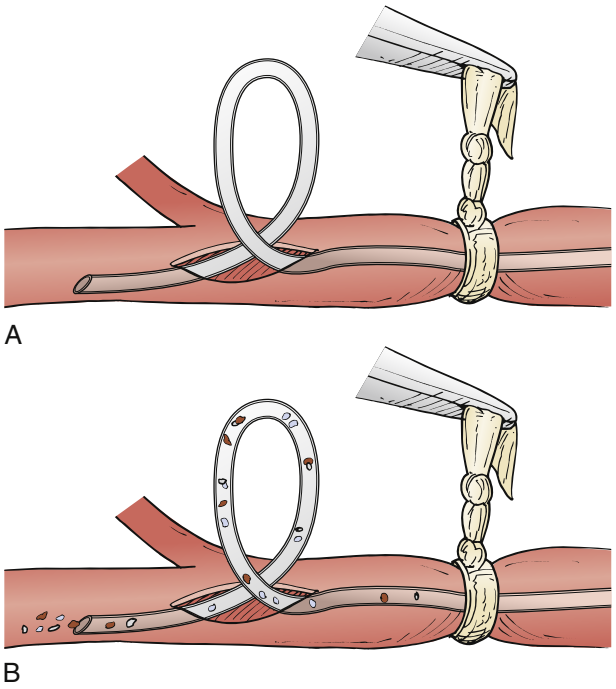

FIGURE **25-11** Pitfalls of carotid shunt placement. **A,** Potential traumatic injury to the distal internal carotid artery intima. **B,** Potential for embolization of atherosclerotic debris or air. (From Cronenwett JL, Johnston W. *Rutherford's Vascular Surgery*. 7th ed. Vol. 2. Philadelphia: Saunders; 2010:1452.)

Anesthetics, except for etomidate, have cerebral protective properties and may be used to minimize the degree of cerebral ischemia. Shunt placement is commonly used during carotid artery clamping to augment cerebral blood flow during intimal plaque dissection. The application of a shunt imposes the risk of embolic complications and intimal dissections. Potential complications of carotid shunt placement are depicted in Figure 25-11.

Cerebral ischemic events are most often the result of embolic complications. The need for shunt placement is based on information obtained using intraoperative monitoring techniques that determine CBF.

Cerebral Metabolism

Propofol decreases cerebral metabolism to 40% below normal values.[86] Dexmedetomidine also decreases cerebral oxygen consumption and cerebral blood flow in animal models.[161]

During transient focal ischemia, propofol decreases the cerebral metabolic rate of oxygen consumption, which results in cerebral protection. The disadvantages of administering propofol during CEA surgery include myocardial depression and delayed emergence. The surgeon may request that one of these cerebral depressants be administered before the carotid artery is cross-clamped. The inhalation agents also decrease cerebral metabolic rate of O_2 consumption ($CMRO_2$) in a dose-dependent fashion. Nitrous oxide should be avoided.[143,150]

Blood Pressure Control

The presence of hypertension in patients with cerebrovascular disease is well known. Therefore, one of the most challenging aspects of care associated with anesthesia for CEA is blood pressure control. Patients with cerebral insufficiency are vulnerable to perioperative blood pressure instability. Hypotension occurs in 10% to 50% of patients who undergo CEA and is believed to be the result of carotid sinus baroreceptor stimulation. Conversely, 10% to 66% of patients experience hypertension, which is attributed to surgical manipulation of the carotid sinus.[162] Preoperative blood pressure control, volume status, and depth of anesthesia also can contribute to intraoperative hemodynamic instability.

Blood pressure control must begin in the preoperative phase. All patients should continue taking their antihypertensive medications until the time of surgery. Patients with systolic blood pressure greater than 180 mmHg may be at increased risk of stroke and death.[150] Additional pharmacologic adjuncts may be required in the preoperative period, especially during the insertion of intravenous and intraarterial catheters, to reduce increases in heart rate and blood pressure. The induction of anesthesia, the initial incision, the dissection, the manipulation of the carotid sinus, and the emergence from anesthesia are all events that precipitate blood pressure fluctuations. The use of pharmacologic adjuncts, such as short-acting β-adrenergic blockers, may stabilize blood pressure during induction and emergence. Continuous intravenous use of nitroglycerin or sodium nitroprusside should be available to treat hypertension. Patients with chronic hypertension are predisposed to dramatic decreases in blood pressure after the induction of general anesthesia. This condition must be treated promptly and can be successfully managed by providing intravenous fluids or administering appropriate vasopressors. Hypotension and bradycardia, which result from carotid sinus baroreceptor manipulation, may be inhibited by stopping surgical stimulation and infiltrating with a local anesthetic.

Anesthetic Management

The anesthetic objectives for vascular surgery are similar to those for any type of elective procedure: to provide analgesia and amnesia, to facilitate surgical intervention, and to minimize operative morbidity and mortality. Goals that are specific to CEA include maintaining cerebral and myocardial perfusion and oxygenation, minimizing the stress response, and facilitating a smooth and rapid emergence. However, it may be difficult to maintain the integrity of one system without adversely affecting the other. For example, raising the arterial blood pressure to augment cerebral perfusion can increase myocardial oxygen demand, which may lead to ischemia. In addition, significantly decreasing blood pressure can lead to cerebral hypoperfusion. Therefore, the anesthetic goal is to optimize perfusion to the brain, minimize myocardial workload, ensure cardiovascular stability, and allow for rapid emergence. An understanding of the physiology of the cerebrovascular system is important for optimal anesthetic management. Figure 25-12 illustrates the anatomy of structures in this region. This knowledge enables the selection of appropriate monitoring and anesthetic techniques that will protect and improve cerebral and myocardial perfusion.

Anesthetic Selection

The long-standing question has been whether there is an advantage of regional versus general anesthesia for CEA. The General Anesthetic versus Local Anesthetic for Carotid Surgery Trial (GALA) as well as a Cochrane meta-analysis indicate no significant difference between the two anesthetic techniques.[163,164] The anesthetic selection is based on the surgeon's preference, the patient's condition, and the preoperative evaluation. Advantages of a regional technique are that an awake patient can respond to commands and allow for continuous assessment of neurologic function. Other potential benefits include high patient satisfaction, lower shunting requirements, less cost, and minimizing potential postoperative cognitive effects associated with general anesthesia.[165-167] Disadvantages include patient agitation and inability to remain still, minimal airway control, seizure or stroke during clamping, and limited ability to give cerebral neuroprotectants. Advantages of general anesthesia include the ability to perform more extensive and difficult surgical procedures, better airway control, ability to administer cerebral protectants, and improved blood pressure control.[143,150]

Regional Anesthesia. A regional anesthetic technique during CEA requires anesthesia of cervical nerves II to IV (CN II-CN IV). [143] This can be accomplished by local infiltration, superficial and deep cervical plexus block, or a combination of these techniques. Superficial cervical blocks do not anesthetize the angle of the mandible, which is innervated by the trigeminal nerve. Local infiltration may be required. As noted above, the greatest advantage of regional anesthesia is the ability to directly assess neurologic function in an awake individual. Assessing level of consciousness is the most effective method of assessing the adequacy of cerebral blood flow and detecting cerebral ischemia. In fact, assessment of consciousness in the awake patient may be more sensitive than conventional EEG in detecting cerebral ischemia. Corson et al.[168] reviewed data from 399 patients who underwent CEA in which general and regional techniques were used. The authors concluded that perioperative strokes occurred less often when a regional anesthetic was provided, especially in high-risk patients. McCarthy et al.[169] compared middle cerebral artery blood flow velocity using transcranial Doppler monitoring in patients undergoing CEA with either local or general anesthesia. It was determined that preservation of cerebral circulation was better maintained in patients who received local anesthesia. In addition, 67% of the general anesthesia group and 15% of the local anesthesia group received shunts.[170-174] However, despite these seemingly physiologic advantages, no differences occurred in outcomes between the local and general anesthesia groups. The use of regional anesthesia has been associated with shorter operative times, less frequent cardiopulmonary complications, and shorter postoperative hospitalization.

One limiting factor for use of a regional technique is patient acceptance. Because the individual is awake, preoperative education is essential, and their cooperation during surgery is vital. Anxiety, fear, and apprehension can initiate sympathetic stimulation, and as a result, extreme hemodynamic responses can occur. Deep sedation, which can be required in an apprehensive patient, may confound the neurologic assessment, negating the advantages of a regional technique. Additionally, hypercarbia can result from hypoventilation, and dysphoria is more likely to occur. Furthermore, converting to a general anesthetic technique once surgery

has begun can be problematic. If adequate cerebral perfusion is compromised, symptoms include dizziness, contralateral weakness, decreased mentation, and loss of consciousness. In the event this scenario occurs, immediate shunt placement is warranted. Emergent airway management may be necessary.

General Anesthesia. Although the use of regional anesthesia has numerous advantages, general anesthesia is also used during CEA. Perhaps the greatest benefit of this technique is that it counters the most cited disadvantage of regional anesthesia: lack of patient cooperation. General anesthesia promotes a motionless field during surgery. In addition, inhalation agents may provide hemodynamic stability and may have beneficial effects on cerebral circulation.[175] By decreasing cerebral and cardiac metabolism, the inhalation agents provide a degree of protection against ischemia, an effect called *anesthetic preconditioning*.[176-178]

Comparison of inhaled agents with narcotic-based techniques yields no scientific evidence to suggest that patient outcome is improved. In studies of inhalation agents, the critical regional CBF (the blood level below which electroencephalographic signs of ischemia occur) during isoflurane anesthesia was less than when other volatile anesthetics were used.[175,179] The effects of sufentanil on cerebral hemodynamics were similar to those of isoflurane.[180] Remifentanil can be used; its rapid metabolism improves neurologic recovery. The inhalation agents may alter the monitoring methods used for detecting cerebral ischemia, such as EEG and SSEP monitoring. In these cases, general anesthetic techniques may require modification, and direct communication is required between the anesthesia and surgical teams. The use of nitrous oxide during CEA can potentially increase the incidence of a clinically significant pneumocephalus. During shunt placement and carotid artery cross-clamp release, microbubbles can be entrained into carotid artery blood flow. When carotid artery cross-clamping without shunting occurs, MAP values should approximate or be slightly above preoperative levels to help ensure adequate cerebral perfusion through the contralateral carotid artery. Most clinicians avoid nitrous oxide. If nitrous oxide is used, it should be discontinued before removal of the carotid artery cross-clamp.[143,150,181]

In summary, there is no scientific consensus supporting the idea that one anesthetic technique is superior in terms of decreasing perioperative morbidity and mortality. An anesthetic plan that allows for a rapid assessment of neurologic function at the completion of surgery should be selected.

Postoperative Considerations

Perhaps the most common problem experienced in the postoperative period is hypertension. Although the specific cause remains unclear, postoperative hypertension is likely related to changes in sensitivity of the carotid baroreceptor reflex. A systolic blood pressure greater than 180 mmHg is associated with an increased incidence of TIA, stroke, or myocardial infarction.[151] Those patients with systolic blood pressures of 145 mmHg or less had fewer postoperative complications.[137] Postoperative hypotension

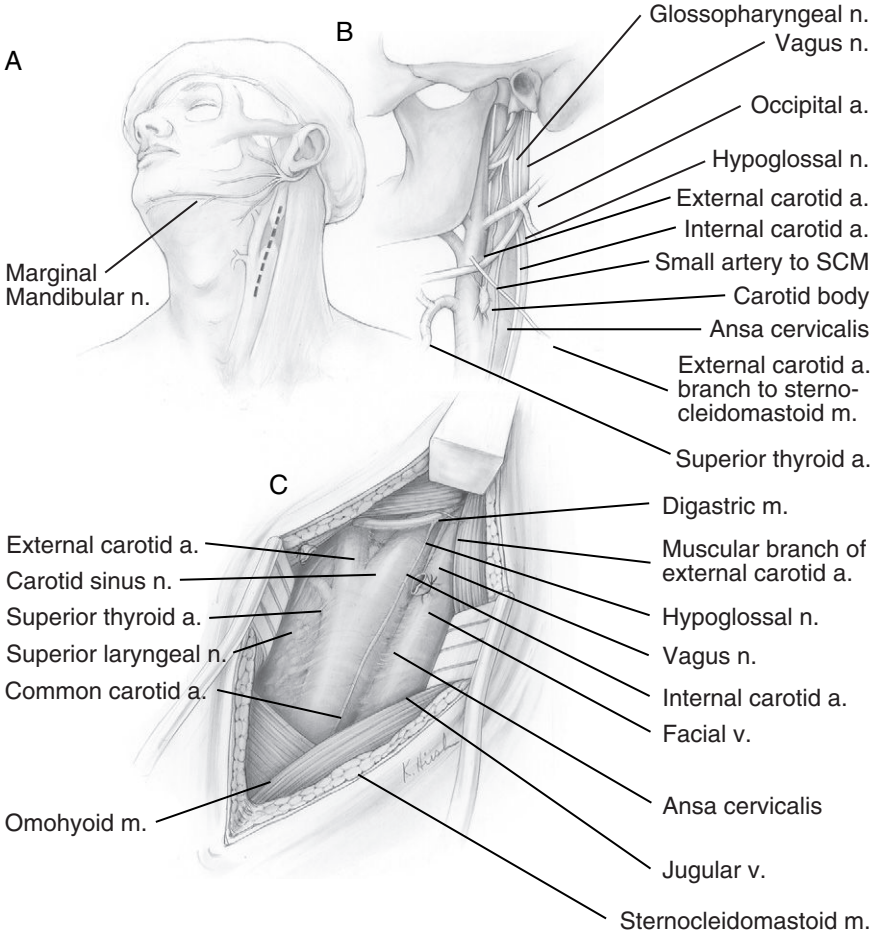

FIGURE **25-12** Carotid endarterectomy. **A,** Incision site. **B** and **C,** Anatomic structures presented at the carotid surgical site. *a.*, Artery; *n.*, nerve; v., vein. (From Zarins CK, Gewertz BL. *Atlas of Vascular Surgery*. 2nd ed. Philadelphia: Churchill Livingstone; 2009.)

is less common but can be a more difficult problem to treat because raising the blood pressure too much may unduly stress the heart. Reestablishing normal pressures can be accomplished by careful titration of fluids and vasopressors.

Although an uncommon complication, carotid artery hemorrhage can occur in the postoperative phase. Hemorrhage is a devastating event that requires immediate surgical intervention. Initial manifestations of hemorrhage may be those of upper airway obstruction, which may make reintubation difficult because of tracheal deviation. Emergency management of a patient with airway compromise as a result of carotid artery hemorrhage includes immediate evacuation of the hematoma. In addition, recurrent laryngeal nerve damage can occur and routinely manifests as inspiratory stridor. Respiratory insufficiency can be problematic for patients who have preexisting respiratory conditions. Tension pneumothorax also can occur, because the apices of the lungs extend above the clavicles toward the surgical site. Treatment includes immediate needle decompression. Damage to the carotid body can lead to a blunting of the chemoreceptor reflex, and therefore supplemental oxygen should be administered. Lastly, cerebral hyperperfusion syndrome (CHS) may result from increased blood flow to the brain as a result of loss of cerebral vascular autoregulation. The mechanism of action causing this phenomenon is unclear; however, it is hypothesized that CHS may occur as a result of chronic cerebral ischemia or altered cerebrovascular autoregulation. Signs and symptoms of CHS include severe headache, visual disturbances, altered level of consciousness, and seizures. CHS may occur more often in patients who have had a contralateral CEA within the last 3 months and undergo a second CEA for occlusion on the ipsilateral side.[182]

The incidence of postoperative stroke after CEA was discussed previously. Unfortunately, even after successful revascularization of the carotid artery, occlusion can recur at a rate of 3% per year.[147] Although symptoms are present in only a small percentage of patients (3% to 5%), the incidence of recurrent carotid stenosis may be much larger than that reported, because asymptomatic cases may be overlooked.[182] As many as 25% of patients experience a neurocognitive decline up to 1 month after surgery. Patients who are predisposed are those with diabetes and advanced age.[183] The exact mechanism responsible for the cognitive dysfunction has not been scientifically identified. Postoperative complications of CEA are listed in Box 25-15.

Owing to the anatomic location and potential neurologic complications after CEA, postemergence neurologic integrity should be assessed. In addition to neurocognitive functioning, clinical assessment of cranial nerve function should be performed (Table 25-8). The anatomic location of the cranial nerves in relation to the internal, external, and common carotid arteries are shown in Figure 25-13.

BOX 25-15

Postoperative Complications After Carotid Endarterectomy

- Hemodynamic instability
- Myocardial ischemia/infarction
- Cerebral hyperperfusion syndrome
- Stroke
- Respiratory insufficiency
- Recurrent/superior laryngeal nerve damage
- Hematoma
- Carotid body dysfunction
- Tension pneumothorax
- Acute carotid occlusion

CAROTID ARTERY ANGIOPLASTY STENTING

A less invasive surgical approach for treatment of carotid artery stenosis is carotid artery angioplasty and stenting (CAS). Controversy exists regarding the degree of success that this procedure affords as an alternative to CEA. The best application of CAS is still evolving and many studies comparing stenting with endarterectomy are ongoing. Best practices regarding proper patient selection, technique, and timing of the procedure are still being explored.[184,185] The current incidence of stroke after CEA is approximately 2%. A recent meta-analysis noted that when comparing CEA with CAS, endarterectomy decreases the risk of stroke at 30 days, increases the risk of myocardial infarction, and does not have an effect on the risk of death.[186]

The first large multicenter randomized controlled trial comparing CEA versus CAS was the Stenting and Angioplasty with Protection Patients at High Risk for Endarterectomy (SAPPHIRE) trial.[187] The rate of event-free survival at 1 year postsurgery was

TABLE 25-8 Cranial Nerve Assessment for the Patient Scheduled for CEA

Cranial Nerve	Function	Abnormal Response
VII (facial)	Muscles of facial expression, saliva secretion	Inability to smile symmetrically; contralateral asymmetry indicates possible stroke; nerve injury on ipsilateral side
IX (glossopharyngeal)	Swallowing, pharyngeal muscle	Difficulty swallowing with ipsilateral Horner syndrome (i.e., ptosis, miosis, exophthalmos, reduced sweating)
X (vagus) → superior and recurrent laryngeal nerves	Laryngeal muscles movement	Minor swallowing problems, fatigued voice; vocal cord paralysis, hoarseness, inadequate gag reflex; may test speech by having the patient say "EEE"
XI spinal accessory	Shoulder muscles	Ipsilateral weakness in neck and shoulder with shrugging
XII (hypoglossal)*	Muscles of tongue	Stick tongue out, move tongue side to side; tongue droops to ipsilateral side, difficulty with speech and chewing, high-pitched sounds, hoarseness

From Heffine MS. Care of the vascular surgical patient. In: Odom-Forren J, ed. *Drain's Perianesthesia Nursing: A Critical Care Approach.* 6th ed. St Louis: Saunders; 2013.
*This nerve traverses the internal carotid artery.
CEA, Carotid endarterectomy.

88% for the CAS group and 79.9% for the CEA group. The stroke rate after 1 year was lower in the CAS group as compared with the CEA group—6.2% versus 7.9%, respectively. As for cardiac morbidity, the rate of myocardial infarction for CAS versus CEA was 1.9% versus 6.6% 30 days postoperatively. Overall cardiac morbidity was 3% for CAS and 6.2% for CEA. The conclusion from the SAPPHIRE trial was that CAS does not yield inferior outcomes as compared with CEA. However, the study methodology was criticized and some experts questioned whether the results could be replicated.[188] A new 3-year follow-up report of the SAPPHIRE study group indicates that in patients with severe carotid artery stenosis and increased surgical risk, no significant difference could be shown in long-term outcomes between patients who underwent carotid artery stenting with an emboli-protection device and those who underwent endarterectomy.[189]

The Endarterectomy versus Angioplasty with Symptomatic Severe Carotid Stenosis (EVA3S) trial was designed to compare the outcomes from CAS versus CEA. The study population included patients with symptomatic carotid stenosis of at least 60%. The study was stopped early because of a high incidence of stroke and death—9.6% compared with 3.9% for CEA 30 days after surgery. The conclusion was that CEA was superior to CAS for this patient population when considering risk of stroke at 30 days and 6 months postoperatively.[190] Another randomized controlled trial, the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE), yielded high but similar statistics for 30-day stroke death rates—CAS 6.8% and CEA 6.3%.[191]

The goal of the Carotid Revascularization versus Stenting Trial (CREST), a randomized controlled trial, was to determine which procedure, CAS or CEA, was more effective in preventing stroke and death. Inclusion criteria were patients who were symptomatic and had greater than 50% carotid artery stenosis and those who were asymptomatic with greater than 60% carotid artery stenosis. The preliminary results from the first stage of the trial, which included 1000 patients, are encouraging and compare favorably with CEA. Death or stroke rates from any cause during the 30 days after procedure include 3% for asymptomatic patients younger than 80 years of age and 2.7% for symptomatic patients younger than 80 years of age.[192] Initial indications were that CAS was associated with an increased incidence of stroke in octogenarians. However, it has now been determined the incidence of stroke resulting from CAS is similar to the CEA results for all age groups.[193] The health-related quality of life comparing CAS with CEA using CREST data show that CAS is superior to CEA for as long as 1 year postoperatively.[194]

Case selection guidelines for carotid artery stenting are listed in Table 25-9.

Prior to the CAS procedure, patients receive an aortic arch, carotid, and cerebral angiogram or a high-resolution MRI. This allows evaluation of the individual anatomy and angiopathology of the aortic arch, brachiocephalic artery (for right carotid artery stent), or left common carotid artery. Determination of the type of sheaths, stents, and cerebral embolic protection device can then be planned. Femoral artery access is obtained, then a sheath is threaded through the aortic arch and into the operative carotid artery. The guide wire/embolic protection device is advanced through the sheath and positioned across the stenotic region. An embolic protection device sequesters emboli during angioplasty and stenting to avoid distal occlusion in cerebral arteries (Figure 25-14). A distal embolic protection lowers the risk of intraoperative and postoperative adverse events.[195] This filter-like device is inserted distal to the area of stenosis prior to the angioplasty and stent deployment to catch microthrombi and pieces of plaque that could lodge within the brain. Angioplasty with a 5-mm balloon dilates the carotid artery, then the stent is deployed. The guide wire/device wire is removed after angiographic confirmation that carotid artery dissection or occlusion has not occurred. Figure 25-15 shows carotid artery patency after angioplasty and stent placement.

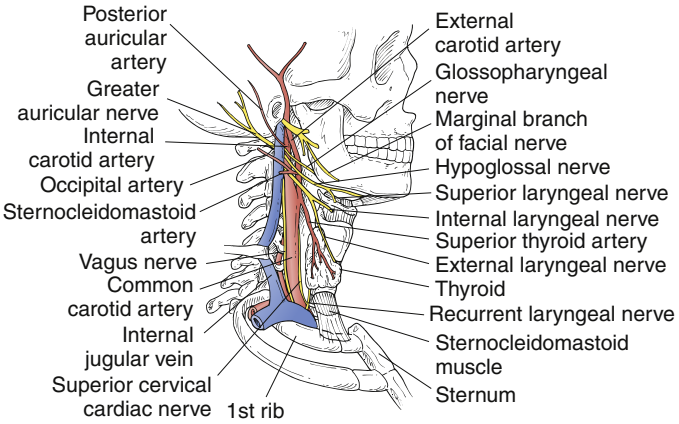

FIGURE **25-13** Relationship of the cranial nerves and their major branches to the common, internal, and external carotids in the neck. (From Eisele DW, Smith RV, eds. *Complications in Head and Neck Surgery*. Philadelphia: Mosby; 2009.)

TABLE **25-9** Case Selection for Carotid Artery Stenting

CAS Worse	CAS Better
Clinical Features	
Advanced age (80 yr or older) Intolerance of antiplatelet agents Severe renal dysfunction	COPD CHD with an abnormal cardiac stress test, unstable angina, or myocardial infarction less than 1 month ago Valvular heart disease Congestive heart failure (EF less than 30%) Contralateral recurrent laryngeal nerve dysfunction Severe obesity
Anatomic Features	
Access related Shaggy aorta Eggshell aorta Severely angulated type III aortic arch Aortoiliac occlusive disease	Previous neck irradiation Previous radical neck surgery Tracheostomy Neck immobility Recurrent stenosis High lesions (above C2) Contralateral carotid occlusion
Target vessel related Heavy calcification Severe tortuosity String sign Fresh thrombus Unstable plaque	

CAS, Carotid artery stenting; *COPD*, chronic obstructive pulmonary disease; *CHD*, coronary heart disease; *EF*, ejection fraction. (From Cronenwett JL, Johnston W. *Rutherford's Vascular Surgery*. 7th ed. Vol. 2. Philadelphia: Saunders; 2010;1473.)

Anesthetic Considerations

The anesthetic technique used most often for patients having CAS is local anesthesia at the femoral insertion site and minimal sedation, antithrombotic therapy, and observation for hypotension and bradycardia.[196] Anticoagulation is initiated with a heparin bolus, 50 to 100 units/kg, to maintain activated clotting time (ACT) at greater than 250 seconds.[197] Balloon inflation in the internal carotid artery can stimulate the baroreceptor response, resulting in prolonged bradycardia and hypotension. Glycopyrrolate or atropine can be given prior to inflation to offset this vagal response. Fluoroscopy will be used throughout the surgery, so it is important that all operating room personnel are protected with lead shielding.

Complications associated with CAS are listed in Box 25-16. The most common complication associated with this procedure is stroke caused by thromboembolism.[198] Interventions for a patient with an acute stroke include airway and hemodynamic management. Currently, the only treatment approved for acute ischemic stroke is intravenous recombinant tissue plasminogen activator (rt-PA). Mechanical devices such as snares and balloons are being developed so that the surgeon will be able to physically remove a thromboembolic material and restore blood flow.

Patients typically remain in the postanesthesia care unit for 30 minutes after carotid stent placement and then are transferred to a monitored floor. A carotid duplex scan is performed prior to discharge, and then routinely obtained at 6 weeks, 6 months, 1 year, and then yearly. Patients remain on aspirin therapy for anticoagulation for life.[199]

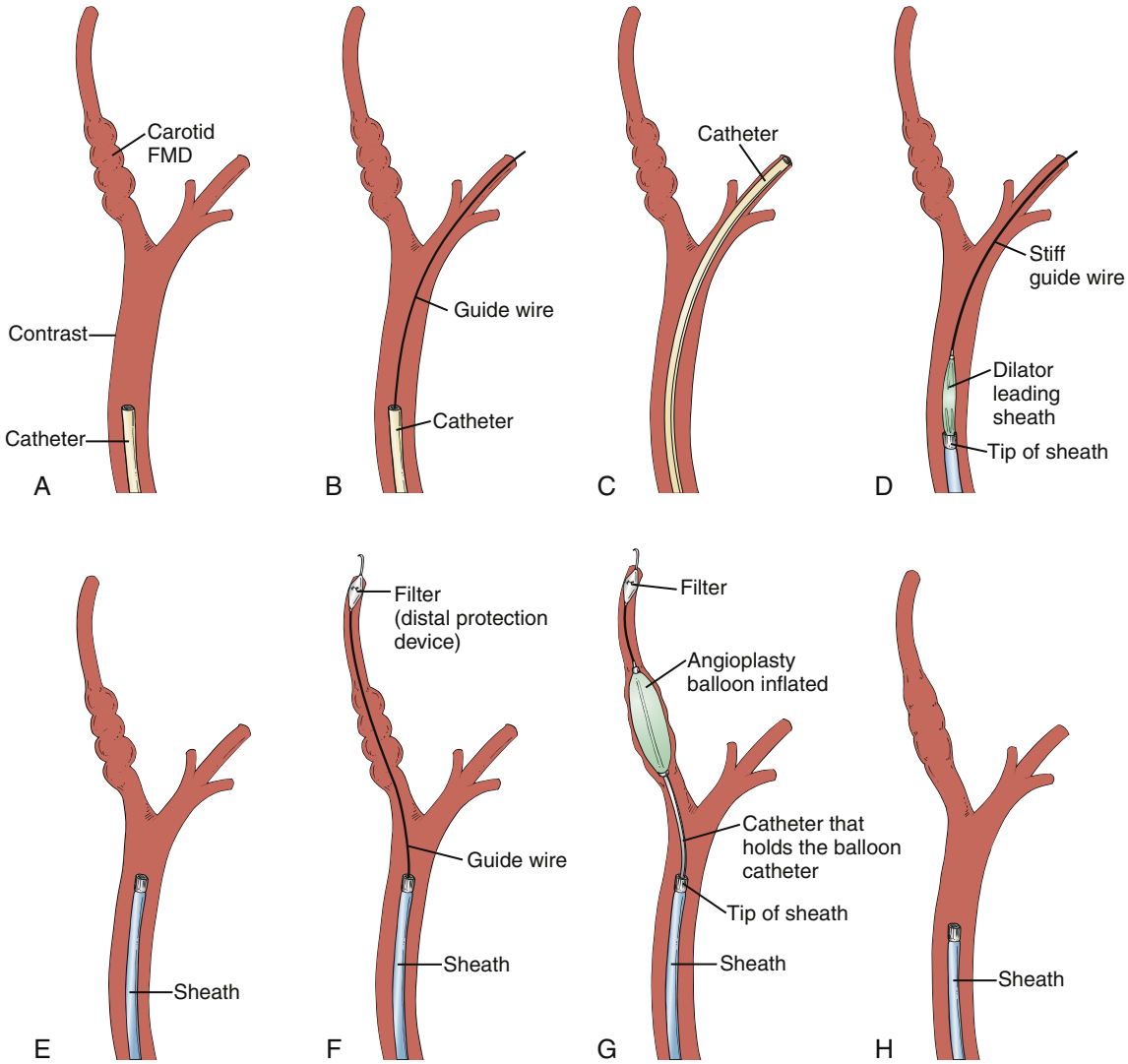

FIGURE **25-14** Endovascular technique. **A,** Internal carotid artery narrowed by fibromuscular dysplasia (FMD). An arteriogram was performed through a carotid catheter. **B,** Guide wire placed in the external carotid artery by using a roadmap of the carotid bifurcation. **C,** Cerebral catheter advanced into the external carotid artery. **D,** Stiff guide wire advanced into the external carotid artery. The carotid access sheath is advanced over the exchange guide wire. **E,** Carotid sheath in place with the tip of the sheath in the distal common carotid artery. **F,** Cerebral protection device in place in the distal internal carotid artery. **G,** Balloon angioplasty of the fibromuscular lesion in the internal carotid artery. **H,** After balloon angioplasty, the lumen has improved significantly. (From Cronenwett JL, Johnston W. *Rutherford's Vascular Surgery*. 7th ed. Vol. 2. Philadelphia: Saunders; 2010:1496.)

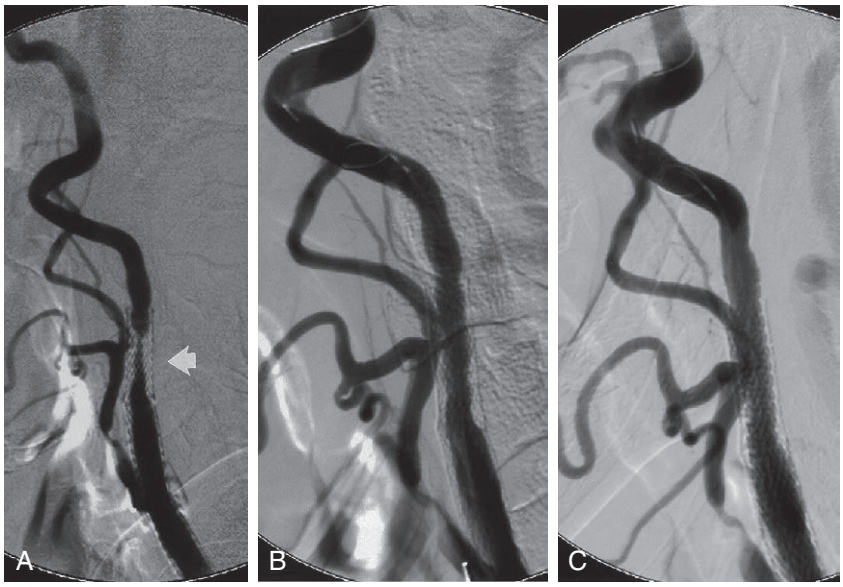

FIGURE **25-15** **A,** High-grade restenosis of internal carotid artery *(arrowhead)* 11 months after carotid angioplasty/stenting with Wallstent. **B,** After angioplasty alone. **C,** After placement of Nitinol stent. Note filter protection device in distal internal carotid artery. (From Rutherford RB, et al. *Vascular Surgery*. 6th ed. Vol. 2. Philadelphia: Saunders; 2005.)

BOX **25-16**

Complications Associated with Carotid Artery Stenting

- Stroke
- Myocardial ischemia/infarction
- Bradycardia
- Hypotension
- Deformation of expandable stent
- Stent thrombosis
- Horner syndrome
- Cerebral hyperperfusion syndrome
- Carotid artery dissection
- Carotid artery rupture
- Hemorrhage resulting from anticoagulation

SUMMARY

Because of the increase in the mean age of people in the United States, treatment of vascular disease is one of the fastest changing areas of medicine. Minimally invasive vascular surgical techniques are being introduced that are revolutionizing the options available for treatment. Many highly invasive surgical techniques are now being performed as interventional radiologic procedures. Anesthetic management for vascular procedures is far different from just a few years ago and requires that we adapt to ever-new treatment strategies. As practice evolves, we will be better able to assess growing evidence that suggests the superiority of these procedures in decreasing patient morbidity, mortality, and convalescence.

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26 CHAPTER Respiratory Anatomy, Physiology, Pathophysiology, and Anesthetic Management

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Knowledge of the respiratory system is essential to the practice of anesthesia. Anesthetists are known as the airway experts, but they are also expected to possess an excellent command of the entire respiratory system. This is not surprising considering that they administer oxygen to the majority of patients, administer inhaled anesthetics down a cascade of concentration gradients through the lungs, provide artificial ventilation for many patients under general anesthesia, and monitor and interpret blood gas analysis, capnography, and oximetry. Indeed, the visual hallmark of an anesthetist is frequently a stethoscope earpiece pinned to the scrub top; a device that places each patient breath at the forefront of the anesthetist's consciousness.

Besides the basic functions of the respiratory system, which include extracting oxygen (O_2) from the atmosphere and delivering it to the blood while excreting carbon dioxide (CO_2), the respiratory system functions in the processes of maintaining acid-base balance, phonation, pulmonary defense, and metabolism (synthesis and breakdown of bioactive materials). These functions are all discussed in this chapter.

ANATOMY OF THE RESPIRATORY SYSTEM

Knowledge of airway anatomy is not only necessary for understanding respiratory physiology but also essential for the practice of anesthesia nursing. The airway consists of the nose, mouth, pharynx, larynx, trachea, and lower airways.

The components of the respiratory system are the conducting airways, the lungs and their blood supply, the portions of the central nervous system responsible for control of the muscles of ventilation, the chest wall, and the thoracic muscles responsible for ventilation.

Nose

Inhaled air enters the body through the nose or mouth. Air passing through the nose is filtered, heated to body temperature, and humidified. The external nose is only a small part of the nasal air passageway, the major portion of which lies directly behind the nose and includes three scroll-shaped turbinate bones, also called the *nasal conchae*.

The cartilage around the entrance to the nostrils that can flare during heavy breathing is called the *alar cartilage* or *ala nasae* ("nasal wings"). Each nostril opening (anterior naris) leads directly into the vestibule, which is the forwardly expanded portion of the nasal cavity. The vestibule is lined with cutaneous epithelium. In its lower half, it has sebaceous glands and coarse hairs, which serve to filter incoming air. The floor of the nose is at a level higher than the opening of the nostril; therefore, during nasal intubation, the apex of the nose should be elevated superiorly with gentle pressure while the tube is inserted parallel to the roof of the mouth. The tube should not be directed upward into the turbinates but rather along the floor of the nose formed by the superior aspect of the palatine bone, which forms the hard palate of the mouth directly below the nose. Prolonged nasotracheal intubation is associated with obstruction of the nasal sinuses, sinus infection, and fever. Intranasal infections can produce intracranial infection via vascular connections, as discussed later in this section.

The anterior portion of the external nose, the vestibule, expands above and behind into triangular spaces, or fossae. The fossae are separated from each other by the nasal septum, which also separates the two nostrils. The septum is formed by the ethmoid and vomer bones superiorly and the vomeronasal and nasal septal cartilages inferiorly. The nasal fossae usually communicate freely with the paranasal air sinuses (frontal, ethmoid, maxillary, and sphenoid). They open into the nasopharynx by the posterior nares (also known as *choanae*) and are bordered medially by the nasal septum and laterally by three turbinates arranged one above the other.

Choanal atresia is a birth defect characterized by obstruction of the posterior nasal airway. This obstruction may be life threatening in the obligate nose-breathing newborn.

The conchae are scroll-shaped prominences projecting from the lateral walls and have their free margins directed downward and inward. The conchae overlie the superior, middle, and inferior meatus, which contain the openings to the paranasal sinuses. The superior concha is by far the smallest of the three, and the middle concha extends forward much farther than the superior concha. The inferior concha, which lies along the lower part of the lateral wall of the nasal cavity, is in the pathway of airflow in the nose, and it is the one most commonly injured during nasal intubation. It extends to within approximately 2 cm of the middle of the anterior naris, and its posterior tip lies approximately 1 cm in front of the pharyngeal orifice of the eustachian tube. Eustachian drainage can become obstructed when the inferior concha or adenoid tonsils become inflamed. Such obstruction can lead to middle ear pathology.

The nasal cavities are lined with mucous membranes that are continuous with those of the pharynx. The mucosa can be divided into respiratory and olfactory areas because it not only lines the tracts followed by respired air but also covers the cells that act as the receptors for smell. The olfactory epithelium occupies the apical third of the nasal cavity. This epithelium contains afferent fibers from the olfactory nerves (cranial nerve I) that communicate through the cribriform plate of the ethmoid bone to the adjacent olfactory bulb. Signals then progress to the other parts of the rhinencephalon. The respiratory mucosa lines the lower two thirds of the nose and consists of pseudostratified ciliated columnar epithelium interspersed with goblet cells that produce mucus. Although the morphology of cells changes progressively toward the terminal bronchioles, this general arrangement of stratified ciliated epithelium with goblet cells persists throughout the majority of the air passages of the respiratory system. The direction of motion of the cilia is toward the exterior of the nasal cavity.

The principal arterial supply of the nasal fossae comes from the ophthalmic arteries through the anterior and posterior ethmoid

branches and from the internal maxillary artery through the sphenopalatine arteries. Because of the location of the interior maxillary artery, it is sometimes ligated for the treatment of persistent nosebleed. The veins accompany the arteries; the ethmoid veins open into the superior sagittal sinus, and the nasal veins drain into the ophthalmic veins and then into the cavernous sinuses. Infections in the nose can result in meningitis because of this venous communication between the intracranial and intranasal circulation. The sensory nerves from the upper respiratory tract come from the ophthalmic nerve and the maxillary nerve (both are branches of cranial nerve V). Lymphatic drainage from the cavities of the nose is via the deep cervical lymph nodes adjacent to the internal jugular vein.

Through the functioning of the nasal hairs, the mucus-producing epithelium, and the rich arterial supply, the nose carries out important functions that include filtration, humidification, and heating of inspired air. As long as the incoming air is not extremely cold, the nose can warm the inspired air to nearly body temperature and moisten it to nearly 100% relative humidity. The heating and humidifying functions of the nose are affected by general anesthesia. The inspiration of cold, dry gas often dries the nasal and pharyngeal passageways, causing sore throat even if no instrumentation of the airway takes place.

The hairs at the entrance to the nostrils are of minor importance to filtration because they remove only large particles. Much more important is the removal of particles by turbulent precipitation. Air passing through the nasal passageways hits many obstructions including the septum, the turbinates, and the pharyngeal wall. When the inspired air is forced to change direction, the inhaled particles cannot change course as rapidly, and they become embedded in the mucus-covered surfaces of these processes. The particles trapped in the mucus are moved by the cilia either to the naris or posteriorly to the pharynx to be expectorated or swallowed. This occurrence is important because it denies entry of infectious, carcinogenic, or irritating substances. Nasal filtration is extremely effective for particles above 10 μm and less than 1 nm, but filtration efficiency is inverse to particle size for particles that are between 10 nm and 1 μm.[1]

Pharynx

The pharynx is a wide muscular tube that is a part of both the respiratory tract and the alimentary canal. Its upper border is the base of the skull, and it extends to the level of the C6 vertebra, where it becomes continuous with the esophagus. At this level, ingested foreign bodies, such as coins, are frequently lodged. The pharynx is lined by a musculomembranous coat and divided into three parts: the nasopharynx, which extends from the posterior nares (choanae) to the end of the soft palate; the oropharynx, which is bounded superiorly by the soft palate and anteriorly by the tonsillar pillars and oral cavity and extends inferiorly to the tip of the epiglottis; and the hypopharynx (laryngopharynx), which extends from the tip of the epiglottis to the level of C6, or the beginning of the esophagus.

The pharyngeal region includes the tonsils, which are composed of three aggregations of lymphoid tissue: the palatine tonsils (major tonsils), which lie in the tonsillar fossae at the boundary of the oral cavity and oropharynx; the lingual tonsils, which extend across the tongue from the base of each palatine tonsil; and the pharyngeal tonsils (adenoids), which lie on the lateral walls of the nasopharynx. The lymphoid tissue of the tonsils forms the Waldeyer tonsillar ring, which acts as a first line of defense against bacterial invasion of the nasal and buccal passages. If inflamed, the pharyngeal tonsils may obstruct airflow through the choanae and are sometimes removed by an adenoidectomy. Likewise, chronic tonsillitis may lead to removal of the palatine tonsils by tonsillectomy.

TABLE 26-1 The Nine Cartilages of the Larynx

Unpaired Cartilages		Paired Cartilages	
Number	**Name**	**Number**	**Name**
1	Epiglottic	4 and 5	Arytenoids
2	Thyroid	6 and 7	Corniculates
3	Cricoid	8 and 9	Cuneiforms

Larynx

The adult larynx extends from vertebrae C3 to C6 and is a protective structure that prevents aspiration during swallowing; vocalization evolved secondarily. The larynx consists of one bone, nine cartilages (Table 26-1), ligaments, muscles, and membranes.

The hyoid bone is the chief support for the larynx and is the only bone that does not form a joint with another bone. Its anterior aspect can be easily palpated, and its location is sometimes used as a measure of airway assessment for laryngoscopy. The thyroid cartilage and the cricoid cartilage make up the principal part of the framework of the larynx, whereas the epiglottis guards its entrance.

Laryngeal Cartilages

The epiglottic cartilage lies closest to the root of the tongue and is vertical to the opening of the larynx. It is attached to the body of the thyroid cartilage by the thyroepiglottic ligament just above the vocal cords and to the base of the tongue by the glossoepiglottic folds. The furrow between the glossoepiglottic fold and the base of the tongue is called the *vallecula epiglottica* and serves as the situation point for the tip of a curved laryngoscope blade. The epiglottis serves to protect the larynx from foreign body entry. During swallowing or laryngospasm, elevation of the larynx closes the epiglottis, effectively "sealing off" the trachea.

The thyroid cartilage is the largest cartilage of the larynx, formed by two quadrangular plates or laminae fused near the midline anteriorly. Its strength affords a great deal of protection to the larynx. The thyroid cartilage forms the Adam's apple. Being larger and covered with less subcutaneous fat, the thyroid cartilage is more prominent in adult males.

The cricoid cartilage is palpable just below the thyroid gland, and its level corresponds to the beginning of the trachea and the esophagus. It is the only true ring of cartilage encircling the airway. Anteriorly, the cricoid cartilage lies below the thyroid cartilage, with the cricothyroid membrane intervening. The cricoid is the most inferior of the nine laryngeal cartilages. The arytenoid cartilages articulate on the superior posterior aspect of the cricoid cartilage, which is slanted forward. The paired arytenoid cartilages are attached to the posterior ends of the vocal cords. The paired corniculate (median) and cuneiform (more lateral) cartilages are embedded in the aryepiglottic folds and give support to these structures. These cartilages cause the two bumps seen in the aryepiglottic folds, which are often (but incorrectly) called the "arytenoids" when visualized during laryngoscopy.

In adults, the narrowest portion of the larynx is the cricoid opening between the vocal cords; in children younger than 10 years, the narrowest part is just below the vocal cords at the cricoid cartilage. This anatomic difference is of clinical significance: a tube with adequate clearance through the vocal cords may create

BOX **26-1**

Intrinsic Muscles of the Larynx

Laryngeal Inlet
- Closed by the aryepiglottic and oblique arytenoid muscles
- Opened by the thyroepiglottic muscle

Glottic Opening
- Opened by the posterior cricoarytenoid muscles
- Closed by the transverse arytenoid and the lateral cricoarytenoid muscles

True Vocal Cords
- Lengthened by the cricothyroid muscles
- Shortened by thyroarytenoid muscles

mucosal pressure at the level of the cricoid ring. For this reason, traditionally, uncuffed endotracheal tubes have been used in children less than 8 to 10 years of age. Although an uncuffed tube may offer advantages in terms of positioning,[2] it is becoming more commonplace to use an adjusted-size cuffed tube in pediatric patients for the added assurance of tidal volume delivery and to reduce the necessity to change the tube because of incorrect sizing.[3]

Membranes of the Larynx

The thyrohyoid membrane suspends the larynx from the hyoid bone. The cricothyroid membrane lies between the cricoid and the thyroid cartilages. The easiest and most rapid laryngotomy can be performed through this membrane. Cricothyrotomy is recommended for the emergency establishment of an airway when both endotracheal intubation and mask ventilation are unsuccessful. The *transtracheal block* to deposit local anesthetic inferior to the vocal cords is also performed through the cricothyroid membrane.

Interior of Larynx

The cavity of the larynx is divided into three compartments by the false vocal cords and the true vocal cords. The supraglottic area, also called the *vestibule*, extends from above the false cords to the tip of the epiglottis. On each side of the vestibule is located a pharyngeal sinus (the pyriform sinus). This recess is a potential location for lodging of foreign bodies that enter the pharynx or for noncentered endotracheal tubes. The second compartment of the larynx is the area between the false cords and the true cords known as the *laryngeal ventricles*. The third area is the infraglottic region below the true cords and above the beginning of the trachea. The rima glottidis (cricoid opening) is the space between the true cords.

Movements of the Vocal Cords

The true vocal cords are fibromembranous folds attached anteriorly to the thyroid cartilage and posteriorly to the arytenoids. The focal points of movement are the arytenoid cartilages, which rotate and slide up and down on the sloping cricoid cartilage. The muscles controlling laryngeal movement (Box 26-1) are most conveniently thought of as pairs having opposing actions. The laryngeal inlet is closed by the aryepiglottic muscle and opened by the thyroepiglottic muscle. The cricoid opening is dilated by the posterior cricoarytenoid muscles and closed by the interarytenoid muscles assisted by the lateral cricoarytenoid muscles. The cricothyroid muscles lengthen the true vocal cords, and the thyroarytenoid muscles shorten them. Both sets of muscles can alter the tension on the vocal cords and are important for determining the pitch of the voice.[4]

Nerve Supply to the Larynx

Both the superior and inferior laryngeal nerves are branches of cranial nerve X, the vagus nerve. The superior laryngeal nerve arises from the ganglion nodosum of the vagus and divides into two branches, the internal and external. The external segment gives a branch to the inferior constrictor muscle of the pharynx and also to the cricothyroid muscles. These muscles change the position of the cricoid and thyroid cartilages and in doing so lengthen or increase the tension of the vocal cords. If these muscles are paralyzed, the voice becomes weak, rough, and easily fatigued. Voice hoarseness, particularly of recent onset, should be investigated in the preoperative evaluation as a potential indicator of vocal cord palsy or airway obstruction. The internal branch of the superior laryngeal nerve enters the larynx and then the thyrohyoid membrane and is distributed to the mucous membranes of the larynx and epiglottis. It provides sensation from the inferior side of the epiglottis down to the true cords (the superior side of the epiglottis is innervated by the glossopharyngeal nerve). The internal branch also innervates the interarytenoid muscles, which are important in phonation.

The inferior (or recurrent) laryngeal nerves arise from the two vagus nerves at different levels. The left nerve descends with the vagus and then loops around the arch of the aorta to come back up to the neck. The right nerve travels with the vagus nerve as far as the subclavian artery; it loops around this artery and then comes back up the neck. The recurrent laryngeal nerve supplies sensation to the larynx below the level of the vocal cords and innervates all the muscles of the larynx except the cricothyroid and part of the interarytenoid muscles. Damage to the recurrent laryngeal nerve(s) during surgery on the neck or from airway devices or anesthetic blocks can lead to unilateral or bilateral vocal cord paralysis with hoarseness or dyspnea, respectively.[5,6] Blood supply to the larynx is provided by the superior thyroid artery (a branch of the external carotid artery) and the inferior thyroid artery (a branch of the thyrocervical trunk, which arises from the subclavian artery).

Trachea

The trachea is lined by pseudostratified ciliated columnar epithelium, and it extends from the inferior larynx to the carina, where it bifurcates into the two mainstem bronchi. In adults of normal size, the distances are fairly constant: the distance from the incisors to the larynx is approximately 13 cm, as is that from the larynx to the carina. Therefore, the distance from the incisors to the carina is approximately 26 cm (note the length markings on endotracheal tubes). The blood supply to the trachea is through the inferior thyroid artery, which comes from the thyrocervical branch of the subclavian artery. Some perfusion is also received from the superior thyroid, bronchial, and internal thoracic arteries. Blood is drained by the inferior thyroid veins. Sensory innervation of the trachea is via the vagus nerve for both parasympathetic and nociceptive stimuli.

The trachea has a diameter of approximately 2.5 cm and is supported by incomplete rings of cartilage that open posteriorly and prevent tracheal collapse under the negative pressure generated during spontaneous respiration. The trachea extends down to the level of T4-T5, where the carina is located. This level corresponds anteriorly to the angle of Louis on the sternum, which is the articulation of the second rib. The trachea is not a rigid structure; it expands and contracts to accommodate head and neck movement. In an intubated patient, flexion of the neck elevates the carina. As a result, the endotracheal tube moves downward and endobronchial intubation may result. During extension of the head and

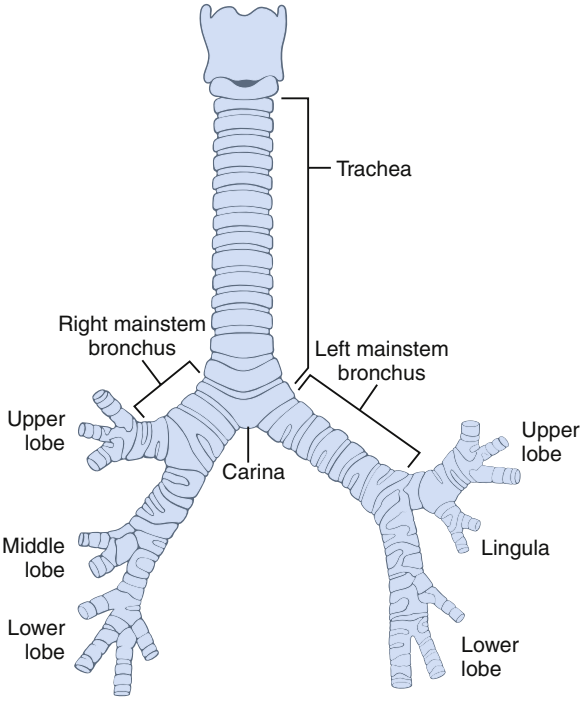

FIGURE **26-1** Tracheobronchial anatomy. (From Miller RD, Pardo Jr MC. *Basics of Anesthesia*. 6th ed. Philadelphia: Saunders; 2011:438.)

BOX 26-2

Lung Lobes and Segments

I. Right lung
  A. Right upper lobe (3 segments)
    1. Apical
    2. Anterior
    3. Posterior
  B. Right middle lobe (2 segments)
    1. Medial
    2. Lateral
  C. Right lower lobe (5 segments)
    1. Superior
    2. Anterior basal
    3. Posterior basal
    4. Lateral basal
    5. Medial basal
II. Left lung
  A. Left upper lobe (4 segments)
    1. Apical posterior
    2. Anterior
    3. Superior lingular
    4. Inferior lingular
  B. Left lower lobe (4 segments)
    1. Superior
    2. Anteromedial basal
    3. Posterior basal
    4. Lateral basal

neck, the trachea moves downward, the endotracheal tube moves upward, and extubation can occur. In pediatric patients, the range of this movement was demonstrated to increase with patient age and height.[7] The apparent movement of the endotracheal tube in relation to head flexion may seem paradoxical; the mnemonic "the hose follows the nose" can be used as a memory aid. Neck rotation to the left or right tends to cause tracheal elevation and risk of endobronchial intubation.

Bronchi

At the carina, the trachea divides into the right and left bronchi (Figure 26-1). The cellular structure begins to change at this point from columnar to cuboidal epithelium, and the cartilaginous rings thin into plates once the bronchi penetrate the lungs. From the carina, the bronchi branch off at slightly different angles. The right bronchus takes a less acute angle from the trachea, about 25 degrees, whereas the left bronchus takes off at 45 degrees. Also, the right mainstem bronchus is wider and shorter (2 cm) than the left one (4 cm).[8] Because the right bronchus is more nearly vertical than the left, the tendency is much greater for endotracheal tubes, suction catheters, or aspirated foreign materials to enter the right side after passing the carina. Additionally, the beveled tip of an endotracheal tube makes right-sided intubation more likely. The side hole (Murphy's eye) near the end of the endotracheal tube allows the delivery of gas if the beveled tip of the tube is closely opposed to the similarly angled right main bronchus.

Each mainstem bronchus divides into lobar bronchi (three on the right; two on the left), that lead to the major lung lobes. The right mainstem bronchus ends only 2 to 2.5 cm from the carina before giving rise to the right upper lobe (RUL) bronchus. After the RUL takeoff, the main bronchus then continues for 3 cm as the *bronchus intermedius* before giving rise to the right middle lobe bronchus and the right lower lobe bronchus. The left main bronchus is 4 to 5 cm long and terminates by bifurcating into the left upper lobe bronchus and the left lower lobe bronchus. The left upper lobe bronchus further branches into a superior division and an inferior division (the lingular branch).

Each successive division of the airways is referred to as a *generation*, with the mainstem bronchi representing the first generation, the lobar bronchi representing the second, and so on. The lobar bronchi divide into the third generation of airways, called *segmental bronchi*, which deliver ventilation to the various bronchopulmonary segments of the lung. There are 10 bronchopulmonary segments in each lung, but on the left, the apical and posterior segments and the anterior basal and medial basal segment pairs each arise from a single bronchial branch (Box 26-2). Therefore, only eight third-generation bronchi are found on the left. Segments whose names contain the word *basal* are located adjacent to the diaphragm. The bronchopulmonary segments create distinct anatomic and functional units. The segments are separated by connective tissue, so gas-exchange properties or pathology tend to be isolated to a segment. A bronchopulmonary segment also can be excised as a unit.

Each subsegmental bronchus divides several times, giving rise to many bronchioles. With succeeding generations and multiplication of the number of airways, the total cross-sectional area becomes very large, and the airflow velocity decreases. There are 20 to 25 total generations before the alveoli. By the seventh generation, the diameter of bronchioles is about 2 mm, beyond which they are referred to as *small airways*. When the diameter has decreased to 1 mm they are referred to as *terminal bronchioles*. The terminal bronchioles are the last structures perfused by the bronchial circulation and are the end of the conducting airways (anatomic dead space, as discussed later). In the latter generations, the cross-sectional area of the airway has expanded so much that the velocity of airflow becomes very slow, and gas moves largely by diffusion rather than by bulk flow.

With succeeding generations, the histology of the airways changes, in a progression characterized by thinning of the walls, to transition to the gas-exchanging morphology of the *respiratory*

BOX 26-3

Characteristics of Progressive Airway Divisions

With each succeeding generation:
- Number of airways ↑
- Cross-sectional area ↑
- Airflow velocity ↓
- Muscular layer ↑
- Cartilage ↓
- Mucous glands ↓ (absent in bronchioles)
- Goblet cells ↓
- Ciliated cells ↓
- Cuboidal, then squamous cells ↑

zone (Box 26-3). The terminal bronchioles divide into the respiratory bronchioles that are perfused by the pulmonary circulation and are the first place in the airway at which exchange of gas with the blood occurs. These airways are characterized by occasional outpouching of alveoli, or air sacs. The respiratory bronchioles divide into several alveolar ducts that lead to circular spaces called *atria*. Each atrium opens into two to five alveolar sacs, which are spaces lined by alveoli. The terminal airways are very small, and their walls are no longer tented open by cartilage but rather by connection with the adjacent matrix of pulmonary parenchyma in which they are situated. For this reason, they are prone to closure from compression of the pulmonary tissue during respiration or if emphysema, for example, expands the volume of adjacent air spaces and compresses the airways. The lung volume at which small airways tend to close is called the *closing volume*. In those with obesity and chronic obstructive pulmonary diseae (COPD), the closing volume increases into the range of normal tidal breathing such that some airways close before the intended tidal volume has been expired. Small pores in the alveoli, known as the *pores of Kohn*, serve to allow collateral gas flow between alveoli and provide a mechanism of relief from gas stagnation from airway closure.[9]

Respiratory Zone

The respiratory bronchioles and alveolar ducts, sacs, and alveoli comprise the *respiratory zone*, the area where gas exchange takes place. All parts of the airway prior to this (nose to terminal bronchioles) conduct gas without exchanging gas with the blood and are referred to as the *conducting zone*. Some refer to the respiratory bronchioles and alveolar ducts where limited gas exchange takes place as the *transitional zone* because structures here function both to conduct gas and also to participate in some gas exchange. The alveoli are the air sacs that are tightly packed and closely approximated with pulmonary capillaries. The typical maximum number of approximately 300 million alveoli is reached by age 9 years. The alveoli are characterized by very thin walls composed of squamous epithelium. There are three types of cells that form the alveoli: type I pneumocytes, which are the structural cells; type II pneumocytes, which produce surfactant to reduce alveolar collapse from surface tension; and type III pneumocytes, which are macrophages. The average alveolar diameter is approximately 250 µm; therefore the total surface area available for gas exchange is 60 to 80 m^2.[10]

Pulmonary Hila and Coverings

The nerve supply to the bronchi and lungs arises chiefly from the sympathetic nerves and the vagus nerve (which supplies sensory and parasympathetic innervation). All conduits to the lung pass through the hilum, which is the connection of the mediastinum to the pedicle of each lung. The structures included in each hilum include the mainstem bronchus, pulmonary artery and vein, bronchial arteries and veins (which drain into the azygos system), lymphatics, lymph nodes, pulmonary nerve plexuses, and pulmonary ligament. All of this is surrounded by connective tissue. The serous membrane covering the lung is called the *pleura*. The parietal pleura lines the chest wall, mediastinum, and diaphragm, and at the hilum is then reflected back to cover the lungs as the visceral pleura. Between these two layers is a potential space called the *pleural cavity*. The touching surfaces of the two layers of pleura are kept slippery by a small amount of serous fluid. Certain conditions can result in occupation of the pleural space by liquids or gas (Table 26-2) and may affect ventilation and lung expansion. Infected intrapleural blood can clot and organize to form a fibrothorax, which must be peeled from the surface of the lung (in a procedure called *lung decortication*) so the lung can reexpand.

TABLE 26-2 Conditions That Affect the Pleural Space

Material in Pleural Space	Medical Name
Air	Pneumothorax
Air under pressure	Tension pneumothorax
Blood	Hemothorax
Serous fluid	Pleural effusion
Pus	Empyema or pyothorax
Organized blood clot	Fibrothorax
Lymph	Chylothorax

TABLE 26-3 Divisions of the Mediastinum

Subdivision	Location	Contents
Superior	Above level of the sternal angle, extending superior to the thoracic inlet	Thymus, esophagus, trachea, great vessels
Anterior	Between sternum and pericardium	Thymus
Posterior	Between vertebral column and posterior pericardium	Esophagus, thoracic aorta, thoracic duct
Middle	Between anterior and posterior divisions, bounded laterally by the parietal pleura	Heart, distal trachea, mainstem bronchi, and great vessel trunks

Mediastinum

The mediastinum is the region between the two pleural sacs. It lies roughly in the center of the thoracic cavity but is slightly displaced to the left by the presence of the heart. Therefore the left lung represents 45% of the total lung capacity (TLC), whereas the right lung represents 55%. Perforation of the larynx, trachea, pharynx, or esophagus, which sometimes occurs during esophagoscopy, bronchoscopy, or traumatic intubation, can produce mediastinitis, a life-threatening infection of an area containing the trachea, esophagus, and major blood vessels and heart. The mediastinum is divided into four divisions separated by the pericardium (Table 26-3). Common procedures involving the mediastinum include coronary artery bypass, cardiac valve replacement, aortic aneurysm repair, thymectomy for myasthenia gravis, resection of tumors, and mediastinoscopy for diagnosis and staging of cancer.

Pleura

The pleura is a serous membrane that lines the thoracic wall and lungs. The parietal pleura is attached to the chest wall, diaphragm, and mediastinum but is then reflected back to cover the lungs and afterward referred to as the *visceral pleura*. These two layers are closely opposed, with only a capillary-thin layer of pleural fluid between them in a potential space known as the *pleural space*. The parietal pleura is very sensitive to pain, and conditions that cause accumulation of pleural fluid or friction between the layers can be very uncomfortable. Different areas of the pleura may produce characteristic pain patterns: the costal pleura creates localized pain, the diaphragmatic pleura creates diffuse pain, and areas supplied by the phrenic nerve may radiate pain to the neck or back. Posterior to the mediastinum, the pleura doubles up and descends downward as the "pulmonary ligament."

If communication is created across the pleura, accumulation of air in the pleural space is referred to as *pneumothorax*. In a closed chest (e.g., a pulmonary bleb ruptures, creating a communication to the pleural space) a tension pneumothorax develops as inspired air accumulates in the pleural space and is not expelled. With an opening through both pleura (such as with open chest trauma) the external wound may create a simple pneumothorax, which does not tend to cause high intrathoracic pressures. In either type of pneumothorax, the elastic recoil of the lung tends to favor lung collapse once the negative pressure of the pleural space is disrupted by the breach.

MECHANICS OF BREATHING

Contraction of the muscles of inspiration lowers intrathoracic pressure and causes the volume of the thoracic cavity to increase. Boyle's law explains that the increase in volume creates a reduction in pressure, which causes air to enter from the atmosphere. Spontaneous respiration therefore involves passive movement of gas, as opposed to positive-pressure ventilation, which requires generation of positive pressure in the upper airway to overcome intrathoracic pressure and expand the lungs.

The diaphragm and external intercostal muscles contract during normal breathing (eupnea). While the diaphragm increases the superior-inferior dimension of the chest, the external intercostals increase the anterior-posterior diameter by elevating the ribs and sternum. Each half of the diaphragm is innervated by a branch of the phrenic nerve, which arises from the third, fourth, and fifth cervical spinal nerve roots. This anatomy gives rise to the mnemonic "C-3, 4, and 5 keep the diaphragm alive." The diaphragm is almost solely responsible for quiet respiration, and loss of the function of intercostal muscles (by a thoracic spinal cord injury or high spinal or epidural block) usually does not impair respiration. However, if coupled with paralysis of the phrenic nerve and resulting paralysis of a hemidiaphragm (such as may occur with interscalene blocks), dyspnea may result. Spinal cord injuries above the level of C-5 usually lead to dependence on mechanical ventilation.

Normally, eupneic expiration results from passive recoil of the chest wall and does not require muscular contraction, although the internal intercostal muscles may be used to augment exhalation. During forced exhalation (e.g., with coughing and the clearing of secretions), the abdominal muscles, particularly the rectus abdominis, the transversus abdominis, and the external and internal oblique muscles, are used. For forced inhalation, the intercostal muscles play a more prominent role, and accessory breathing muscles in the neck are also used. The diaphragm descends approximately 1 to 2 cm during eupneic breathing, but this excursion can increase to as much as 10 cm during forceful breathing. For air to move into the alveoli, alveolar pressure must be less than atmospheric pressure. This can be achieved either through an increase in atmospheric pressure (as in positive-pressure ventilation) or a reduction in alveolar pressure, as during spontaneous ventilation (negative-pressure breathing). During forceful inspiration, the sternocleidomastoid and scalene muscles contract in conjunction with the diaphragm and intercostals.

The muscles of ventilation are attached to the cartilaginous and bony components (ribs, sternum, and vertebrae) of the chest. Conditions that impede chest excursion, such as thoracic kyphosis, may require reduction to further increase the chest diameter. The two domes of the diaphragm separate the thoracic and abdominal cavities and function separately, such that injury to a phrenic nerve results in paralysis in the diaphragm only on that side. The central tendon on the underside of the diaphragm provides a site of rigidity, allowing the diaphragm to tense and flatten without pulling against an external insertion point, as do other muscles. The central tendon includes an orifice for passage of the inferior vena cava. There are two other prominent openings through the diaphragm; the esophagus passes through the esophageal hiatus, and the aorta, azygous vein, and thoracic duct pass through the aortic hiatus. When the diaphragm contracts during spontaneous inspiration, it flattens and moves the abdominal contents downward, raising intraabdominal pressure while lowering intrathoracic pressure. Pressure within the alveoli becomes slightly negative with respect to atmospheric pressure, and gas flows inward through the conducting airways to expand the lungs. When the diaphragm is paralyzed, it cannot contract; therefore, it moves upward from its normal position, owing to the effects of intraabdominal pressure and negative intrapleural pressure. When the normal diaphragm contracts (moving downward), the paralyzed diaphragm moves upward, and when the normal diaphragm relaxes (moving upward), the paralyzed diaphragm moves downward, resulting in paradoxical movements.

Lung Compliance

Lung compliance is defined as the change in volume divided by the change in pressure (V/P). For a given change in pressure, a more compliant lung has a greater change in volume than a less compliant one. Figure 26-2 shows pressure-volume relationships for a lung. As with many concepts in respiratory physiology, the reader must make the jump from considering the application to a single alveolus (which aids in understanding) to conceptualizing the overall average state in the pulmonary system, which involves many regions existing along a continuum of conditions. In considering lung compliance, the curve in Figure 26-2 represents the collective contribution of alveoli that are almost collapsed at the beginning of inspiration, alveoli that are distended, and alveoli that exist at various intermediate volumes.

Static effective compliance describes the pressure-volume relationship for a lung when air is not moving; that is, reflecting compliance of the lung and chest wall alone. Static compliance is decreased by conditions that make the lung difficult to inflate, such as fibrosis, obesity, vascular engorgement, edema, acute respiratory distress syndrome (ARDS), and external compression (e.g., that caused by tight dressings or a surgeon leaning on the patient's chest). Static compliance is increased by emphysema, which destroys the elastic tissue of the lung. This makes the emphysematous lung easier to inflate. The problem with emphysema is not inflation but rather deflation, because the loss of elastic tissue results in small airway collapse as the lung deflates, which causes

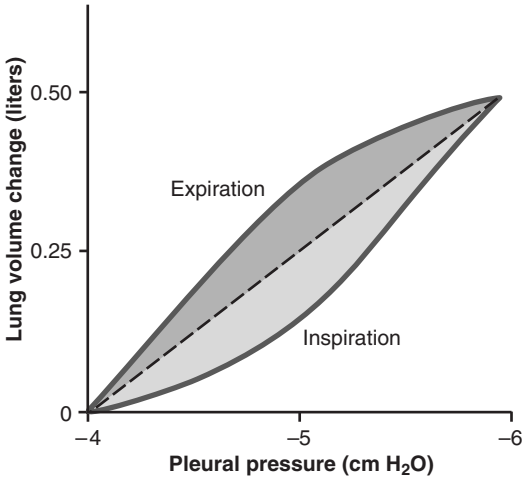

FIGURE **26-2** Compliance curve of the lungs. (From Hall JE. *Guyton and Hall Textbook of Medical Physiology.* 12th ed. Philadelphia: Saunders; 2011:467.)

gas trapping. It is important to note that compliance changes as lung volume changes. In other words, compliance is volume dependent. Figure 26-2 shows that the lung is less compliant both at very low and at very high lung volumes. Alveoli require greater pressure to be inflated when they are almost empty or almost full, respectively. When an alveolus is collapsed, a great increase in pressure is necessary for inflation to begin. Observe in Figure 26-2 that the slope of the inspiratory curve is less at both low volumes and very high volumes. At low volumes, it takes more energy (more negative pressure, i.e., less compliant) to begin to expand the lungs. At high volumes, the alveoli are almost at capacity, and further changes in pressure result in less change in volume (less volume per given pressure = less compliant). As you follow the curve along the expiratory side, notice that an initial increase in pressure (with slower volume change) as the chest wall relaxes is followed by a smooth reduction in volume back to the resting level. Lung compliance results from the interplay of various factors that tend to either expand the lungs or restrict lung expansion. Much of the energy required to expand the lungs, particularly at low volumes, is created by surface tension in the fluid lining of the alveoli, which tends to attract the alveoli toward a smaller volume. Perhaps counterintuitively, a lung filled with fluid (and therefore without an air/fluid interface and the resulting surface tension) has a very high compliance—it requires much less energy to expand. Although not a high-fidelity measurement, static effective compliance can be calculated easily using the following equation:

$$\text{Static effective compliance} = \frac{\text{tidal volume}}{\text{(plateau pressure-PEEP)}}$$

Plateau pressure is the pressure observed if you retard exhalation momentarily when the lungs are at end-inspiration. An inspiratory pause on the ventilator is an easy way to observe the plateau pressure. After subtracting the added pressure of PEEP, the plateau pressure is then divided into the measured tidal volume of that breath, producing a measure of lung compliance. A static compliance of 60 to 100 mL/cm H_2O is considered normal. However, the most useful clinical application of compliance measurement is in monitoring trends to evaluate changing physical status or the effectiveness of positive end-expiratory pressure (PEEP) or other treatment modalities.

Dynamic compliance is the compliance of the lung while the air is moving. Dynamic compliance is influenced by the forces involved in static compliance as well as the effects of airway resistance. Airway obstruction (e.g., that caused by bronchospasm or the presence of foreign bodies in the airway) can greatly decrease dynamic compliance.[11] Dynamic compliance is calculated as the tidal volume divided by peak inspiratory pressure − PEEP. Many modern anesthesia ventilators can calculate and trend compliance through tracing of pressure-volume curves.

Lung Elastic Recoil

The forces that cause elastic recoil of the lung are responsible for emptying the lung during exhalation and have a significant influence on lung compliance. In addition to actual elastic fibers, the surface tension of the liquid film that lines the alveoli contributes to elastic recoil of the lung. Surface tension occurs at a gas/liquid interface and is generated by the cohesive forces among the molecules of the liquid. Surface tension is what causes water to bead and form droplets.

Surface tension at the gas-fluid interface between the alveolar walls and the gas inside them contributes to reducing the size of alveoli, particularly when the alveoli are at low volumes. At end-expiration, surface tension increases the pressure required to inflate the alveoli, contributing to the flat portion of the lung compliance curve. This concept is often attributed to the law of Laplace (P = T/r), which states that if surface tension (T) is constant, pressure (P) would increase as radius (r) decreases. *Pulmonary surfactant* secreted by alveolar type II cells counteracts the influence of surface tension on the lungs. With surfactant present, as alveolar radius decreases, surface tension also decreases, so that pressure remains more constant. Surfactant consists of proteins and phospholipids, primarily, dipalmitoylphosphatidylcholine. The surface active agent serves to lower the surface tension of the fluid lining the alveoli and decrease the work of breathing.

Although the law of Laplace has traditionally been applied to understanding alveolar pressure-tension relationships, there is controversy over whether alveoli should be treated as spherical (and thus subject to the law) or not. Geometricians postulate that closely packed alveoli would not maintain the shape of spheres, but rather of polyhedrons because their sides would be flattened against each other. The classical application of LaPlace described the concept of alveoli as distinct balloon-like structures wherein pressure differentials can cause small alveoli to collapse and expel their gas into larger ones. The fact that alveoli are not individually suspended, but rather part of a connective tissue mesh, argues against this concept. The presence of pores of Kohn also argues against this theory, because the pores allow pressure equalization between adjacent alveoli. Connective tissue and elastic forces probably play the most important role in preventing alveolar closure.[12]

In any case, it is clear that surfactant is crucial for reducing surface tension and preventing collapse of alveoli and, perhaps more importantly, small airways. The cylindrical shape of airways lends to the application of the law of LaPlace to the role of surfactant in these structures. Surfactant probably also helps prevent fluid bridging (connection of fluid lining from opposite sides of an airway at low volumes), which could impair gas flow.[13] In the fetus, surfactant is not produced until approximately 28 to 32 weeks of gestation and does not reach mature levels until approximately 35 weeks' gestation. The lack of surfactant is the prevalent cause of respiratory distress syndrome (RDS) in premature infants. Formation of surfactant can be hastened by the administration of glucocorticoids (particularly a steroid that crosses the placenta,

such as betamethasone) to the parturient mother when premature delivery is threatened or imminent. The direct administration of synthetic surfactant to the airways of premature newborns has also greatly reduced the incidence of RDS. Amniocentesis is sometimes performed to determine whether mature surfactant levels are present in the premature fetus. The ratio of lecithin to sphingomyelin (the L/S ratio) indicates the amount of mature surfactant (dipalmitoyl lecithin) in proportion to the amount of surfactant precursor (sphingomyelin).

Respiratory Pressure

Although the elastic forces of the lung tend to favor lung collapse, the chest wall is constantly under tension to expand. This is why normal inspiration requires very little energy. At the end of eupneic exhalation, the outward recoil of the chest wall is balanced by the inward elastic recoil of the lung. At this resting end-expiratory point, the opposing forces of the lungs and chest wall produce negative pressure in the pleural space.

The difference between intraalveolar pressure and intrapleural pressure is called the *transpulmonary pressure*. Under normal circumstances, the pleural pressure is always slightly negative, owing to the opposing forces of lung tissue contraction and chest wall expansion. The intrapleural pressure becomes slightly more negative during inspiration and slightly less negative during expiration. The transpulmonary pressure fluctuates as the alveolar pressure oscillates between slightly negative during inspiration to slightly positive during expiration, returning to zero whenever airflow is stopped at end-inspiration or end-expiration (Figure 26-3). During normal inspiration, intraalveolar pressure fluctuates only by 1 to 2 mmHg. Therefore very little pressure is applied during eupneic ventilation. During maximal expiration with a closed glottis (such as during coughing), intraalveolar pressure may exceed 100 mmHg, whereas during obstructed inspiration, it may be reduced to as low as −90 mmHg. During the first few breaths of life, a newborn can attain an intraalveolar pressure from −40 to −60 mmHg as the fluid-filled lungs are first aerated. In conditions of low lung compliance, more work is required to expand the lung, and the transpulmonary pressure rises (greater difference between intrapleural and intraalveolar pressure required to increase the lung volume).

Resistance to Breathing

In addition to the static elastic recoil of the lung, frictional resistance of lung tissues and resistance to airflow opposes inflation of the lung. Rheologic characteristics of airflow affect its ability to pass through conducting airways. Laminar flow is an orderly movement, where molecules are moving along a generally straight path. In laminar flow, the gas in the center of the stream moves faster than that closer to the wall because frictional resistance slows molecules near the vessel wall. Laminar flow is characterized by lower pressure than turbulent flow. During turbulent flow, resistance greatly increases because molecules move in various directions. The rheologic calculation of Reynolds number predicts when flow of a fluid (or gas) will be laminar or turbulent. Reynolds number (Re) is calculated as follows:

$$Re = \rho v d/\eta$$

where v = velocity of fluid flow, d = diameter of the vessel, p = density of the fluid, and η = viscosity of the fluid. This version of the formula would apply to flow through a tube (such as the airways). In open systems, *length* is substituted for diameter. When the inertial forces of density, velocity of flow, and diameter increase, Reynolds number increases. Increasing viscosity of the fluid reduces the product. Products up to 2000 predict laminar flow; above 4000 predict turbulent flow, and a transitional area exists when results are between those numbers.

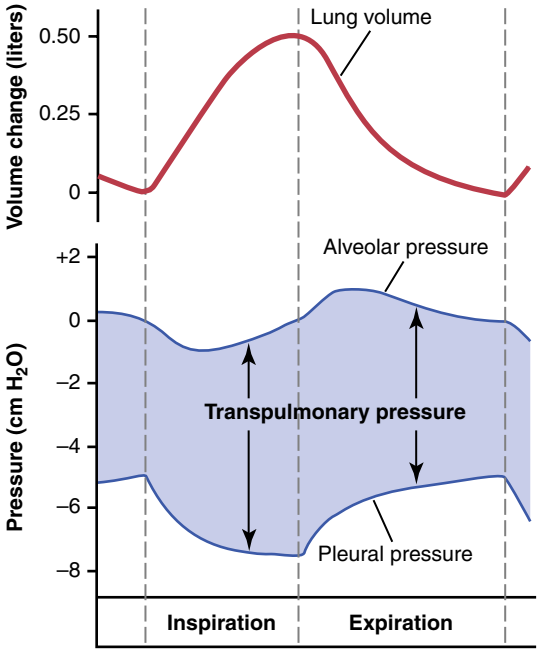

FIGURE **26-3** Alveolar, pleural, and transpulmonary pressures. (From Hall JE. *Guyton and Hall Textbook of Medical Physiology.* 12th ed. Philadelphia: Saunders; 2011:466.)

Throughout the airways, both laminar and turbulent flows occur. True laminar flow occurs in smaller airways, where the diameter is small and linear velocity is very low. Linear velocity is inversely proportional to cross-sectional area for any flow rate. Turbulence is greatest in large airways, and turbulence caused by branching of the airways produces the breath sounds heard on auscultation. Resistance to laminar flow follows Poiseuille's law ($R = 8\eta l/r^4$, where η equals viscosity). Resistance (R) to laminar airflow is directly proportional to the length (l) of the tube and inversely proportional to the fourth power of the radius (r). Therefore doubling the radius of the tube decreases resistance 16 (2^4) times. Normally, about 40% of the total airway resistance resides in the upper airways (nasal cavity, pharynx, and larynx).

Although resistance to airflow is greatest in individual small airways, the net total resistance to airflow of the small airways is very low because they represent a massive number of parallel pathways. Under normal circumstances, the greatest resistance to airflow resides in medium-sized bronchi, whose smooth muscle tone greatly affects airway resistance. During lung inflation, increasing lung volumes exert retractive forces on the airways, resulting in a reduction in airway resistance. During forced expiration, dynamic compression of the airways increases airway resistance and may promote airway collapse (most likely in small airways with no cartilaginous support).

The clinical application of these concepts resides in strategies to reduce airflow resistance. Bronchodilators will reduce resistance to airflow by increasing the radius of the pathway, as predicted by Poiseuille. Selection of an endotracheal tube size may confer greater or lesser resistance, based on the length and (much more significantly) the internal diameter of the tube. Clinical application of Reynolds number suggests that lower velocity (lower inspiratory flow or lower inspiratory:expiratory ratio) and lower density would promote laminar flow and create lower ventilating

TABLE 26-4 Glossary for Static Lung Volumes and Capacities

Measurement	Symbol	Definition	Capacity (mL)
Volumes			
Residual volume	RV	Volume of air remaining in the lungs after maximum expiration	1200
Expiratory reserve volume	ERV	Maximum volume of air expired from the resting end-expiratory level	1100
Tidal volume	V_T	Volume of air inspired or expired with each breath during quiet breathing	500
Inspiratory reserve volume	IRV	Maximum volume of air inspired from the resting end-inspiratory level	3000
Capacities			
Inspiratory capacity	IC = IRV + V_T	Maximum volume of air inspired from the end-expiratory level (the sum of IRV and V_T)	3500
Vital capacity	VC = IRV + V_T + ERV	Maximum volume of air expired from the maximum inspiratory level	4500
Functional residual capacity	FRC = RV + ERV	Volume of air remaining in the lungs at the end-expiratory level (the sum of RV and ERV)	2300
Total lung capacity	TLC = IRV + V_T + ERV + RV	Volume of air in the lungs after maximum inspiration (the sum of all volume compartments)	5800

pressures. The reduction in density is the conceptual basis for combining helium with oxygen ("heliox") to improve pulmonary gas distribution in obstructive lung disease.[14]

Other influences on airflow include the autonomic nervous system and pathologic conditions. The autonomic nervous system affects the tone of the bronchial smooth muscle. The sympathetic nervous system, as well as sympathomimetic drugs (e.g., norepinephrine, epinephrine, and isoproterenol), produce bronchodilation. The parasympathetic nerves and parasympathomimetic drugs (e.g., acetylcholine) cause bronchoconstriction. Parasympatholytic drugs (e.g., atropine and ipratropium) therefore cause bronchodilation (though mildly). Irritation of the airway by foreign bodies or inhaled irritants causes reflex bronchoconstriction.

Lung Volumes

The following discussion of lung volumes uses the parameters of a normal 70-kg male. Table 26-4 gives an overview of related terms and normal values. The amount of gas that enters and leaves the body with each eupneic breath is approximately 350 to 500 mL and represents the *tidal volume* (V_T). The *minute volume* (MV) equals V_T multiplied by the respiratory rate. However, because some ventilation occupies the conducting zone, only a portion of the minute ventilation ($\dot{V}_E$) participates in gas exchange. The amount of *alveolar* ventilation in a minute equals V_T minus anatomic dead space (the volume of the conducting airways, which is approximately 2 mL per kg of body weight) multiplied by the ventilatory rate. The rate of alveolar ventilation will be indirectly proportional to the arterial CO_2 tension. The residual volume (RV) is the volume of gas left in the lung after a maximal exhalation (approximately 1.5 L). The RV cannot be removed from the lungs voluntarily and is important because it is a component of the functional residual capacity, which represents alveolar gas used for oxygenation of the blood between breaths or in periods of apnea. The expiratory reserve volume is the volume of gas expelled from the lungs during a maximal forced exhalation, starting at the end of a normal tidal exhalation. The inspiratory reserve volume is the volume of gas inhaled into the lungs during a maximal forced inhalation, starting at the end of a normal tidal inspiration (2.5 L).

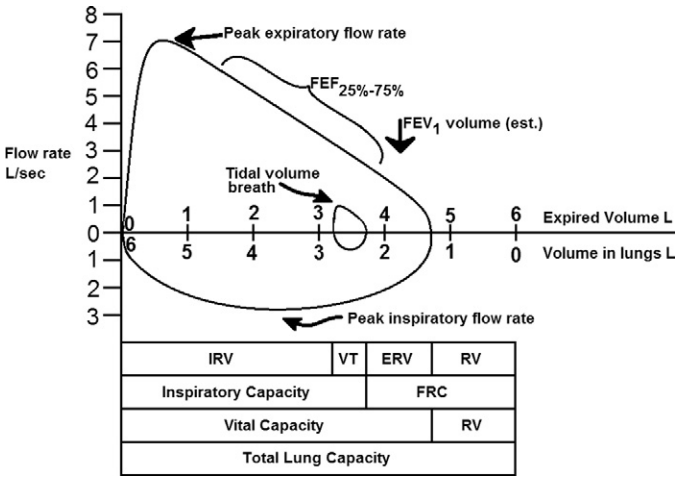

FIGURE **26-4** Pulmonary flow-volume loop indicating key pulmonary function test measurements and static lung volume divisions.

The sum of the four basic lung volumes is the total lung capacity (TLC). Several types of lung capacity measures exist, each of which is the sum of two or more lung volumes. TLC is the volume of air in the lungs after a maximal inspiratory effort (approximately 6 L in a 70-kg adult). The vital capacity is the amount of air that can be forcibly exhaled from the lungs after a maximal inspiratory effort (approximately 4.5 L). The functional residual capacity (FRC) is the volume of gas contained in the lungs after normal quiet expiration. It is the sum of the RV and expiratory reserve volume (approximately 3 L). The inspiratory capacity is the volume of air inhaled into the lungs during a maximal inspiratory effort that begins at FRC (approximately 3 L). Figure 26-4 gives a graphic representation of lung volumes and normal flow measurements.

Closing volume describes the phenomenon during exhalation when small airways collapse, hindering further emptying of lung units distal to them. Closing volume is defined as the volume above residual volume where small airways close, whereas closing capacity describes the absolute volume of gas in the lung

when small airways close (the closing capacity is the sum of the closing volume plus the residual volume). The closing volume increases from approximately 30% of the TLC at age 20 years to approximately 55% at age 70 years. Certain conditions increase the closing volume, such as supine positioning, pregnancy, obesity, COPD, congestive heart failure, and aging.[15] In abnormal conditions, if the closing volume exceeds the FRC, airway closure occurs during tidal breathing, resulting in poorly ventilated or unventilated alveoli and intrapulmonary shunting. The shearing forces of repetitive airway opening and closing also leads to airway injury.[16] Measurement of closing volume analyzing washout characteristics of inert gas is a more sensitive indicator of small airway disease (such as from smoking) than is measurement of spirometry.[15]

GAS EXCHANGE IN THE LUNGS

Dead Space

Dead space refers to ventilation that does not participate in gas exchange. The volume of the conducting airways represents the *anatomic dead space* and normally equals approximately 2 mL/kg of body weight. Alveoli that are ventilated but not perfused comprise the *alveolar dead space* because they do not deliver oxygen nor do they remove CO_2 from the blood. The sum of the anatomic dead space plus the alveolar dead space is the physiologic dead space (V_D). Because perfused ventilation equilibrates with arteriolar CO_2 and nonperfused (dead space) ventilation does not, the proportion of dead space ventilation can be calculated by comparing the ratio of CO_2 in the arterial blood and in the exhaled gas. This is calculated with the Bohr equation:

$$\%\,V_D = (Paco_2 - Peco_2) / Paco_2$$

where $Paco_2$ is the arterial partial pressure of CO_2 as determined from arterial blood gas (ABG) measurement, and $Peco_2$ is the Pco_2 of mixed expired gas as determined with a capnogram. Certain pathologic conditions, such as pulmonary embolus, increase the alveolar dead space and can abruptly decrease the end-tidal CO_2 levels monitored with capnography.

Regional Distribution of Alveolar Ventilation

Gravity and other factors influence ventilation and perfusion such that both are unevenly distributed throughout the lungs. In the normal upright lung, the alveoli at the base are more compliant than those at the apex, meaning that those at the base exhibit a greater change in volume with each breath. This is considered to be a result of the effect of gravity on the interconnected parenchyma of the lung, whereby the greatest "pull" is exerted on the more superior portions of lung. Therefore, the alveoli in those areas are held in a more open state even at rest, whereas alveoli at the base are more compressed. During inspiration then, the alveoli at the bases are able to accept more new gas (Figure 26-5). Alterations to the resting volume or impingements on lung compliance may change this relationship. Pregnancy or obesity may hinder expansion of lower units or may cause compression that results in collapsed dependent areas. In that case, other lung areas become the most compliant. The sigmoidal shape of the compliance curve (see Figure 26-2) reveals that alveoli become less compliant at higher volumes (e.g., in nondependent alveoli at high lung volume) and also at very low volumes (e.g., in dependent alveoli at very low resting lung volumes).

Alveolar Oxygen and Carbon Dioxide Levels

The levels of O_2 and CO_2 in alveolar gas are determined by several factors. These include the amount of alveolar ventilation, the inspired concentrations of O_2 and CO_2, the flow of mixed venous blood to the lungs, and the body's consumption of O_2 and production of CO_2. In a person spontaneously breathing room air, each breath brings approximately 350 mL of fresh air (21% of which is O_2) into the alveoli, which already contain over 2 L of gas (the FRC). Each exhalation removes approximately 350 mL of gas consisting of 5% to 6% CO_2. Every minute, approximately 250 mL of O_2 diffuse from the alveoli into the pulmonary capillary blood, whereas approximately 200 mL of CO_2 diffuse from the pulmonary capillary blood into the alveoli. The ratio of the amount of CO_2 produced to the quantity of O_2 consumed is called the *respiratory quotient* (RQ = 200 mL CO_2 produced divided by 250 mL O_2 consumed = 0.8). The proportion of CO_2 production and O_2 consumption varies with energy source (greater with more carbohydrates and lower with more fat), but 0.8 is the typical result from a mixed diet.

Approximately 21% of dry atmospheric air is O_2; therefore, at the standard barometric pressure of 760 mmHg, Po_2atm equals 0.21 × 760 mmHg, or 160 mmHg. Only 0.04% of atmospheric air is CO_2, so Pco_2atm = 0.3 mm Hg. As the inspired air passes through the upper airways, it is heated to body temperature and humidified to a relative humidity of nearly 100%. The partial

FIGURE **26-5** Concept of gravity effect on regional alveolar compliance. A suspended helical coil demonstrates compression of lower coils and extension of upper coils at rest, such that upon expansion (as in inflation of the lung), lower units undergo greater change in volume.

pressure of water vapor at body temperature is a fairly constant 47 mmHg. The P_{O_2} of inspired air (P_{IO_2}) saturated with water vapor at standard atmospheric pressure = 0.21 × (760 mmHg − 47 mmHg), or 149 mmHg.

The inspired gas mixes with the gas already in the alveoli (FRC) and rapidly equilibrates with the pulmonary capillary blood. The alveolar P_{O_2} (P_{AO_2}) can be calculated with the alveolar air equation:

$$P_{AO_2} = P_{IO_2} - (P_{ACO_2} / RQ)$$

Thus during the breathing of atmospheric air, when P_{ACO_2} is 40 mmHg and the RQ is 0.8, then P_{AO_2} = (0.21 × [760 mmHg − 47 mmHg]) − 40 mmHg/0.8 = 99 mmHg. Therefore, using the alveolar air equation, one can calculate the P_{AO_2} if the atmospheric pressure, inspired O_2 concentration, and P_{ACO_2} (which is approximately equal both to the end-tidal P_{CO_2} and the arterial P_{CO_2} [Pa_{CO_2}]) are known, because water vapor pressure and RQ are fairly constant. If the inspired O_2 concentration differs from that of room air, then that fraction replaces the 0.21. P_{AO_2} is less than P_{IO_2} because the CO_2 is delivered to the alveoli by the pulmonary blood flow at the same time that O_2 is taken up from the alveoli. Therefore P_{ACO_2} divided by the RQ approximates the amount of O_2 that was removed from the alveoli by the pulmonary capillary blood flow.

Effects of Alveolar Ventilation on Carbon Dioxide and Oxygen

Within certain limits P_{ACO_2} is inversely proportional to alveolar ventilation. If alveolar ventilation is doubled, then P_{ACO_2} and Pa_{CO_2} are reduced by half (if CO_2 production remains unchanged).

As alveolar ventilation increases, P_{AO_2} also increases slightly. However, doubling alveolar ventilation does not double P_{AO_2}; according to the alveolar air equation, reduction of the P_{ACO_2} raises the P_{AO_2}, bringing P_{AO_2} closer to the P_{IO_2}.

PULMONARY BLOOD FLOW

The lungs have a dual blood supply: (1) the bronchial arteries (usually one on the right and two on the left), and (2) the pulmonary arteries, which bring unoxygenated blood to the lungs from the right ventricle. The bronchial arteries arise from the descending aorta and carry approximately 2% of the cardiac output to nourish the nonrespiratory tissues: lung parenchyma, bronchi, nerves, pulmonary vessels, and visceral pleura. Bronchial arteries do not participate in fresh gas exchange with the alveoli. The branches of the bronchial arteries accompany the bronchial divisions as far as the respiratory bronchioles. The bronchial veins return deoxygenated blood from the first part of the bronchi and drain into the azygos, hemiazygos, or posterior intercostal veins. The remainder of the deoxygenated blood is returned by the pulmonary veins.

The pulmonary circulation provides blood flow to the structures distal to the terminal bronchioles, including distal nonrespiratory tissues and the respiratory units. The pulmonary artery arises from the right ventricle and branches into the right and left pulmonary arteries, which further branch to accompany the bronchi. Although the pulmonary artery carries the entire cardiac output of the right ventricle, its walls are less muscular and more distensible that those of the aorta, and the pulmonary artery pressure is considerably less than the pressure in the aorta. The pulmonary arteries rapidly subdivide into terminal branches, which have thinner walls, much less smooth muscle, and greater internal diameters than corresponding branches of the systemic arterial tree. Pulmonary vessels are also much shorter than systemic vessels, and according to Poiseuille's law, a decrease in length decreases resistance. Subsequently, pulmonary vascular resistance is very low, being approximately one-eighth of systemic vascular resistance.

Pulmonary vascular resistance is fairly evenly distributed among the arteries, capillaries, and veins, whereas most of the resistance in the systemic circulation is in the muscular arteries. Although pulmonary venous resistance is very low, it can decrease further when blood flow increases. This is because of passive changes in resistance caused by recruitment and distensibility of the pulmonary vessels. *Recruitment* is the opening to perfusion of pulmonary vessels that were previously not perfused. *Distensibility* is an increase in diameter of a pulmonary vessel that is already being perfused, and it results from the vessel's compliance.

The sympathetic nervous system has some influence on pulmonary vascular resistance, as do certain substances circulating in the pulmonary blood. Pulmonary vascular resistance is increased by norepinephrine, serotonin, histamine, hypoxia, endothelin, leukotriene, thromboxane, prostaglandin (e.g., $PGF_2\alpha$), and hypercapnia.[17] It is decreased by prostacyclin analogs (e.g., epoprostenol), endothelin receptor antagonists (e.g., bosentan), phosphodiesterase type 5 inhibitors (e.g., sildenafil),[18] acetylcholine,[19] and isoproterenol (minimal effect).[20] Short-term or limited-use medications to reduce pulmonary vascular resistance include inhaled nitric oxide, calcium channel blockers (e.g., amlodipine), and adenosine.[18]

The respiratory units are the site of gas exchange between alveolar air and the pulmonary capillary blood. After participating in gas exchange in the respiratory zone, blood is returned to the heart by way of the pulmonary veins. The pulmonary vessels also anastomose with the bronchial vessels at the junction of the terminal and respiratory bronchioles. Therefore, the pulmonary veins carry oxygenated blood from the respiratory units and deoxygenated blood from the visceral pleura and distal bronchi. The venous bronchopulmonary anastomoses are significant in their contribution to the normal anatomic shunt (the addition of unoxygenated blood to the left chambers of the heart). Evidence of this crossover is observed during complete cardiopulmonary bypass: blood enters the left atrium, even though all blood is shunted from the right heart by the venous cannula. This is because blood flow continues through the bronchial vessels, which anastomose with the pulmonary veins, which in turn ultimately drain into the left atrium—one reason a ventricular drain may be inserted during the surgery to prevent overdistention of the heart. Five pulmonary veins ultimately return blood to the left heart.

Influences on Pulmonary Blood Flow

Although pulmonary vessels have less muscular content than systemic arteries, the low pressure of the system makes pulmonary blood flow very sensitive to small changes in arterial tone. Unlike the systemic circulation, where hemodynamic influences are more global, pulmonary blood flow is more prevalently regulated locally by changes in oxygen and carbon dioxide tension. In contrast to the systemic circulation, high oxygen tension and hypocapnea vasodilates pulmonary vessels (which helps those vessels pick up more oxygen), whereas hypercarbia and acidosis cause vasoconstriction. Having the strongest influence on pulmonary local regulation, blood flow to hypoxic or atelectatic alveoli is actively diverted at a precapillary site by a process known as *hypoxic pulmonary vasoconstriction*. This decreases blood flow away from focal diseased areas of the lung and improves matching of ventilation and perfusion. See Chapter 27 for a discussion of the significance of hypoxic pulmonary vasoconstriction during pulmonary surgery.

Relationship of Pulmonary Blood Flow and Ventilation

In the normal upright lung, a greater portion of the blood flow is distributed to the dependent regions because of the effects of hydrostatic pressure and greater distention of dependent pulmonary vessels. Likewise, differences in compliance of the ventilating tissue also result in a general increase in the proportion of ventilation from nondependent (least ventilation) to dependent (most ventilation) of the lungs. There are two caveats to these rules. Although they fit the spontaneously breathing patient fairly well, the spatial distribution of these relationships are altered during positive-pressure ventilation. Also, the lung zones are commonly portrayed in textbooks in nicely demarcated lines of latitude, a model appreciated for its simple elegance.

Although there may be a general increase in perfusion from top to bottom of the lung, it should be noted that gravity alone does not determine physiologic perfusion. If it did, then it would be observed that the greatest blood flow in the body would be in the lower extremities, with the least in the head, a cogent point of explanation offered by Levitzki.[21] Gravity interacts with elastic forces to influence ventilation and with vessel recruitment to alter distribution of perfusion. There is evidence that regional perfusion zones may be situated with the greatest blood flow in the lower, core areas of the lungs, with zones 2 and 1 more resembling concentric spheres radiating toward the periphery.[22] Nonetheless, the classic explanation of ventilation-perfusion zones described by West in 1964 serves as a useful model for considering the relationships between ventilation and perfusion,[23] and more specifically, the conditions under which intraalveolar pressure may impede vascular flow.[24] In this model, regions of the lung are considered in zones, according to the relative intravascular and intraalveolar pressure (Figure 26-6).

In the parts of the lung where alveoli exist at a greater resting volume, alveolar pressure can exceed pulmonary artery pressure (PAP), so that perfusion is impeded. This is called *zone 1* and represents alveolar dead space because the region is ventilated but not perfused. Normally, zone 1 exists only in a very small margin of lung area around the apical border during spontaneous ventilation, but the use of PEEP or high airway pressures during mechanical ventilation can create or expand this zone.

The intermediate zone, where there is a variable relationship between vascular and alveolar pressure, is *zone 2*. A point is described in zone 2 along the continuum of decreasing intraalveolar pressure where arterial pressure exceeds alveolar. Below that point, flow is solely dependent upon arterial flow, and unrelated to alveolar or venous pressure. This concept is described as a waterfall zone, as when rising water finally overflows a dam. At that point, the height of the dam does not influence the flow, only the upstream inflow does. The zone 2 relationship is not static, but fluctuation in alveolar pressure related to respiration can variably occlude capillary flow.

The dependent portion of the lung, where both pulmonary arterial and venous pressures exceed alveolar pressure, is known as *zone 3*. This zone represents continuous blood flow, and it is in this zone that the tip of a pulmonary artery catheter should lie, for example, to ensure continuous communication with the left heart. Alveoli in this zone rest at a lower volume than in zone 1, and so they have greater compliance and represent the greatest proportion of ventilation in the lung; however, the perfusion is also greatest here, and so there is no obstruction to blood flow. West later described a fourth zone in the most dependent portions of lung, wherein extravascular pressure from mechanical compression or interstitial fluid compresses the vessels and occludes their flow.[25]

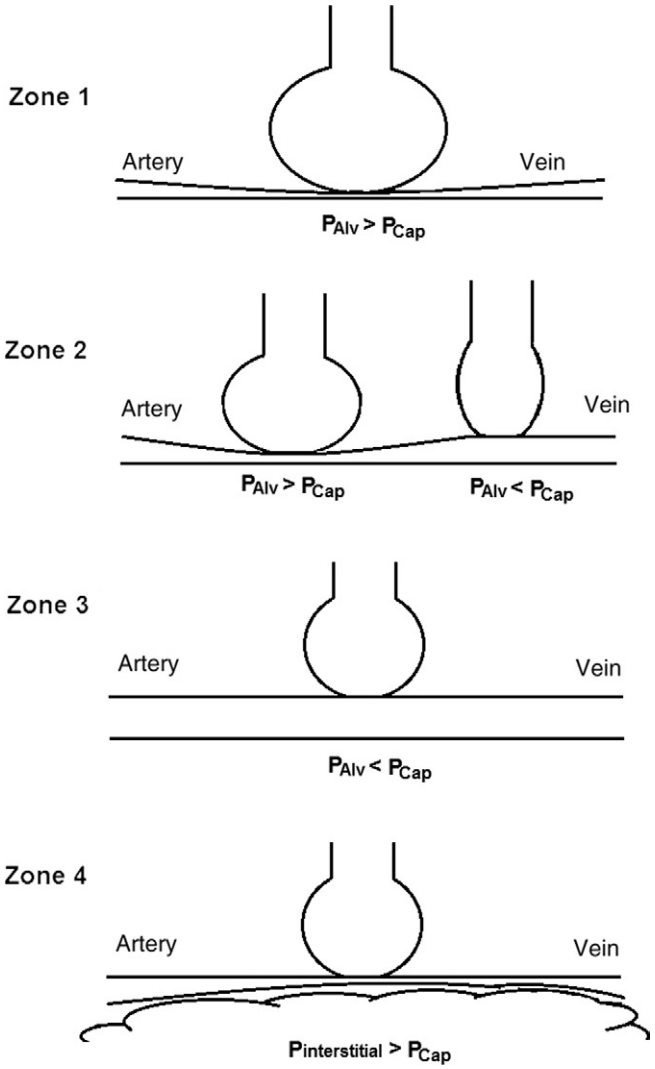

FIGURE **26-6** Ventilation-perfusion relationships described as the "Zones of West." *Zone 1*, Gravity induces low perfusion pressure in capillary and larger resting volume of alveoli, owing to traction from parenchyma below. Alveolar air pressure is greater than capillary pressure, causing high $\dot{V}/\dot{Q}$ dead-space effect. *Zone 2*, Systolic capillary pressure rises higher than alveolar air pressure, but diastolic capillary pressure falls below alveolar air pressure. Blood flow is intermittent, depending on the relationship of both throughout the respiratory cycle. *Zone 3*, Capillary pressure is highest because of hydrostatic gradient. Alveoli are relatively compressed by weight of parenchyma above and therefore have highest compliance. Ventilation and perfusion are both greatest in this zone, although not perfectly matched. *Zone 4*, Interstitial fluid or mechanical compression creates extravascular pressure which creates a high $\dot{V}/\dot{Q}$ area in the most dependent portion of lung. P_{Alv}, Alveolar pressure; *PCap*, pulmonary capillary pressure.

Pulmonary Edema

The normal distance for diffusion from the alveolar air space into the pulmonary capillary blood cells is less than 1 micrometer. The gas must traverse the surfactant layer, the flat alveolar type I cells, the interstitial space, the endothelial cells that make up the wall of the pulmonary capillary, a minute amount of plasma, and then finally the membrane of the red blood cell. The pulmonary system is designed to allow free passage of gases across this series of structures, collectively called the *respiratory membrane*. However, that inherent "leakiness" does predispose this area to unintended movement of fluid.

BOX 26-4

Management of Pulmonary Edema

- Correct underlying cause
- Support oxygenation with supplemental O_2, CPAP, mechanical ventilation, and PEEP, as necessary
- Consider steroids to stabilize capillary membranes
- For cardiogenic pulmonary edema:
  - Administer diuretics
  - Improve hemodynamics—morphine or nitroglycerin to reduce preload; inotropes or vasodilators to promote forward flow

CPAP, Continuous positive airway pressure; *PEEP,* positive end-expiratory pressure.

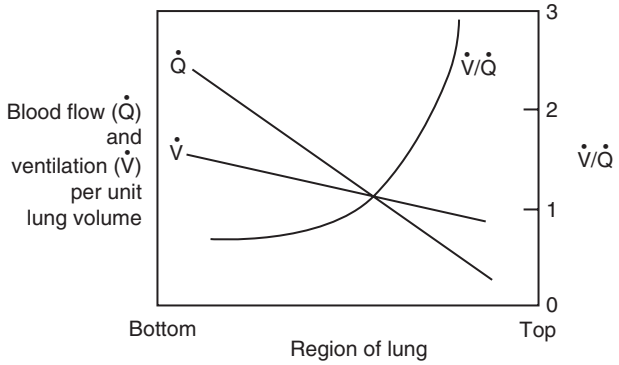

FIGURE **26-7** Ventilation-perfusion relationships throughout the lung.

There is a fine balance between the plasma colloid oncotic pressure, which tends to hold fluid in the pulmonary capillaries, and the capillary hydrostatic pressure, interstitial fluid colloid oncotic pressure, and negative interstitial fluid pressure, which all tend to favor fluid movement into the interstitial space. In normal circumstances, the net of these forces favors movement into the interstitium, helping to divert fluid from the adjacent "leaky" capillaries away from the alveoli and thereby prevent accumulation there.[26] Although the interstitium has a large compliance for removing accumulating transudated fluid, derangements in the factors above can lead to fluid accumulation in the interstitium or alveoli and disrupt gas exchange.

Pulmonary vascular congestion causes increased capillary leakage into the interstitium, which can increase the distance for gas diffusion. If the capillary leak overcomes the compliance of the interstitial space, the fluid may then begin to pass into the alveoli. Pulmonary edema affects oxygenation more than CO_2 excretion because CO_2 is 20 times more diffusible than O_2. Many conditions can result in pulmonary edema. The high capillary pressures associated with heart failure or the excessive administration of intravenous fluids can increase lung water content. The size of the pulmonary capillary pores can be increased by sepsis, smoke inhalation, and other toxic conditions. Brain trauma can produce an intense sympathetic discharge, resulting in neurogenic pulmonary edema.

A condition that occasionally occurs during emergence from anesthesia is postobstructive pulmonary edema, also referred to as *negative-pressure pulmonary edema* (NPPE). After extubation, if the patient experiences laryngospasm and then attempts forceful inhalation against the closed glottis, the drastic decrease in intrathoracic pressure pulls fluid from the pulmonary capillaries. The onset of pulmonary edema is rapid and relatively easy to treat. The symptoms resolve rapidly; in most cases, patients are discharged within 24 hours. Treatment includes removing the precipitating condition (relieving airway obstruction) and general supportive measures: oxygen, maintenance of a patent airway, noninvasive continuous positive airway pressure (CPAP), and intubation with PEEP if required to maintain oxygenation. Unlike pulmonary edema related to fluid overload, NPPE does not call for diuretic therapy. However, many reported cases do include the use of controversial treatments of diuretics and corticosteroids.[27] The three mainstays of treatment remain treatment of the precipitating condition, normalization of ventilation and oxygenation, and reduction of lung congestion and fluid. Treatment summary is in Box 26-4.

Ventilation-Perfusion Relationships in the Lung

Normally, ventilation ($\dot{V}$) is approximately 4 L/min, whereas pulmonary blood flow ($\dot{Q}$) is approximately 5 L/min. Therefore, the ventilation-perfusion ratio ($\dot{V}/\dot{Q}$) for the whole lung is 0.8. However, $\dot{V}$ and $\dot{Q}$ must be matched at the alveolar-capillary level for gas exchange to occur in the lung.

Dependent portions of the lung receive relatively more blood flow than nondependent portions because of the effects of gravity and vessel recruitment and distensibility. Additionally, ventilation goes to the more compliant portions of the lung. Normally at FRC, the dependent regions of the lung are more compliant, and the alveoli of the nondependent portions are more inflated ("tented open") and less compliant. Therefore, relatively more ventilation and perfusion go to the dependent portions, and this results in optimal gas exchange.

Although distribution of ventilation normally decreases moving from dependent to nondependent regions of the lung, the accompanying decrease in perfusion is even greater; therefore the ratio, $\dot{V}/\dot{Q}$, increases as measured progressively from dependent to nondependent lung areas (Figure 26-7). Also, $\dot{V}/\dot{Q}$ varies: in alveoli that are ventilated but not perfused, $\dot{Q}$ equals 0, so $\dot{V}/\dot{Q}$ equals infinity (i.e., dead space); in alveoli that are perfused but not ventilated, $\dot{V}$ equals 0, so $\dot{V}/\dot{Q}$ equals 0 (i.e., a shunt). Similarly, alveoli that are ventilated but poorly perfused are described as "deadspace-like," whereas alveoli that are perfused but poorly ventilated are termed *shuntlike*; the latter contribute to the $\dot{V}/\dot{Q}$ mismatch of the lung. Shuntlike alveoli (low $\dot{V}/\dot{Q}$) have relatively low P_{O_2} and high P_{CO_2} when compared with deadspace-like alveoli (high $\dot{V}/\dot{Q}$), which have relatively high P_{O_2} and low P_{CO_2}.

$\dot{V}/\dot{Q}$ mismatch can result from a number of causes. A pulmonary embolus of thrombus, air, or other material that passes through the pulmonary artery to obstruct blood flow through the pulmonary capillaries creates alveolar dead space. Likewise, very high airway pressure from aggressive ventilation or PEEP can produce alveoli that are ventilated but not perfused. Similarly, very low cardiac output (CO) results in low pulmonary blood flow and therefore increases the $\dot{V}/\dot{Q}$ ratio. This is reflected by a low end-tidal CO_2 on capnography and a wide gradient between the end-tidal and the arterial P_{CO_2}.

Total pulmonary venous admixture (unoxygenated blood delivered to the left side of the heart) is the sum of the shunt and shuntlike states. It can be calculated with the shunt equation, which is discussed later. Bronchopulmonary anastomoses are a cause of normal anatomic shunt, along with thebesian veins, which drain into the left side of the heart and usually account for less than 2% of the CO. Airway obstruction, alveolar collapse (atelectasis), and alveolar filling processes, such as pneumonia, also produce shunt.

Some diagnostic studies can definitively identify ventilation-perfusion abnormalities. A lung scan after a single breath of xenon 133 (^{133}Xe) gas or aerosolized technetium-99m can be used to

determine the location of poorly ventilated areas in the lung, whereas IV injection of dissolved radioisotope reveals areas of the lung that are poorly perfused. Together, these comprise a ventilation-perfusion scan. Pulmonary angiography (radiography with injection of IV contrast dye) of the pulmonary vasculature can be used to demonstrate whether any pulmonary blood vessels are obstructed, such as in pulmonary embolism.

Effects of General Anesthesia on Respiratory Physiology

General anesthesia affects the matching of ventilation and perfusion in several ways. Changing position from upright to supine and induction of general anesthesia produce a significant decrease in the FRC (see Chapter 27). With positive-pressure ventilation, the distribution of ventilation becomes more uniform throughout the lung, so both the dependent and nondependent alveoli receive about the same amount of ventilation. This leads to a wider scatter of ventilation and perfusion because there is relatively more ventilation of underperfused alveoli. General anesthesia usually also causes a significant decrease in the CO, which is exacerbated by positive-pressure ventilation, especially if it is accompanied by PEEP. This may promote an extension of zone 1 areas, although this theoretic effect is probably overstated. Atelectasis is a common finding with general anesthesia and is the main cause of the 10% shunt commonly observed in patients under anesthesia.[26]

Although hypoxic pulmonary vasoconstriction is partially effective in diverting blood flow away from poorly ventilated lung regions, most inhaled anesthetics (as well as potent vasodilators, such as nitroprusside and nitroglycerin) decrease the effectiveness of hypoxic pulmonary vasoconstriction, whereas most intravenous anesthetics do not. The inhibition of hypoxic pulmonary vasoconstriction contributes to the decrease in Pa_{O_2} and the increase in the alveolar-arterial P_{O_2} difference usually seen when volatile inhaled anesthetic agents are used in significant concentrations.

Although general anesthesia, particularly when administered in combination with muscle relaxants, tends to increase chest-wall compliance, the decrease in FRC actually produces a large decrease in the compliance of the respiratory system. Laryngoscopy and endotracheal intubation can increase airway resistance by stimulating airway irritant receptors, thereby decreasing dynamic compliance. However, most inhaled anesthetics (except for nitrous oxide [N_2O]) act as bronchodilators. Also, general anesthesia depresses the ventilatory response to CO_2, metabolic acidosis, and hypoxia (as discussed later in this chapter).[28]

Oxygen and Carbon Dioxide Exchange

As blood flows through the lungs, the mean pulmonary transit time is approximately 4 to 5 seconds, with the blood spending approximately 0.75 second in the pulmonary capillaries. However in the normal lung, it takes only one third of this, or 0.25 second, for equilibration to occur between the alveolar air and the pulmonary capillary blood. During exercise, CO may be so greatly increased that the time a blood cell spends in a pulmonary capillary can be reduced to 0.25 second. This decreased time available for diffusion has a much greater effect on exchange of O_2 than on that of CO_2 because CO_2 diffuses approximately 20-fold times more rapidly than O_2 does. *Diffusivity* is defined as the solubility divided by the square root of the molecular weight. CO_2 is a slightly heavier molecule than O_2, but it is 24-fold as soluble in body fluids as O_2.[4]

Oxygen Transport

The blood carries O_2 in two ways: (1) physically dissolved in the plasma, and (2) bound to hemoglobin (Hgb) in the red blood cells.

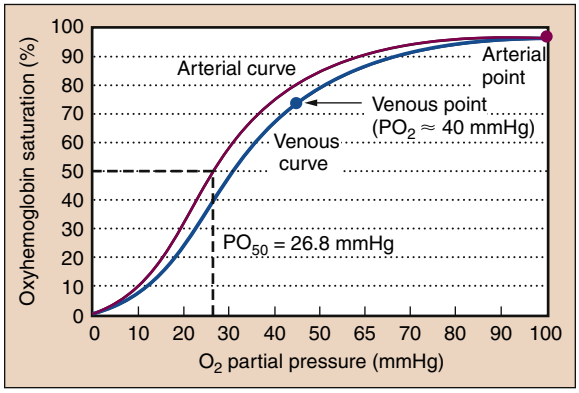

FIGURE **26-8** Oxyhemoglobin dissociation curve. *Dotted line* indicates P_{50}, the measure used to quantify any shift in the curve. (From Miller RD, Pardo Jr MC. *Basics of Anesthesia*. 6th ed. Philadelphia: Saunders; 2011:56.)

Normally 99.7% of the O_2 carried is bound to hemoglobin. Without adequate hemoglobin, the cardiovascular system could not transport sufficient O_2 to meet the metabolic demands of the tissues.

The solubility coefficient of oxygen in plasma is 0.003, so there is 0.003 mL of O_2 per every 1 mmHg partial pressure of P_{O_2} dissolved in 100 mL of whole blood. Therefore, with a Pa_{O_2} of 100 mmHg, only 0.3 mL of O_2 is transported dissolved per deciliter of plasma. Each gram of hemoglobin can combine with 1.39 mL of oxygen; however, because of factors that contaminate this process (such as the presence of methemoglobin), a factor of 1.36 is applied in clinical calculations. Therefore, if the level of hemoglobin is 10 g/100 mL, then at 100% saturation, 1.36 mL of O_2 is bound to hemoglobin per 100 mL of blood. Note that a hemoglobin level of 10 g/100 mL of blood corresponds to a hematocrit of 30%—the hematocrit is normally approximately equal to the hemoglobin level multiplied by 3.

The normal hematocrit for a male is approximately 45% (Hgb 15 g/dL) and for a female is approximately 39% (Hgb 13 g/dL). Centrifugation of the blood in a capillary tube separates the cells from the plasma. A thin layer called the *buffy coat* separates the plasma and the red blood cells (erythrocytes). This thin layer (approximately 1% of the volume of the blood) consists of white blood cells and platelets.[4]

Oxyhemoglobin Dissociation Curve

The affinity of hemoglobin for oxygen fluctuates with various conditions in the physiologic milieu. This unique characteristic means that hemoglobin can more efficiently carry oxygen, because in the lung it can bind much more oxygen than simple diffusion would allow, and it can readily unload that oxygen for delivery in the tissues. The affinity is described by the relationship between the saturation of hemoglobin at a given P_{O_2} in the plasma and is represented by the oxyhemoglobin ($HgbO_2$) dissociation curve (Figure 26-8). This relationship between P_{O_2} and $HgbO_2$ is described by a sigmoidal curve that is steep at lower P_{O_2} values and nearly flat when the P_{O_2} is greater than 70 mmHg. As the P_{O_2} of the plasma increases, the amount of O_2 bound to the hemoglobin also increases, but not in a linear manner. This is because each of the four hemoglobin subunits combines with O_2, and each combination facilitates the next. Similarly, when the O_2 is being unloaded at the peripheral tissues, each dissociation facilitates the next. Therefore, this S-shaped curve is extremely important physiologically. Interaction between O_2 and hemoglobin is also influenced by pH, P_{CO_2}, temperature, and 2,3-diphosphoglycerate (a metabolite of glucose hydrolysis) levels.

The changing affinity of hemoglobin for O_2 facilitates loading at the pulmonary capillaries and unloading of the O_2 at the peripheral tissues. The S-shaped $HgbO_2$ dissociation curve is displaced to the left of the normal curve by hypocapnea, a decrease in temperature, alkalosis, and a decrease in 2,3-diphosphoglycerate levels, resulting in an increased affinity of the hemoglobin for O_2 (a higher saturation for a given P_{O_2}). When exposed to increased temperature, hypercapnia, acidosis, and elevated 2,3-diphosphoglycerate levels, the affinity of hemoglobin for O_2 decreases. This results in a shift of the $HgbO_2$ dissociation curve to the right, and therefore the O_2 is given up to the tissues. Note that the conditions that favor the release of O_2 from the hemoglobin to the tissues are likely to be associated with increased tissue metabolism, which would increase the O_2 demand of the tissues. The influence of pH and P_{CO_2} on the $HgbO_2$ dissociation curve is referred as the *Bohr effect*. The position of the oxyhemoglobin curve can be quantified by the P_{50}. The P_{50} is the Pa_{O_2} at which 50% of the hemoglobin is saturated. Under normal conditions, adult human blood has a P_{50} of 26 to 27 mmHg. If the $HgbO_2$ dissociation curve shifts to the right, the P_{50} increases; if it shifts to the left, the P_{50} decreases.

Other factors that affect O_2 transport include carbon monoxide poisoning and methemoglobinemia. Carbon monoxide binds to hemoglobin (forming carboxyhemoglobin) with 210 times the affinity of O_2.[29] The carbon monoxide binds with hemoglobin at the site that O_2 would occupy, making the carboxyhemoglobin unable to transport O_2. Without a multiple-channel oximeter, carboxyhemoglobin provides a misleadingly high reading because it interprets the hemoglobin as being "saturated," without distinguishing the inability of the hemogloibn to unload its cargo.

Methemoglobin is hemoglobin with its iron in the ferric state (Fe^{3+}) instead of the normal ferrous state (Fe^{2+}). In the ferric state, the hemoglobin iron atoms do not combine with O_2. Methemoglobinemia can be caused by nitrate poisoning (nitroglycerin overdose) or toxic reactions to oxidant drugs, such as the local anesthetic prilocaine. Methemoglobinemia is treated with O_2 therapy and methylene blue at a dose of 1 to 2 mg/kg intravenously over 5 minutes.[30]

Oxygen Content Calculations

Hemoglobin saturation is continuously monitored in anesthetized patients, but the saturation provides only a relative value; 100% saturation of a hemoglobin level that is one half of normal represents the same amount of oxygen as a 50% saturation of the normal amount of hemoglobin. Absolute values for the amount of O_2 in arterial blood are yielded by the O_2 content equation:

$$Ca_{O_2} = (1.36 \times Hgb \times \%\ \text{arterial Hgb saturation}) + (Pa_{O_2} \times 0.003)$$

where Ca_{O_2} is the arterial O_2 content, and Pa_{O_2} and percent of Hgb saturation are obtained from ABG analysis. Ca_{O_2} is normally approximately 20 mL of O_2 per 100 mL of arterial blood (when hemoglobin is 15 g/dL and Pa_{O_2} greater than 90 mmHg).

The amount of O_2 in mixed venous blood is calculated with the following equation:

$$C\bar{v}o_2 = (1.36 \times Hgb \times \%\ \text{mixed venous Hgb saturation}) + (P\bar{v}o_2 \times 0.003)$$

where $C\bar{v}_{O_2}$ is the mixed venous O_2 content, and $P\bar{v}_{O_2}$ and percent of hemoglobin saturation are obtained from mixed venous blood gas analysis of blood drawn from the distal lumen of a pulmonary artery catheter (the only site in the body with truly mixed venous blood). $C\bar{v}_{O_2}$ is normally about 15 mL of O_2 per 100 mL of mixed venous blood when hemoglobin is 15 g/dL and $P\bar{v}_{O_2}$ is 40 mmHg.

Subtraction of $C\bar{v}_{O_2}$ from Ca_{O_2} yields the arteriovenous O_2 content difference. This difference is useful in determining the relationship between O_2 delivery to the body's tissues and the O_2 demand of the tissues. Normally the difference is approximately 5 mL/dL of blood. A difference greater than 5 mL/dL of blood can be associated with low CO because the blood takes longer to traverse the capillaries in the tissues; therefore, more O_2 is extracted. A difference of less than 5 mL/dL of blood can be associated with systemic arteriovenous shunts, which allow blood to bypass the tissue capillaries; such shunts occur during hyperdynamic sepsis.

The amount of O_2 in pulmonary capillary blood is calculated with the following equation:

$$Cpco_2 = (1.36 \times Hgb \times \%\ \text{pulmonary capillary Hgb saturation}) + (Ppco_2 \times 0.003)$$

where $Cpco_2$ is the pulmonary capillary O_2 content. $Ppco_2$ (partial pressure of oxygen in the pulmonary capillary) is derived from the alveolar air equation described earlier in this chapter; the assumption is made that pulmonary capillary blood equilibrates completely with the partial pressure of oxygen in the alveolar air. The pulmonary capillary oxygen saturation cannot be measured, but is estimated by plotting the $Ppco_2$ on the oxyhemoglobin dissociation curve and determining the corresponding hemoglobin saturation. $Cpco_2$ is normally approximately 21 mL of O_2 per 100 mL of pulmonary capillary blood (when Hgb is 15 g/dL and $Ppco_2$ is 99 mmHg).

The Ca_{O_2}, $C\dot{V}_{O_2}$, and $Cpco_2$ are used in the shunt equation:

$$\dot{Q}S / \dot{Q}T = (Cpco_2 - Ca_{O_2}) / (Cpco_2 - C\bar{v}o_2)$$

In this equation, $\dot{Q}S$ is the shunt blood flow, $\dot{Q}T$ is the total blood flow (CO), $Cpco_2$ is the pulmonary capillary O_2 content, Ca_{O_2} is the arterial O_2 content, and $C\bar{v}_{O_2}$ is the mixed venous O_2 content.[28] The shunt equation estimates the fraction of cardiac output that perfuses alveoli that are absolutely nonventilated. In actuality, the shunt calculation represents the sum effects of countless lung units of varying ($\dot{V}/\dot{Q}$) relationships throughout the lung; however, the calculation is useful to monitor trends in oxygenation, help diagnose the cause of observed hypoxemia, and guide alveolar recruitment maneuvers, such as PEEP. The proof of this equation is illustrated in Figure 26-9 and lies in the assumption that if there were no shunt (Figure 26-9, *A*), all arterial blood would have been fully oxygenated in the alveolar capillaries. Therefore, ($Cpco_2 = Ca_{O_2}$), and the numerator of the equation would be zero, thus so would its quotient. On the other hand, with a theoretic 100% shunt (Figure 26-9, *B*), no blood would become oxygenated and thus ($C\bar{v}_{O_2} = Ca_{O_2}$); the difference of each from $Cpco_2$ would be the same, and the number divided by itself would equal 1.0, denoting 100% shunt. Figure 26-9, *C*, illustrates a theoretic 50% shunt, where the Ca_{O_2} equilibrates between the $Cpco_2$ and the $C\bar{v}_{O_2}$, so its difference from the $Cpco_2$ is twice that from the $C\bar{v}_{O_2}$, denoting a 0.5 shunt fraction.

One characteristic of the existence of a significant shunt proportion is hypoxemia unresponsive to supplemental oxygen administration. When blood is passing through the lungs unoxygenated, no increase in Fi_{O_2} delivered to other regions can overcome the hypoxemia (Figure 26-10). This is because under normal circumstances, those normal lung regions are already achieving 100% saturation of the hemoglobin. Therefore they cannot overcompensate for the venous admixture contributed by the shunt areas. In assessing hypoxemia, once hypoventilation and low inspired oxygen are ruled out, improvement in PaO_2 in response to supplemental oxygen favors $\dot{V}/\dot{Q}$ mismatch, as opposed to true shunt or possibly a diffusion disorder (the latter of which can be identified through a test of diffusing capacity of carbon monoxide in the lung [DLCO]).

Transport of Carbon Dioxide

The blood carries CO_2 in three forms: (1) in physical solution, (2) chemically combined with the amino acids of blood proteins, and (3) as bicarbonate ions. Approximately 5% to 10% of the total CO_2 transported in the blood is carried in physical solution. Chemical combination of CO_2 with the terminal amine groups of blood proteins forms carbamino compounds. The reaction occurs rapidly and does not require enzymes. Carbamino compounds constitute another 5% to 10% of the blood's total CO_2 content. The remaining 80% to 90% of the CO_2 in the blood is carried as bicarbonate. In the presence of carbonic anhydrase, CO_2 combines with water to form carbonic acid. The carbonic acid can dissociate into a bicarbonate ion and hydrogen (H^+) according to the following chemical reaction:

$$CO_2 + H_2O \xrightarrow{\text{carbonic anhydrase}} H_2CO_3 \rightarrow H^+ + HCO_3^-$$

When HCO_3^- leaves the blood cells, chloride ions enter to maintain electrical neutrality (the so-called "chloride shift" or "hamburger shift").[31]

Carbon Dioxide Dissociation Curve

As expected, decreases in the P_{aCO_2} correspond to a decrease in the total CO_2 content of the blood. This is because of corresponding decreases in the levels of bicarbonate and carbamino compounds. When the P_{aCO_2} falls, the amount of the total CO_2 decrease is affected by the presence of O_2 in the blood. When blood contains mainly oxygenated hemoglobin, the CO_2 dissociation curve shifts to the right, reducing the blood's capacity to hold CO_2. When the blood contains mostly deoxyhemoglobin, the curve shifts to the left, increasing the capacity to carry CO_2. This effect is known as the *Haldane effect*, and it allows the blood to load more CO_2 at the tissue level, where more deoxyhemoglobin is present, and to unload CO_2 at the lung, where more $HgbO_2$ is present (Figure 26-11).

The fact that deoxyhemoglobin is a weaker acid than $HgbO_2$ accounts for the Bohr and Haldane effects. Deoxyhemoglobin more readily accepts the H^+ produced by the dissociation of carbonic acid. This permits more CO_2 to be carried in the form of bicarbonate ions (Haldane effect). Conversely, the association of H^+ with the amino acids of hemoglobin lowers the affinity of hemoglobin for O_2, shifting the $HgbO_2$ dissociation curve to the right at low pH or high P_{CO_2} (Bohr effect).[28]

ACID-BASE BALANCE

The respiratory system plays an important role in maintaining a normal pH balance in the body. It works along with the kidneys and the buffer systems to balance the acids and bases of the blood and other body tissues, allowing them to function normally. Hydrogen ions interact with negatively charged regions of other molecules, such as proteins, altering their structural conformation and in doing so altering their behavior. Besides affecting the $HgbO_2$ dissociation curve, blood pH alters the activity of various

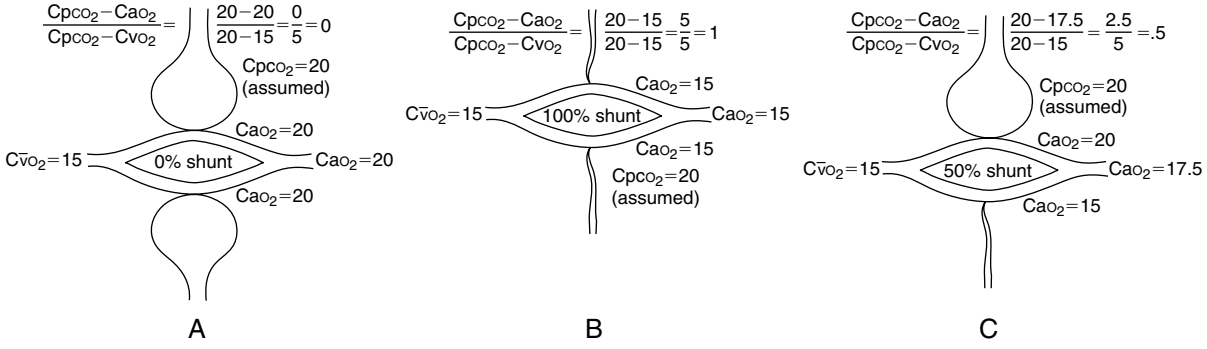

FIGURE **26-9** Calculation of the shunt fraction for various theoretic conditions. **A,** No shunt; **B,** complete shunt; **C,** 50% shunt.

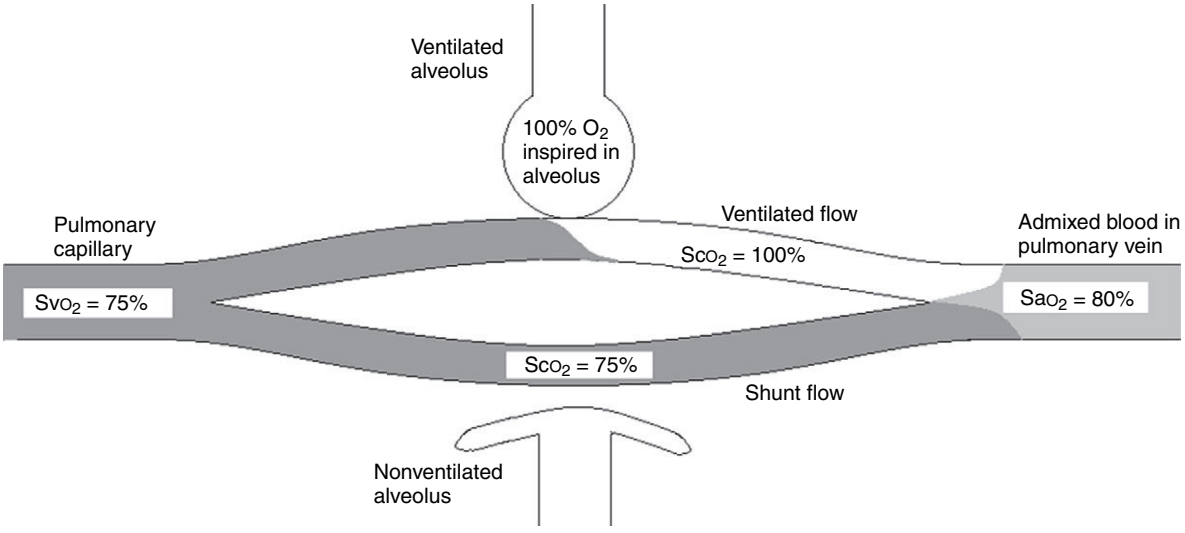

FIGURE **26-10** True shunt; unresponsiveness to supplemental oxygen. Sa_{O_2}, arterial oxygen saturation; Sc_{O_2}, capillary oxygen saturation; Sv_{O_2}, venous oxygen saturation.

enzymes, thereby changing metabolic functions in all body tissues. Severe metabolic acidosis that results from prolonged cardiopulmonary arrest must be treated with sodium bicarbonate because protein-receptor sensitivity and other enzymatic functions must be restored before epinephrine can be effective in resuscitation.

Metabolism of substances ingested as food produces mainly acidic metabolic waste products. Under normal conditions, a tremendous amount of the acid produced daily can be removed from the body by the respiratory system as exhaled CO_2. The acidic products are known as *volatile acids* because they can be converted from carbonic acid into CO_2 gas that is exhaled. Through exhalation of CO_2, the lung eliminates over 10,000 mEq/day of carbonic acid. A much smaller amount of nonvolatile or fixed acids also is produced during normal metabolic breakdown of food at the rate of approximately 100 mEq/day; these acids are primarily removed by the kidneys.[28]

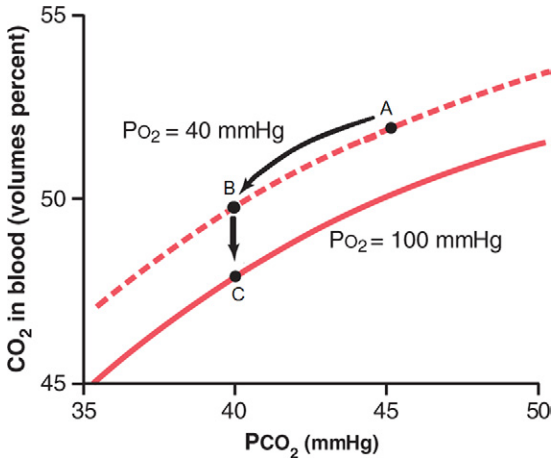

FIGURE **26-11** Carbon dioxide dissociation curve demonstrating the Haldane effect. At a P_{aCO_2} of 45 mmHg in the tissues (Point A), 52 vol% of carbon dioxide are carried in blood (including all forms). Upon entering the lungs, the drop in P_{aCO_2} would be from 52 to 50 vol% (*A-B*). However, in the presence of high oxygen concentration, CO_2 dissociation from hemoglobin is enhanced by the Haldane effect, doubling the drop in P_{CO_2} (Point *B* to Point C) to 48 vol%. (Modified from Hall JE. *Guyton and Hall Textbook of Medical Physiology.* 12th ed. Philadelphia: Saunders; 2011, p. 504.)

In addition to the efforts of the respiratory system and kidneys to regulate pH levels, buffers in the human body maintain pH in the physiologic range. The buffers consist mainly of bicarbonate, phosphate, and proteins. A buffer is a mixture of substances that usually consists of a weak acid and its conjugate base. When a strong acid or base is added to a buffer system, the changes in H^+ concentration are much smaller than those that would occur if the same amount of acid or base were added to pure water or another nonbuffered solution.

Interpretation of Arterial Blood Gases

Analysis of ABGs can provide useful information concerning the relationship of acid production and acid removal by the lungs and kidneys. Acid-base disturbances can be categorized into four major groups: respiratory acidosis, metabolic acidosis, respiratory alkalosis, and metabolic alkalosis.

Although it may seem that a great number of acid-base states are possible, actually only 11 conditions exist (Table 26-5). Blood gases in a normal individual have a pH in the range of 7.35 to 7.45, P_{aCO_2} ranges from 35 to 45 mmHg, and bicarbonate concentration is normally 22 to 26 mEq/L.

Acidosis

Any process that leads to an elevation in P_{aCO_2} tends to lower the arterial pH, resulting in respiratory acidosis. An acute change in P_{aCO_2} of 10 mmHg is associated with a change in pH of 0.08 units. An increase in P_{aCO_2} with a normal bicarbonate level is termed *uncompensated respiratory acidosis*.

TABLE 26-5 Acid-Base States

Physiologic State	pH	P_{aco_2} (mmHg)	HCO_3^- (mEq/L)	Examples
Normal	7.40 ± 0.05	40 ± 5	25 ± 4	
Uncompensated respiratory acidosis	↓↓	↑↑	↔	Acute hypoventilation (opioid overdose)
Uncompensated respiratory alkalosis	↑↑	↓↓	↔	Acute hyperventilation (neurogenic, or pain)
Uncompensated metabolic acidosis	↓↓	↔	↓↓	Metabolic acidosis with controlled mechanical ventilation (respiratory compensations not possible)
Uncompensated metabolic alkalosis	↑↑	↔	↑↑	Metabolic alkalosis with controlled mechanical ventilation
Compensated respiratory acidosis	↓	↑↑	↑↑	Chronic hypoventilation (as in chronic obstructive pulmonary disease)
Compensated respiratory alkalosis	↑	↓↓	↓↓	Chronic hyperventilation (as in chronic increased intracranial pressure)
Compensated metabolic acidosis	↓	↓↓	↓↓	Renal failure or diabetic ketoacidosis
Compensated metabolic alkalosis	↑	↑↑	↑↑	Long-term hypokalemia or bicarbonate ingestion
Mixed respiratory and metabolic acidosis	↓↓↓	↑↑	↓↓	Respiratory and circulatory arrest
Mixed respiratory and metabolic alkalosis	↑↑↑	↓↓	↑↑	"Over-resuscitation" (hyperventilation and excess bicarbonate administration)

Metabolic acidosis should more properly be referred to as *nonrespiratory acidosis* because it does not always involve alterations in metabolism. Causes of this condition include ingestion (poisoning), infusion, production of a fixed acid (lactic acidosis), and decreased excretion of acid by the kidneys. A base change of 10 mEq/L is associated with a pH change of 0.15 unit (in the absence of a change in Pa_{CO_2}). Therefore, if the bicarbonate level increases by 10 mEq/L, then the pH also increases by 0.15 unit. A decrease in bicarbonate level when the P_{CO_2} remains at approximately 40 mmHg is termed *uncompensated metabolic acidosis*. The combination of respiratory acidosis and metabolic acidosis is termed *mixed acidosis* and can produce a drastically decreased arterial pH.

Alkalosis

When alveolar ventilation exceeds that necessary to keep up with CO_2 production in the body, both P_{ACO_2} and Pa_{CO_2} decrease to below 35 mmHg. As the pH rises, this hyperventilation results in respiratory alkalosis. Elevated pH accompanied by a decrease in Pa_{CO_2} in the presence of a normal bicarbonate level is termed *uncompensated respiratory alkalosis*. The relationship between alveolar ventilation and CO_2 production that results in hyperventilation can occur because of an increase in alveolar ventilation or a decrease in CO_2 production, as occurs with hypothyroidism or hypothermia, if alveolar ventilation is maintained at normal levels.

Metabolic alkalosis occurs when fixed acid loss is increased or when the intake of bases is abnormally high. Elevated pH accompanied by above-normal increases in the bicarbonate level when the P_{CO_2} is maintained at approximately 40 mmHg is termed *uncompensated metabolic alkalosis*. The combination of respiratory alkalosis and metabolic alkalosis produces mixed alkalosis, in which the arterial pH is markedly elevated.

Compensatory Mechanisms

The respiratory system can rapidly compensate for metabolic acidosis or alkalosis by altering alveolar ventilation. It normally occurs because changes in blood H^+ concentrations affect the chemoreceptors, which in turn increases or decreases alveolar ventilation, altering Pa_{CO_2} within minutes. The kidneys can compensate for respiratory acidosis and metabolic acidosis of nonrenal origin by excreting fixed acid and retaining bicarbonate. Conversely, the kidneys compensate for respiratory alkalosis or metabolic alkalosis of nonrenal origin by decreasing H^+ excretion and decreasing retention of bicarbonate. Renal compensatory mechanisms act more slowly than do respiratory mechanisms and may take several days. When evaluating blood gas analyses, *compensated acidosis* involves finding abnormalities of both the CO_2 and the HCO_3^- in the same direction, with the pH below 7.4 but above 7.35. Conversely, *compensated alkalosis* involves finding abnormalities of both the CO_2 and the HCO_3^- in the same direction, with a pH above 7.4 but less than 7.45. Ascribing the abnormality to respiratory or metabolic is then based upon which abnormality (CO_2 or HCO_3^-) in their present level would be responsible for the directional change in pH (toward acidosis or alkalosis). In spite of observing a compensatory change in CO_2 or bicarbonate, an acid-base disorder is considered *uncompensated* if that mechanism has not been able to bring the pH back into a normal range. Compensation will not "overshoot" and create a pH disorder in the other direction, because the drive for compensatory mechanisms is diminished as the pH approaches normal. Acid-base disorders wherein the CO_2 and HCO_3^- are both abnormal in different directions (one high, the other low) are termed *mixed acidosis* or *alkalosis*.

Treatment of Blood Gas Abnormalities

For the patient being mechanically ventilated, respiratory acidosis and respiratory alkalosis can be treated with a simple increase or decrease in the amount of alveolar ventilation. Respiratory acidosis should not be treated with sodium bicarbonate, because through the reversible reaction in the equation on p. 607, the bicarbonate dissociates into more CO_2, worsening the acidosis. To restore a stable spontaneous circulation, mild to moderate metabolic acidosis can be treated with hyperventilation and correction of shock. Certain types of severe metabolic acidosis (pH less than 7.20) may be treated with sodium bicarbonate. The total body bicarbonate deficit equals the base deficit (in mEq/L) that is obtained from the blood gas values: the patient's bicarbonate level is subtracted from the normal bicarbonate level; the difference is multiplied by the patient's weight (in kilograms) and then by 0.3 (which is equal to the extracellular fluid compartment and the volume of distribution for bicarbonate). Complete correction of the base deficit is not indicated; only half of the calculated dose of bicarbonate is recommended as an initial dose. Severe lactic acidosis is treated with bicarbonate, but the acidosis associated with renal failure is better treated with dialysis. The hyperosmolarity and high sodium content of bicarbonate are usually contraindicated for patients with renal failure.

CONTROL OF BREATHING

The respiratory centers in the brainstem control breathing by automatically generating a cycle of inspiration and expiration (Figure 26-12). This spontaneously generated cycle can be modified by reflexes or by higher centers in the brain. The respiratory centers affect the nerves of the spinal cord, which innervate the muscles of respiration (the cervical branches of the spinal nerves C3, C4, and C5 form the phrenic nerves, which innervate the diaphragm). The spontaneous respiratory rhythm is generated by the medullary respiratory center, which is found in the reticular formation of the medulla under the floor of the fourth ventricle. The dorsal respiratory group and ventral respiratory group are dense aggregations of respiratory neurons located in the *tractus solitarius*. This area contains projections of cranial nerves IX and X and processes signals related to chemoreceptors, lung stretch receptors, gag and cough reflexes, and others. The dorsal respiratory group is considered the

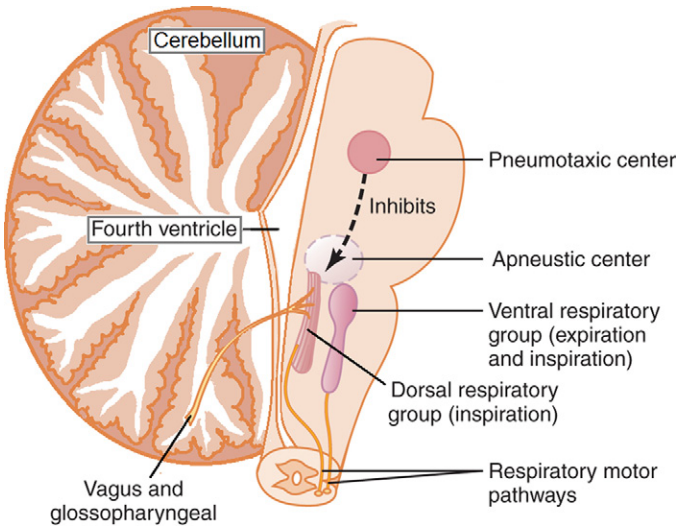

FIGURE **26-12** Organization of the respiratory center. (Adapted from Hall JE. *Guyton and Hall Textbook of Medical Physiology*. 12th ed. Philadelphia: Saunders; 2011:506.)

pacemaker of normal breathing—the area that drives respiration. The ventral respiratory group contains neurons controlling inspiration and expiration, but is quiescent during normal respiration. The pons contains the apneustic center (in the lower pons) and the pneumotaxic center (in the upper pons), both of which modify the output of the medullary respiratory center. The normal function of the apneustic center is unknown, but if it is severed, the result is "apneustic breathing"—prolonged inspiration with occasional expiration. The pneumotaxic center is thought to be the inspiratory "cut-off" switch, which functions to smooth the respiratory pattern.

The activity of the brainstem's breathing centers is modulated by information received from afferent spinal nerves and higher brain centers, as occurs in voluntary control of breathing. Additionally, a great number of sensors in the lungs, cardiovascular system, muscles, tendons, skin, and viscera can affect the control of breathing by eliciting reflex changes. Stimulation of stretch receptors in the lungs can elicit three respiratory reflexes: the Hering-Breuer inflation reflex, the Hering-Breuer deflation reflex, and the paradoxical reflex of Head. The Hering-Breuer inflation reflex may help prevent overdistention of the alveoli at high lung volumes by inhibiting large V_Ts and may decrease the frequency of the inspiratory efforts by causing a transient apnea. The Hering-Breuer deflation reflex may be responsible for the increased ventilation elicited when the lungs are deflated abnormally, such as in pneumothorax, or it may have a role in the periodic spontaneous deep breaths (sighs) that help to prevent atelectasis. The paradoxical reflex of Head results during partial block of the vagus nerves, such that lung inflation results in further deep inspiration instead of the apnea expected when the vagus nerve is fully functional. This reflex may be involved in generating the first breath of the newborn baby.[32]

Chemical or mechanical irritation of the airways may elicit a reflex cough or sneeze, hyperpnea, bronchoconstriction, and increased blood pressure. The vagus nerve provides afferent pathways for all of the airway's irritant receptors, except for the nasal mucosa receptors, which send information centrally by means of the trigeminal and olfactory tracts. Pulmonary embolism (PE) typically causes rapid, shallow breathing, whereas pulmonary vascular congestion causes hyperpnea. The vascular receptors that initiate these responses are named *J receptors* (for "juxtapulmonary capillary"). Stimulation of receptors in the muscles, tendons, and joints can also increase ventilation during exercise. Elevated blood pressure stimulates the arterial (carotid and aortic) baroreceptors, resulting in apnea and bronchodilation. Somatic pain tends to cause hyperpnea, whereas visceral pain usually causes apnea or decreased ventilation. Stimulation of the arterial chemoreceptors by decreased Pa_{O_2}, increased Pa_{CO_2}, or low pH tends to increase lung inflation and cause hyperpnea, bronchoconstriction, and an increase in blood pressure. Table 26-6 summarizes the respiratory control reflexes.

Chemical Control of Breathing

The arterial and cerebrospinal fluid partial pressures of CO_2 are probably the most important inputs to the brainstem centers for establishing the ventilatory rate and V_T. Hypoxemia potentiates the ventilatory response to CO_2. Its effect is that for any particular Pa_{CO_2}, ventilatory response becomes greater as the Pa_{O_2} decreases. Opioids and hypnotic drugs (Figure 26-13) may profoundly depress

TABLE 26-6 Reflex Mechanism of Respiratory Control

Stimulus	Reflex	Receptor	Afferent Pathway	Effects
Lung inflation	Hering-Breuer inflation reflex	Stretch receptors within smooth muscles of large and small airways	Vagus	Respiratory—cessation of inspiratory effort, apnea, or decreased breathing frequency; bronchodilation; Cardiovascular—increased heart rate; slight vasoconstriction
Lung deflation	Hering-Breuer deflation reflex	Possibly J receptors, irritant receptors in lungs, or stretch receptors in airway	Vagus	Respiratory—hyperpnea
Lung inflation	Paradoxical reflex of head	Stretch receptors in lungs	Vagus	Respiratory—inspiration
Negative pressure in upper airway	Pharyngeal dilator reflex	Receptors in nose, mouth, upper airways		Respiratory—contraction of pharyngeal dilator muscles
Mechanical or chemical irritation of airways	Cough	Receptors in upper airways, tracheobronchial tree	Vagus	Respiratory—cough; bronchoconstriction
	Sneeze	Receptors in nasal mucosa	Trigeminal, olfactory	Respiratory—sneeze; bronchoconstriction; Cardiovascular—increased blood pressure
Face immersion	Diving reflex	Receptors in nasal mucosa and face	Trigeminal	Respiratory—apnea; Cardiovascular—decreased heart rate; vasoconstriction
Pulmonary embolism		J receptors in pulmonary vessels	Vagus	Respiratory—apnea or tachypnea
Pulmonary vascular congestion		J receptors in pulmonary vessels	Vagus	Respiratory—tachypnea, possible sensation of dyspnea
Specific chemicals in the pulmonary circulation	Pulmonary chemoreflex	J receptors in pulmonary vessels	Vagus	Respiratory—apnea or tachypnea; bronchoconstriction
Low Pa_{O_2}, high Pa_{CO_2}; low pH	Arterial chemoreceptor reflex	Carotid bodies, aortic bodies	Glossopharyngeal, vagus	Respiratory—hyperpnea; bronchoconstriction, dilation of upper airway; Cardiovascular—decreased heart rate, vasodilation, etc.

TABLE 26-6 Reflex Mechanism of Respiratory Control—cont'd

Stimulus	Reflex	Receptor	Afferent Pathway	Effects
Increased systemic arterial blood pressure	Arterial baroreceptor reflex	Carotid and aortic arch stretch receptors	Glossopharyngeal, vagus	Respiratory—apnea, bronchodilation; Cardiovascular—decreased heart rate, vasodilation
Increased systemic arterial blood pressure		Muscle spindles, tendon, organs, proprioceptors	Various spinal pathways	Respiratory—provide respiratory controller with feedback about work of breathing; stimulation of proprioceptors in joints causes hyperpnea
Somatic pain		Pain receptors	Various spinal pathways	Respiratory—hyperpnea Cardiovascular—increased heart rate, vasoconstriction

Modified from Levitzky MG. *Pulmonary Physiology*. 7th ed. New York: McGraw-Hill; 2007:197-198.

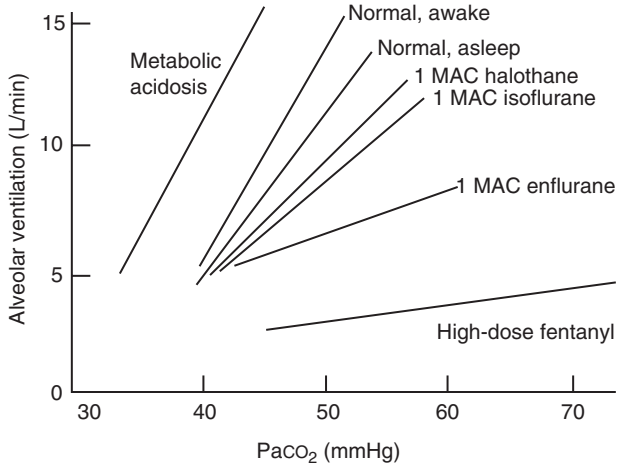

FIGURE **26-13** Carbon dioxide response curve. MAC, Minimum alveolar concentration.

the ventilatory response to CO_2. Chronic obstructive pulmonary disease (COPD) also depresses the ventilatory response to hypercapnia, so the hypoxic drive may be more prominently responsible for maintaining spontaneous breathing in these patients, and administering high FiO_2 may reduce their spontaneous ventilatory drive. Metabolic acidosis shifts the CO_2 curve to the left, so that for any particular PCO_2, ventilation is increased during metabolic acidosis.

A depressed or abnormal response to CO_2 during sleep may be involved in central sleep apnea (characterized by pauses of at least 10 seconds' duration between breaths, with cessation of respiratory effort).[33] Central sleep apnea, which possibly is caused by a defect in the chemoreceptors or brainstem respiratory control center, may be an important contributor to sudden infant death syndrome.

Increased $PaCO_2$ and decreased PaO_2 and arterial pH stimulate the arterial (peripheral) chemoreceptors, with the carotid bodies apparently exerting a much greater influence on the medullary respiratory centers than the aortic bodies. The afferent nerve from the carotid body is Hering's nerve, a branch of the glossopharyngeal nerve. The afferent pathway from the aortic body is the vagus nerve. The central chemoreceptors are in contact with cerebrospinal fluid but are not directly exposed to arterial blood (because of the blood-brain barrier). CO_2 is rapidly diffusible through the blood-brain barrier; therefore, changes in $PaCO_2$ are rapidly transmitted to the cerebrospinal fluid, taking less than 2 minutes. Hydrogen ions and bicarbonate ions are slowly diffusible through the blood-brain barrier, so changes in arterial pH that do not result from changes in PCO_2 take considerably longer to affect the cerebrospinal fluid. The central chemoreceptors are located just beneath the surface of the medulla. They are not stimulated by hypoxia; their activity may even be suppressed by it. The central chemoreceptors are majorly responsible for determining the resting ventilatory level and long-term maintenance of blood CO_2 levels. The central chemoreceptors contribute about two thirds of the ventilatory response, whereas the peripheral chemoreceptors contribute the remaining one third and may be more important in short-term responses to CO_2.[34]

RESPIRATORY SYSTEM PATHOLOGY

OBSTRUCTIVE SLEEP APNEA

Definition

Obstructive sleep apnea (OSA) is a mechanical obstruction to breathing that occurs during sleep, when pharyngeal musculature relaxes. It is characterized by episodes of breathing cessation that last 10 or more seconds. Obesity hypoventilation syndrome (OHS) is a distinct entity from OSA. It is defined as the triad of obesity, daytime hypoventilation, and sleep-disordered breathing without an alternative neuromuscular, mechanical, or metabolic cause.

Incidence and Outcome

OSA occurs in 2% to 4% of the population[35] and affects more than twice as many men as women.[36] Obesity is the most significant precipitating factor, with OSA being noted in 70% of patients presenting for bariatric surgery.[36] OSA is becoming increasingly prevalent in children and bears many of the same characteristics as observed in adults.[37] Between 7% and 10% of children are habitual snorers, and OSA is estimated to exist in 1% to 3% of preschool-aged children.[38] OSA is associated with increased postoperative complications and is an independent risk factor for increased morbidity and mortality.[36]

Etiology and Pathophysiology

The primary causative factor for OSA is obesity, although it can exist in nonobese individuals. Factors in the pharyngeal musculature cause collapse during sleep under negative inspiratory pressure. Chronic hypoxemia and hypercarbia lead to an inflammatory state and a variety of secondary pathologies. OSA has been linked as a causative factor in atherosclerosis, hypertension, stroke, insulin resistance, diabetes, dyslipidemia, and other disorders (Table 26-7).[39,40]

Clinical Features and Diagnosis

Patients with sleep apnea often present with multiple comorbidities related to their obesity or to chronic hypoxemia from the apneic disorder. Common comorbidities include systemic and pulmonary hypertension, ischemic heart disease, and congestive heart failure. A hallmark of OSA is habitual snoring and fragmented sleep, which can lead to daytime somnolence.

Polysomnography (see below) provides an objective measure of sleep apnea, but it is expensive and impractical to apply to every patient with risk factors who presents for surgery. A number of questionnaires such as the Berlin questionnaire have been developed as screening tools for OSA. These provide a low-cost, simple approach to identifying OSA. The components of the STOP questionnaire are as follows: S, snore loudly; T, daytime tiredness; O, observed to stop breathing during sleep; P, high blood pressure. The STOP questionnaire is often paired with four additional variables of the Bang questionnaire: B, body mass greater than 35 kg/m^2; A, age older than 50 years; N, neck circumference greater than 40 cm; G, male gender). Used together, the STOP-Bang questionnaire demonstrates sensitivity of nearly 100% and specificity of approximately 40%.[36] See Chapter 43, Box 43-2.

Polysomnography is used to establish the diagnosis of OSA, which is based upon is the number of abnormal respiratory events per hour of sleep (the apnea plus hypopnea index—AHI). Diagnostic criteria vary among institutions, but an index of greater than 5 if associated with sleep-related symptoms, or an index of greater than 15 alone are diagnostic for the condition.[35] The AHI also describes severity, with AHI greater than 15 being moderate, and AHI greater than 30 being severe.[35]

Treatment

Weight loss is an important goal for the obese patient with OSA. Some surgical procedures are used to relieve the physical obstruction, such as uvulopalatopharyngoplasty in adults and adenotonsillectomy in pediatric patients.[37,41] The use of continuous positive airway pressure (CPAP) devices has become common in the management of OSA. CPAP devices use a facemask held tightly to the face during sleep with a hose attached to the machine that provides positive airway pressure by means of an electrically powered air pump. This pressure tents the airway open, relieves the obstruction, and promotes more continuous breathing and sleep. Adjunctive therapy includes analeptic drugs such as modafinil and armodafinil, methylxanthines, doxapram, serotonin modulators, tricyclic antidepressants, and others. Drug therapy is intended to reduce daytime sleepiness, reduce cardiovascular complications,[42] strengthen pharyngeal musculature, and reduce REM (rapid eye movement) sleep, among other effects.[43]

TABLE 26-7 Comorbidities Associated with OSA

Category	Condition	Prevalence (%)
Cardiac	Treatment-resistant hypertension	63-83
	Congestive heart failure	76
	Ischemic heart disease	38
	Atrial fibrillation	49
	Dysrhythmias	58
Respiratory	Asthma	18
	Pulmonary hypertension	77
Neurologic	First-ever stroke	71-90
Metabolic	Type 2 diabetes mellitus	36
	Metabolic syndrome	50
	Hypothyroidism	45
	Morbid obesity	50-90
Surgical	Bariatric surgery	71
	Intracranial tumor surgery	64
	Epilepsy surgery	33
Others	Gastroesophageal reflux disease	60
	Nocturia	48
	Alcoholism	17
	Primary open-angle glaucoma	20
	Head and neck cancer	76

From Seet E, Chung F. Obstructive sleep apnea: preoperative assessment. *Anesthesiol Clin*. 2010;28(2):199-215.
OSA, Obstructive sleep apnea.

Anesthetic Management

Careful airway evaluation is the first step in management. Redundant tissue in the neck region is common in OSA (even more so than in general obesity) and may impede effective head positioning, mask ventilation, or laryngoscopy. The anesthetist should anticipate airway difficulty and rapid desaturation from reduced FRC. Preoperatively, sedative medications should be used cautiously. As a result of central nervous system sensitization, patients may be hypersensitive to effects of benzodiazepines and opioids. Effective doses may be extremely small. The same concerns apply postoperatively. Extubation must be undertaken carefully, when indications are that the patient will maintain a patent airway. In the recovery area, vigilance must be afforded to the potential for airway obstruction from residual anesthetic effects, which heighten the preexisting sensitivity to respiratory depressant drugs. Airway obstruction occurs in 25% of pediatric patients with OSA after tonsillectomy, in contrast to 1% of those without OSA.[38] Analgesics and general somnolence may lead to airway obstruction in the recovery area. Multimodal analgesia and regional techniques may help limit the need for systemic opioids.

Patients with moderate to severe OSA should be provided with additional monitoring postoperatively. This may include longer postanesthesia care unit (PACU) time, admission to a monitored bed, prolonged Spo_2 (pulse oximetry) monitoring, and disqualification from same-day discharge, depending on the patient condition.[36] CPAP is helpful in the PACU, and patients who use this treatment at home should be encouraged to bring their device for use in the postanesthetic period.

PULMONARY FUNCTION TESTING

An understanding of pulmonary function evaluation will be helpful before discussing pathologies that involve airflow limitations. A number of examinations may be performed to evaluate lung volumes and the inspiratory and expiratory flow of gas. Many of these are derived by having the patient breathe through a closed circuit with measurement of gas flow and composition. Measurement of pulmonary volume over time is called *spirometry*. A glossary of static lung volumes and capacities is presented in Table 26-4. A standard flow-volume loop is drawn in a clockwise direction, with inspiratory flow below the x-axis, and expiratory flow above it. Flow rates (in liters per second) are represented on the y-axis (see Figure 26-4). The zero point on the x-axis represents full inspiration, because the lungs cannot be totally emptied due to the residual volume. In Figure 26-4, the scale below the x-axis provides corresponding approximate absolute values of lung volume. The most important portion of the loop in most cases is the expiratory flow and volume that begins at this point and ends when the loop reaches the x-axis again as it transitions to inspiratory flow.

Values for an individual's flow and volume pattern are measured in absolute terms, and are also compared to "predicted" values based upon performance of healthy subjects with similar anthropometric characteristics (age, gender, and height, and sometimes other factors such as weight and race).

Spirometry is based on a forced air capacity (FVC) maneuver, which requires concerted patient effort; a lack of effort may produce erroneous results.[44] The FVC is divided into several time intervals, of which the FEV_1 (forced expired volume in 1 second) is the most reproducible. The volume of air that is exhaled in 1 second from a maximal inspiration is measured as the FEV_1. Patients with increased airway resistance exhibit decreased FEV_1 and FEV_1/FVC ratios. Normal FEV_1 varies with age, declining as age increases.[45] Normally, the FEV_1 volume is at least 80% of the vital capacity, an important point that is used to differentiate low FEV_1 due to obstruction from low FEV_1 due to restrictive disease (in which later case the vital capacity is also reduced, and the ratio of FEV_1/FVC is preserved).

Respiratory activity represented by the midportion of the expiratory curve is the most effort-independent and the most sensitive indicator of small airway disease. The parameter measured is the $FEF_{25\%-75\%}$ or the forced expiratory flow rate between 25% and 75% of the exhaled breath. The normal $FEF_{25\%-75\%}$ of 4 to 5 L/sec may decrease markedly in those with pulmonary disease, with early changes evident sooner in patients with obstructive disease than in those with restrictive disease. Reduction in the $FEF_{25\%-75\%}$ wherein the curve begins to take a concave shape, usually appears before significant change occurs in the FEV_1.[44] It is not as reproducible as the FEV_1, but it is more sensitive to airway obstruction.[46]

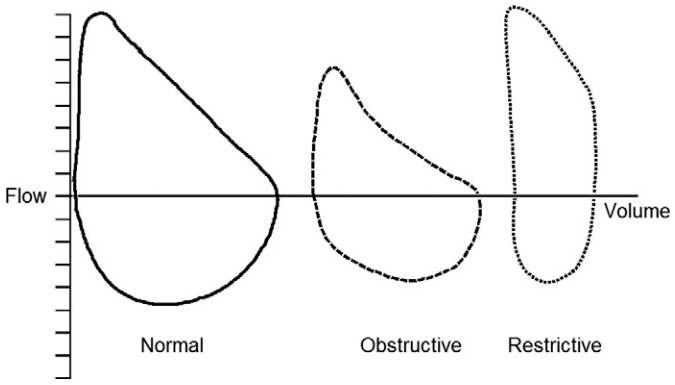

FIGURE **26-14** Flow-volume loops in disease. Characteristic deformities of pulmonary flow-volume loops related to obstructive and restrictive disease.

Flow-volume loops also provide information about disease processes through characteristic shapes (Figure 26-14). Obstructive disease is characterized by a reduced peak flow rate and a sloping of the expiratory limb. This occurs as small airways close during expiration, noticeably reducing the flow rate during expiration. Restrictive disease is characterized by normal or heightened peak expiratory flows, but a very narrow loop, reflecting the reduced vital capacity. Obstructions to airflow also may be variable, as in tracheomalacia, such that changes in pressure may both augment and reverse the obstruction in the course of each respiratory cycle. In this case, the location of the lesion (being intrathoracic or extrathoracic) determines whether the obstruction will be opened or compressed by inspiration or expiration (Figure 26-15). Airway obstructions lead to characteristic patterns on a flow-volume tracing, as well (Figure 26-16).

The diffusion capacity (DL) is another form of pulmonary function testing that assesses the ability of gas to traverse the alveolar-capillary membrane. Factors related to Fick's law of diffusion correlate the diffusion capacity to clinical conditions; that is, thickness of the membrane (fibrosis) and surface area for diffusion (emphysema). The diffusion capacity is also influenced by ventilation-perfusion matching. The DL test is commonly performed by having the patient inhale a single breath containing a small amount of carbon monoxide. Carbon monoxide is highly diffusible and binds avidly with hemoglobin, so that any reduction in transfer to the blood is indicative of loss of surface area of the alveolar-capillary membrane.[46] The diffusion capacity for carbon monoxide (DLCO) is reported as the uptake of CO in mL/min/mmHg or as a percentage of predicted value.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

The American Thoracic Society and European Respiratory Society define chronic obstructive pulmonary disease (COPD) as a "preventable and treatable disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases…"[47] COPD should be considered in any patient with ongoing cough, sputum production, or dyspnea with history of exposure to risk factors. Diagnosis is made by spirometric demonstration of airflow obstruction that is not fully reversible (post-bronchodilator FEV_1/FVC ratio less than 0.7).[48]

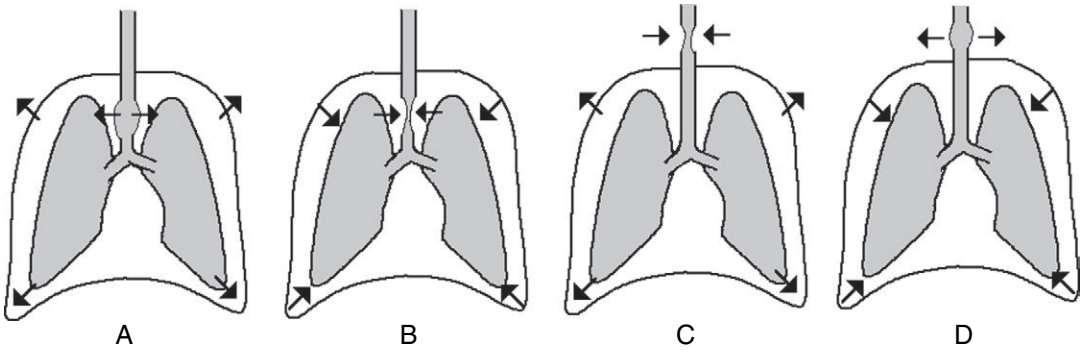

FIGURE **26-15** Variable airway obstructions during spontaneous respiration. A variable intrathoracic obstruction will be subjected to negative pressure during inspiration and will be tented open (**A**); however, as intrathoracic pressure rises during expiration, an intrathoracic obstruction will be compressed (**B**). A variable extrathoracic obstruction will be subjected to negative intratracheal pressure during inspiration and will be compressed (**C**); however, as intratracheal pressure rises during expiration, the extrathoracic obstruction will be pushed open (**D**).

The terms *chronic obstructive pulmonary disease* and *chronic obstructive lung disease* are widely used as synonyms for pathology involving airflow obstruction that does not change over months to years. COPD is caused by a mixture of small airways disease and parenchymal destruction in various combinations and proportions from one individual to the next. Two specific disorders, emphysema and chronic bronchitis, provide the prototypes of pathologic changes in COPD. Emphysema is characterized by the destruction of parenchyma that leads to loss of surface area, elastic recoil, and structural support to maintain airway patency. Bronchitis is characterized by narrowing of small airways by inflammation and mucous production. There are also numerous chronic conditions referred to collectively as *peripheral airways disease* or *small airways disease*. These entities are not mutually exclusive; peripheral airway disease often precedes onset of emphysema, and chronic bronchitis and emphysematous changes often coexist to define COPD. As a rule, COPD is observed most often in individuals with an extensive history of smoking, and the disease process takes 30 years or longer to manifest. Other chronic diseases such as cystic fibrosis, tuberculosis, and bronchiectasis are not included in the definition of COPD,[47] nor are restrictive diseases of scoliosis, other forms of pulmonary fibrosis, or obesity. Differential diagnosis of COPD compared with other common lung disorders is noted in Table 26-8.

Definition

Peripheral airways disease involves inflammation of the terminal and respiratory bronchioles, fibrosis and narrowing of the airway walls, and goblet cell metaplasia.[49] A small sampling of conditions that are characterized as small airways disease includes sarcoidosis, Wegener granulomatosis, mineral dust–associated airways disease, disease from exposure to fumes and toxins, and bronchocentric granulomatosis.[50] Chronic bronchitis refers to chronic or recurrent excess mucous secretion occurring on most days for at least 3 months of the year for at least 2 successive years.[49] A critical element is the presence of airway obstruction of expiratory airflow. Emphysema is defined as "a condition of the lung characterized by abnormal permanent enlargement of the air spaces distal to the terminal bronchiole, accompanied by destruction of their walls and without obvious fibrosis."[49] Destroyed alveolar tissue is largely incapable of regeneration, and therefore the changes that occur in emphysema are irreversible. Emphysema is subclassified as centrilobular, or panlobular. In centrilobular emphysema, dilation predominantly affects the respiratory bronchioles in the upper lung lobes. In panlobular emphysema, tissue destruction is widespread, affecting all areas of the acinus (the cells that define the "berry-bunch" shape of the alveoli) and distributed throughout the lung.[44] Destruction of tissue in emphysema leads to four primary alterations in pulmonary function: (1) increases in size of acini causes compression of adjacent small airways and increases airflow resistance; (2) consolidation of alveoli leads to loss of alveolar surface area and impairs gas diffusion; (3) heterogeneity of disease in different parts of the lungs leads to mismatch of ventilation and perfusion; and (4) loss of alveolar walls also decreases the amount of pulmonary capillaries, resulting in greater work on the right ventricle.[4]

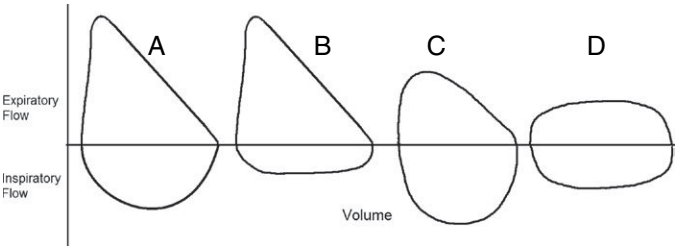

FIGURE **26-16** Flow-volume loops with airway obstructions. The dynamic effects of variable airway obstructions will be reflected in flow-volume loops in comparison to a normal tracing (**A**). An intrathoracic obstruction will be compressed during expiration, thus the expiratory curve will be affected (**B**). An extrathoracic obstruction will be collapsed during inspiration, thus the inspiratory portion of the curve will be affected (**C**). With a fixed obstruction (as in a foreign body in the airway), airflow will be reduced during both phases of breathing, and peak flow rates of inspiration and expiration will be reduced (**D**).

Incidence and Outcome

Chronic obstructive pulmonary disease affects more than 5% of adult Americans and is the third leading cause of death.[48] Chronic bronchitis and emphysema are the most common causes of COPD. The social and economic impacts of COPD are enormous. Patients in advanced stages of obstructive lung diseases are unable to work and frequently cannot participate in activities of daily living. Even in milder cases, activities often are restricted. The economic cost of COPD is estimated to be over $50 billion in the United

TABLE **26-8** Differential Diagnosis of COPD

Diagnosis	Suggestive Features*
COPD	Onset in midlife; symptoms slowly progressive; long-term smoking history; dyspnea during exercise; largely irreversible airflow limitation
Asthma	Onset early in life (often childhood); symptoms vary from day to day; symptoms occur at night or in early morning; allergy, rhinitis, or eczema also present; family history of asthma; largely reversible airflow limitation
Congestive heart failure	Fine basilar crackles on auscultation; chest radiograph shows dilated heart, pulmonary edema; pulmonary function tests indicate volume restriction, not airflow limitation
Bronchiectasis	Large volumes of purulent sputum; commonly associated with bacterial infection; coarse crackles or clubbing on auscultation; chest radiograph or CT scan shows bronchial dilation, bronchial wall thickening
Tuberculosis	Onset at all ages; chest radiograph shows lung infiltrate or nodular lesions; microbiologic confirmation; high local prevalence of tuberculosis, or known exposure
Obliterative bronchiolitis	Onset at younger age, in nonsmokers; may have history of rheumatoid arthritis or fume exposure; CT scan taken on expiration shows hypodense areas
Diffuse panbronchiolitis	Most patients are male and nonsmokers; almost all have chronic sinusitis; chest radiograph and HRCT scan show diffuse small centrilobular nodular opacities and hyperinflation

From Rable KF, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2007;176:532-555.
*These features tend to be characteristic of the respective diseases but do not occur in every case. For example, a person who has never smoked can develop COPD (especially in developing countries, where other risk factors may be more important than cigarette smoking); asthma can develop in adult and even elderly patients.
COPD, Chronic obstructive pulmonary disease; *CT*, computed tomography; *HRCT*, high-resolution computed tomography.

States.[48] Death related to COPD is not only from respiratory failure, but also associated with related comorbidities such as lung cancer and heart disease.[51]

Etiology and Pathophysiology

In general, COPD appears to be an exaggerated inflammatory reaction in the lungs. The principal factor that predisposes a patient to the development of COPD is cigarette smoking.[51] Environmental pollution appears to have some role, but its effects are minor compared with those of cigarette smoking, particularly as the disease occurs in the United States. COPD may develop in some patients because of an imbalance between protease and antiprotease activities in the lungs; α_1-antitrypsin deficiency is the primary genetically related cause. In people with this deficiency, smoking causes release of neutrophil elastase that is inadequately inhibited because of the deficient levels of α_1-antitrypsin. This results in degradation of pulmonary connective tissue and in the early development of COPD.[52] Unfortunately, α_1-antitrypsin administration is expensive and has not demonstrated good results as a treatment.[52,53]

The dominant feature of the natural history of COPD is progressive airflow obstruction, as reflected by a decrease in FEV_1. Three causes of decreases in FEV_1 are as follows: (1) a decrease in the intrinsic size of bronchial lumina; (2) an increase in the collapsibility of bronchial walls (this cause is the most difficult to quantify); and (3) a decrease in elastic recoil of the lungs.[44] Distinct morphologic changes can be found in the airways of patients exposed to ongoing inflammatory challenges. In chronic bronchitis, a proliferation of the compound tracheobronchial mucous glands occurs in the subepithelial layers of the airway wall. Excessive airway mucus and thickened airway walls cause a narrowing of the functional airflow channel. Airway narrowing in COPD is primarily related to a thickening of the airway walls, and not an increase in smooth muscle tone, as is more prominently observed in asthma. Destruction of parenchyma results in a loss of elastic support, which also contributes to airway narrowing.[54] Although COPD is defined as being irreversible, contemporary science is focusing on the limited amount of reversibility that can improve patients' quality of life and slow progression of the disease. Between 25% and 50% of patients with COPD also have enhanced airway reactivity.[55] While bearing similarities to asthmatic bronchial reactivity, it appears that in COPD, airway hyperresponsiveness affects small airways more so than larger ones.[56]

The defense system of a patient with COPD is disrupted by the excessive production of mucus and by paralysis of the mucociliary transport system, which leads to microbial colonization. The presence of microbial organisms in the airway secretions of patients with chronic bronchitis is common and does not necessarily imply the presence of an acute infection. Instead, chronic colonization of the airway plays a cyclic role in the ongoing pathogenesis of COPD, whereby bacteria increase mucous production, reduce ciliary motility, cause influx of neutrophils that lead to fibrosis, alter the host response to cigarette smoke, induce a chronic inflammatory response, and enhance airway reactivity.[57] General changes in lung functioning from COPD include the following:

1. Destruction of lung connective tissue that normally provides elastic pull on the outsides of bronchi and bronchioles reduces the tethering of airways of the pulmonary interstitium, leads to premature collapse of the airways from external pressure, and increases the unevenness of distribution of inspired air to different regions of the lungs. Consequently, the exchange of CO_2 and O_2 between the blood and alveolar air is impeded. Compensation for lower diffusion of gases is partly achieved via collateral ventilation by diffusion across alveolar walls.[58]
2. Injury and inflammation of the bronchial tubes and alveoli increase the resistance to airflow during both inspiration and expiration. More forceful breaths or quicker breaths are needed for maintaining even normal levels of ventilation.[59]
3. Lung compliance increases with the tissue damage, and the airways' narrowing and greater collapsibility impede the ability of the ventilatory muscles to empty the lung completely. Hyperinflation results, raising the resting end-expiratory position of the lungs. Because the lung is more expanded, the inspiratory muscles operate from a shorter initial length and produce less force when shortened.
4. The more horizontally placed diaphragm is less able to lift the rib cage. The diaphragm may contract ineffectively, such that the abdomen moves inward rather than outward with each inspiration.[60]
5. Because of the increased demands for work output placed on the respiratory muscles, the energy requirement of these muscles escalates. A greater proportion of the cardiac output goes to these muscles. If hypoxemia is present and increased ventilation is required (e.g., as in exercise), the energy supply of the muscles may become inadequate, and respiratory muscle fatigue ultimately is produced.[61]
6. The expansion of the lung and thorax also misaligns the intercostal muscles and accessory respiratory muscles. To compensate, patients may assume special postures, such as leaning forward.[62]
7. Inflammation allows noxious agents in the air to reach the more deeply located tissues in the lung and gain access to blood vessels, macrophages, mast cells, and nerves in the lung. Airway irritation increases; as a result, asthmatic episodes occur because the introduction of noxious agents causes the release of spasmogenic agents from tissue cells and nerve endings.[62]

General Gas Exchange Characteristics

The ability of compensatory mechanisms to preserve ventilation and ABG tensions varies. Ventilation usually is very well protected, even more than is gas exchange. CO_2 is 20 times more soluble than O_2 and therefore is more diffusible.[63] Also, if hypercapnia should occur, pulmonary ventilation is stimulated. Minute ventilation ($\dot{V}_E$) in COPD generally is normal to above normal. Usually, P_{aCO_2} does not increase beyond normal levels in COPD until FEV_1 is less than 1 L. In comparison, P_{aO_2} is not appreciably restored by an increase in depth of breathing, and even slight variations in $\dot{V}/\dot{Q}$ ratios in the lung adversely affect oxygenation.[49] O_2 delivery (DO_2) to the tissues is preserved as much as possible by an increase in CO, a greater extraction of O_2 from the blood, polycythemia, or some combination of these three factors. Consequently, respiratory muscle work is greater than normal, and O_2 use by the muscles is increased.

Associated Conditions

Cigarette Smoking

Cigarette smoking has been firmly established as the primary environmental risk factor associated with emphysema and bronchitis.[47] Its pathogenic mechanism is not known. The unchecked protease hypothesis holds that emphysema is caused by damage to elastic fibers because of an imbalance between elastase and antielastase in the lung.[64] Also, evidence that oxidants have a role in lung damage is increasing. The lungs of cigarette smokers are subject to an enhanced oxidant burden. Oxidants are highly reactive electron acceptors capable of removing electrons from a variety of molecules. The process of oxidation may reversibly or irreversibly damage compounds of all chemical classes, including nucleic acids,

proteins and free amino acids, lipids and lipoproteins, and carbohydrates. In this regard, oxidants can damage cells and extracellular matrix components critical for normal lung function. Cigarette smoke and activated lung phagocytes generate an increase in the level of oxidants.[65,66] Additionally, excess sputum production and hyperplasia of the mucous glands of the trachea and large bronchi are linked to cigarette smoking.[65] The risk of COPD is not limited to cigarette smoking; smoking other types of tobacco or marijuana, exposure to secondhand smoke, and even fetal exposure to smoke during pregnancy may predispose to COPD.[67]

Chronic lung hyperinflation results in diaphragmatic flattening, and a reduction in contractile force results, attributable to the Frank-Starling mechanism. Besides this gross effect, oxidative stress leads to loss of contractile proteins (i.e., myosin) and results in a reduction in contractile force.[68]

Peripheral Circulation in Chronic Obstructive Pulmonary Disease

COPD can change the determinants of systemic venous return by altering the mechanical characteristics of either the heart or lungs. When a patient adapts a forced expiratory breathing pattern (e.g., during exercise), positive intrathoracic pressure is generated during expiration. The positive swings in pressure cyclically decrease systemic venous return, leading to an exaggeration of respiratory variation in arterial blood pressure or to pulsus paradoxus.[69] Pulsus paradoxus is present in two thirds of patients with severe COPD, and its severity correlates with the degree of airflow obstruction.[70] Increases in lung volume may directly impede systemic venous return through compression of the vena cava or heart. Normally, inspiration augments systemic venous return because of a decrease in right atrial pressure.[71]

Patients with COPD often have an increase in CO mediated by an increase in catecholamine levels and by a redistribution of blood flow and volume from the high-capacitance splanchnic regions to the lower-capacitance cardiac, cerebral, and muscle regions.[71]

A characteristic enhanced heart rate response also has been identified. Four parameters of airway obstruction (forced vital capacity [FVC], the ratio of FEV_1 to FVC [% FEV_1], the ratio of RV to TLC [RV/TLC], and % RV) have been correlated with the heart rate response to hypoxia. This increased response appears to be the result of an unknown mechanism of diseased lung tissue.[72]

Fluid Retention in Chronic Obstructive Pulmonary Disease. It appears that patients with hypoxic and hypercapnic respiratory failure from emphysema or chronic bronchitis, or from both, have impaired renal function, with reduced renal plasma flow and decreases in glomerular filtration.[73]

Note that cardiac responses to chronic and acute pressure increases are not the same. Chronic pressure overload causes right ventricular hypertrophy, whereas acute pressure changes cause right ventricular dilation.

Other Air Space Abnormalities

Bullae, a manifestation of some forms of emphysema, are air-containing spaces greater than 1 cm in diameter that result from the destruction and dilation of air spaces distal to terminal bronchioles. Bullae have an outer wall consisting of the visceral pleura and an inner wall consisting of tissue derived from confluent alveoli. Bullae can grow to sizes occupying a significant proportion of the hemithorax, in which case they are referred to as "giant."[74] A bulla or bullae that become symptomatic may warrant surgical resection. Similar to bullae, blebs are collections of air within the layers of the visceral pleura. They occur when air migrates from the lung parenchyma, and they usually form near the apices. Because blebs do not involve the acinus, they are not a form of emphysema; however, they do pose the risk of causing pneumothorax.

TABLE 26-9 Clinical Hallmarks of COPD

Assessment	Typical Finding
General appearance	Range from overweight and dusky, to thin, emaciated; pursed-lip breathing; anxious; prominent use of accessory muscles; barrel chest; jugular vein distention; rapid weight loss carries poor prognosis
Cough	Chronic, productive throughout the day (most characteristic with prominent bronchitis)
Dyspnea	Chronic, progressive increase (dyspnea precipitated by decreasing levels of activity)
Breath sounds	Rhonchi, wheezing
Heart sounds	Split S2, pulmonary/tricuspid insufficiency
Radiographic features	Flat diaphragm; areas of increased radiolucency; rapid tapering of vascular markings
Spirometry	Elevated TLC, RV, FRC, RV/TLC ratio; reduced FEV_1, FEV_1/FVC ratio
Echocardiography	Increased pulmonary artery pressure, decreased RV contractility
Blood gas exchange	Reduced DLCO; Hypoxemia (most characteristic of prominent emphysema)

From Qaseem A, et al. Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. *Ann Intern Med.* 2011;155(3):179-91.
COPD, Chronic obstructive pulmonary disease; *DLCO,* carbon monoxide diffusion in the lung; *FEV_1,* forced expiratory volume in 1 sec; *FRC,* functional residual capacity; *FVC,* forced vital capacity; *RV,* residual volume; *TLC,* total lung capacity.

Clinical Features and Diagnosis

The clinical presentation of COPD varies markedly, and crippling changes for one person may be a minor incapacity for another. Chronic productive cough and progressive exercise limitation are the hallmarks of COPD. Other common symptoms are dyspnea and wheezing, but COPD may progress to respiratory failure or cor pulmonale. Key findings in COPD are listed in Table 26-9.

Diagnostic Testing

Pulmonary Function Tests. Spirometry is not recommended as a screening tool, and it has limited benefit in anesthetic risk assessment, in contrast to the cost of performing the procedure.[75] Although the FEV_1 indicates the degree of airflow obstruction, it correlates poorly with symptoms and therefore may not solely indicate the severity of pulmonary disease.[44] Furthermore, severe pulmonary disease will manifest in functional limitations and characteristic physical facies, which will be evident to the anesthetist even in the absence of airflow measurement. Spirometry is most useful to primary care providers in evaluating patients with unexplained dyspnea and in those in whom COPD is suspected. Current evidence-based guidelines note that a smoking history of greater than 40 pack-years is the single best variable for predicting airflow obstruction, and the combination of greater than

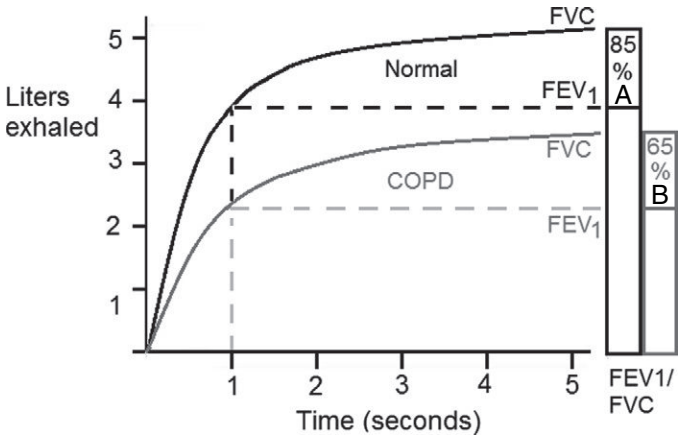

FIGURE **26-17** Schematic diagram of the forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC). The total volume of air exhaled in the first second should be equivalent to at least 80% of the FVC *(A)*. In the presence of obstructive airway disease, the FEV_1 is less than 80% of the FVC *(B)*. (Modified from Miller RD, Pardo Jr MC. *Basics of Anesthesia*. 6th ed. Philadelphia: Saunders; 2011.)

55–pack-year history, wheezing on auscultation, and patient self-reported wheezing almost assures that obstruction (FEV_1/FVC ratio less than 0.7) is present.[48]

Reduction in the FEV_1 is a hallmark of obstructive disease; however, it may also characterize restrictive disease. In severe obstructive lung disease, expiratory flow rates are greatly decreased and the FEV_1/FVC ratio is reduced. The ratio is evaluated in addition to the FEV_1 alone, because in restrictive disease, the FEV_1 is reduced secondary to a reduction in the vital capacity, so the reduction in FEV_1 alone does not indicate expiratory airflow obstruction. A low FEV_1 combined with a normal FEV_1/FVC is indicative of restrictive disease (Figure 26-17). Measurement of lung volumes in obstructive disease demonstrates an increased RV and often an increased FRC. Slowing of expiratory flow and gas trapping behind prematurely closed airways is responsible for the increase in RV. When spirometry is used to grade the severity of COPD (FEV_1/FVC less than 0.7), the post-bronchodilator FEV_1 compared to predicted levels is the primary determinant: FEV_1 ≥ 80% = mild, 50% to 79% = moderate, 30% to 49% = severe, and less than 30% = very severe.[67] The number of exacerbations and hospitalizations per year is also directly correlated with 3-year mortality and can be considered in the evaluation of severity of COPD.[67]

Arterial Blood Gas Analysis. ABG analysis is helpful in determining the severity of gas exchange abnormality and guiding management of patients with COPD. COPD may manifest with retained oxygenation (PaO_2 greater than 60 mmHg, $PaCO_2$ normal) or impaired exchange of oxygen and CO_2 (PaO_2 less than 60 mmHg, $PaCO_2$ greater than 45 mmHg, and presence of cor pulmonale), generally based upon the severity of the disease and the relative contributions of emphysema and chronic bronchitis, respectively. When emphysema predominates, compensatory hyperventilation can maintain oxygenation until the disease is very advanced. Although patients maintain adequate ABG values, they do so at the cost of significantly increased work of breathing, and general muscle wasting occurs. In chronic bronchitis, the alveolar capillary membrane is intact, but excess mucous in the airways impedes gas flow. Chronic hypoxia in the lung causes pulmonary vascular resistance to rise and to increase work on the right ventricle. The patients become polycythemic and hypoxemic. Cyanosis is more common in chronic bronchitis.

Chest Radiography and Computed Tomography. Radiographic abnormalities may be minimal, even in the presence of advanced COPD. Hyperlucency of the lungs (caused by arterial vascular deficiency in the lung periphery) and hyperinflation (flattening of the diaphragm with loss of the silhouette) suggest the diagnosis of emphysema.[4] If bullae also are present, the diagnosis of emphysema is virtually certain; however, only a small percentage of patients who have emphysema have bullae. Computed tomography (CT) can delineate the pulmonary parenchyma much better than standard chest radiography. CT also may be used to quantify the amount of air trapping. Although conventional radiography has 60% to 80% sensitivity to diagnose COPD, CT scanning improves sensitivity to 90%.[46]

Treatment

Treatment of COPD is focused on relieving symptoms and reducing the incidence of exacerbations. There is no treatment to reverse the course of COPD, but smoking cessation can slow the forward progression of the disease. Medical management is aimed at promoting bronchodilation using inhaled β_2-agonists, corticosteroids, or anticholinergics. Although a low baseline level of cholinergic tone normally influences bronchial caliber, cholinergic influence is found to be elevated in COPD, with fluctuations in airway diameter attributable to changes in cholinergic tone.[76] Ideally, anticholinergics that block the M_1 and M_3 receptors would be ideal, because the M_2 acts in negative feedback to reduce acetylcholine release. However, the M_2 receptor also reduces adenylate cyclase, so blockade of the M_2 receptors also confers the advantage of enhancing the response to beta agonists.[54] Tiotropium is a long-acting anticholinergic that is more selective for the M_3 receptor than ipratropium and atropine, and it dissociates more rapidly from the M_2 receptor. Given a 24-hour duration of action, tiotropium is gaining popularity as the ideal anticholinergic for reducing cholinergic tone in COPD.[77,78] The choice of agents in general is largely based on individual patient response and tolerance of different agents. A joint position statement by the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and the European Respiratory Society recommends the following approach to medical management of symptomatic patients[48]:

1. Bronchodilators *may* be used for mild COPD (FEV_1 60%-80%)
2. Bronchodilators are *recommended* for FEV_1 less than 60%. The specific drug prescribed is based upon patient tolerance, side effects, and cost and may consist of a long-acting β_2-agonist, anticholinergic, or corticosteroid. Combination therapy may be used, although combination therapy does not show a consistent advantage over monotherapy.
3. Pulmonary rehabilitation may be used for patients with FEV_1 greater than 50% and is recommended for those with FEV_1 less than 50%.
4. Oxygen therapy is used to maintain PaO_2 greater than 60 mmHg (SpO_2 greater than 88%) for patients who have resting hypoxemia below this level.

At all stages of COPD progression, removal of offending and exacerbating factors is recommended (particularly cessation of smoking and administration of the influenza vaccine). Surgical treatments that are used to reduce symptoms in COPD include lung volume reduction surgery (LVRS), bullectomy, and lung transplantation. LVRS removes severely diseased portions of lung, leaving behind a greater proportion of better-functioning tissue. The result is improvement in elastic recoil, diaphragmatic function, and reduction in exacerbations. LVRS is most effective for predominantly upper lobe emphysema.[67]

TABLE 26-10 BODE Scale: Point Values for Relevant Variables of Obstructive Disease

	POINTS ON THE BODE INDEX			
Variable	**0**	**1**	**2**	**3**
FEV_1 (% of predicted)	≥ 65	50-64	36-49	≤ 35
Distance walked in 6 min (meters)	≥ 350	250-349	150-249	≤ 149
MMRC dyspnea scale	0-1	2	3	4
Body mass index	> 21	≤ 21		

From Ko FW, et al. A longitudinal study of serial BODE indices in predicting mortality and readmissions for COPD. *Respir Med*. 2011; 105(2):266-73.
BODE, *B*ody mass index, degree of airflow *O*bstruction, *D*yspnea, *E*xercise capacity index; *FEV_1*, forced expiratory volume in 1 second; *MMRC*, Modified Medical Research Council.

Preoperative Evaluation

The surgical site and the preoperative status of the patient are critical factors in predicting the incidence of postoperative complications. The risk of respiratory complications is generally proportional to the proximity of the surgical site to the diaphragm.[47] Multiple factors are predictive of postoperative respiratory difficulties, but no preoperative pulmonary function test establishes absolute contraindications to surgery. The preoperative evaluation of patients with COPD should determine the severity of the disease and identify treatments for reducing inflammation, improving secretion clearance, treating underlying infection, and increasing airway caliber to ensure the best surgical outcome. Although the FEV_1 has previously been used as the primary indicator of disease severity, other factors such as body mass index, functional dyspnea, and exercise tolerance along with the FEV_1 provide useful assessment of prognosis in patients with COPD.[51,79] The multidimensional BODE index (*B*ody mass index, airflow *O*bstruction, *D*yspnea, and *E*xercise capacity) provides better insight into the severity of disease than does spirometry alone[80] (Table 26-10).

The causes of acute exacerbations of COPD are multiple and may be explained only partially by airway infection or inflammation. Multiple contributing factors, including bronchitis, underlying airway hyperresponsiveness, inhalation of noxious agents, mucous plugging, pneumonitis, cardiovascular disease, congestive heart failure (CHF), and generalized systemic inflammation, must be considered. Signs of COPD may be subtle. The clinician must assess for increased respiratory effort, altered breathing patterns, abnormal breath sounds, and a productive cough. A consensus statement by the American Thoracic Society defines dyspnea as "a subjective experience of breathing discomfort that is comprised of qualitatively distinct sensations that vary in intensity. The experience derives from interactions among multiple physiologic, psychologic, social, and environmental factors and may induce secondary physiologic and behavioral responses."[81] Because dyspnea, like pain, is a very subjective sensation, it can be difficult to quantify a patient's level of dyspnea or to evaluate the degree of response to therapy. In evaluating dyspnea, visual analog scales, verbal ordinal scales, or combined scales are commonly used[82] (Figure 26-18).

A history of or the presence of atopy (predisposition to allergies), childhood respiratory impairment, high serum immunoglobulin E (IgE) levels, and eosinophilia is suggestive of asthmatic bronchitis, which is generally more responsive to treatment than is smoking-induced COPD. The value of preoperative pulmonary function

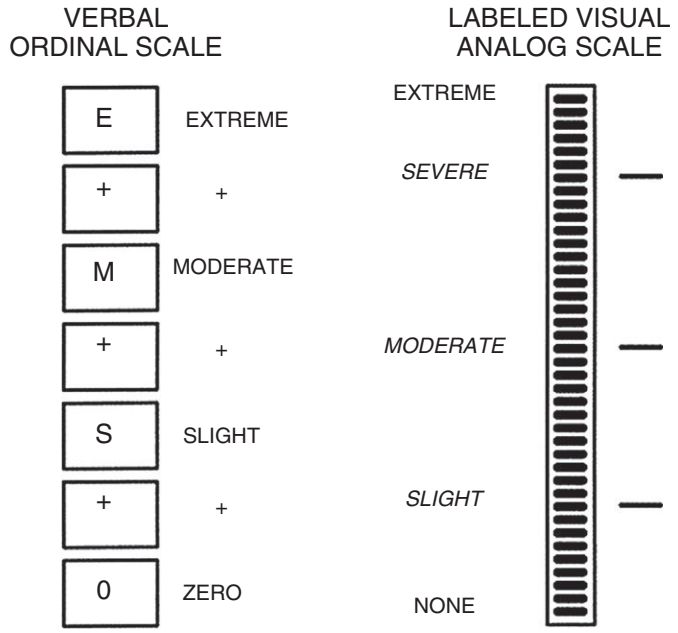

FIGURE **26-18** A verbal ordinal scale and visual analog scale used to evaluate the degree of dyspnea. (From Lansing RW, et al. Measurement of dyspnea: word labeled visual analog scale vs. verbal ordinal scale. *Respir Physiol Neurobiol*. 2003;134[2]:77-83.)

tests is questionable for nonpulmonary surgery.[47] Data from resting Spo_2, dyspnea-related functional limitation, exercise capacity, and body mass index will lead to useful assessment of the patient's pulmonary reserve. If pulmonary function tests (PFTs) are available, spirometry should be assessed before and after bronchodilator or steroid treatment (or both) so that airway disease reversibility can be evaluated. The patient's response to bronchodilators provides important information about the manageability of the COPD, with an improvement in FEV_1 of 12% to 15% from baseline indicating a significant response.[44] Other changes considered significant are improvement in FVC of at least 10% and improvement in $FEF_{25\%-75\%}$ of at least 20%, but a lack of significant improvement does not preclude use of bronchodilators during anesthesia.[46]

Numerous conditions predispose a patient with COPD to infectious complications, including dehydration, decreased ability to cough, immobility, and decreased mucociliary clearance. Optimal control of airway inflammation may require antimicrobial therapy preoperatively. Increasing cough, dyspnea, chest pain, fatigue, worsening blood gas values, and other signs may indicate an acute exacerbation of COPD. The patient may report a change in sputum volume, color, or consistency. Viruses are the most frequent causative organisms in acute exacerbations of chronic bronchitis.[83] Acute infection is associated with epithelial desquamation and correlates with airway hyperreactivity that may persist for 3 to 6 weeks after the resolution of symptoms.[84] Measures to improve respiratory skeletal muscle strength include good nutrition and balanced fluid and electrolyte intake. Bronchodilators should be used if the patient exhibits some degree of airway obstruction (coughing may temporarily increase in frequency as greater quantities of sputum are removed). Some commonly used bronchodilators are listed in Table 26-11. If pulmonary function tests are performed, the degree of reversibility (Figure 26-19) will suggest the potential for and the means of improving ventilation in the perioperative period.

An increased plasma concentration of bicarbonate in the presence of a low or normal $Paco_2$ suggests that acute hyperventilation

TABLE 26-11 Medications Used for COPD

Drug	Formulation	Delivery	Usual Frequency
Short-Acting β_2-Agonists			
Albuterol	90 mcg/inhalation	MDI/Neb	q4-6hr prn
Fenoterol	100-200 mcg/inhalation	MDI, MDI/Neb	q4-6hr prn
Levalbuterol	45-90 mcg/inhalation	MDI/Neb	q6-8hr prn
Pirbuterol	200 mcg/inhalation	MDI/Neb	q4-6hr prn
Terbutaline	0.25-0.5mg	Subcut/Neb	q4hr prn
Short-Acting Anticholinergic			
Ipratropium	20-40 mcg/inhalation	MDI/Neb	q6-8hr prn
Short-Acting β_2-Agonists/Short-Acting Anticholinergic Combinations			
Albuterol sulfate/ipratropium	90 mcg albuterol base/18 mcg ipratropium/inhalation	MDI/Neb	q6-8hr prn
Fenoterol/ipratropium	200 mcg fenoterol/80 mcg ipratropium	MDI/Neb	q6-8hr prn
Long-Acting β_2-Agonists			
Arformoterol	15 mcg	Neb	bid
Formoterol	4.5-12 mcg	MDI/DPI	bid
Indacaterol	75-300 mcg	MDI	once/day
Salmeterol	25-50 mcg	MDI/DPI	bid
Long-Acting Anticholinergic			
Tiotropium	18 mcg	DPI	once/day
Corticosteroid/Long-Acting β_2-Agonist Combinations			
Fluticasone/salmeterol	100, 250, 500 mcg fluticasone/50 mcg salmeterol	DPI	bid
	50, 125, 250 mcg fluticasone/25 mcg salmeterol	MDI	bid
Budesonide/formoterol	320 mcg budesonide/90 mcg formoterol	DPI	bid
	80, 160 mcg budesonide/4.5 mcg formoterol	MDI	bid
Methylxanthines			
Aminophylline	200-600 mg	PO	once/day
Theophylline	100-600 mg	PO	once/day
Corticosteroids			
Beclomethasone	40-80 mcg	MDI/DPI/Neb	bid
Budesonide	90-400 mcg	DPI/Neb	bid
Fluticasone	250-500 mcg	MDI/DPI	bid
Mometasone	200 mcg	MDI	bid
Methylprednisolone	4-16 mg	PO	bid
Prednisone	5-60 mg	PO	bid
Corticosteroid/Long-Acting β_2-Agonist Combinations			
Fluticasone/salmeterol	100, 250, 500 mcg fluticasone/50 mcg salmeterol	DPI	bid
	50, 125, 250 mcg fluticasone/25 mcg salmeterol	MDI	bid
Budesonide/formoterol	320 mcg budesonide/9 mcg formoterol	DPI	bid
Phosphodiesterase Inhibitor			
Roflumilast	500 mcg	PO	once/day

Data from United States Food and Drug Administration. *FDA Approved Drug Products*. Accessed July 20, 2012 at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm; Epocrates, Inc. *COPD Treatment Options*. Accessed July 20, 2012 at https://online.epocrates.com/u/29427/COPD; Global Initiative for Chronic Obstructive Lung Disease. *Global Strategy for the Diagnosis, Management, and Prevention of COPD*, 2011. Accessed July 20, 2012 at www.goldcopd.org.
DPI, Dry powder inhaler; *MDI*, metered-dose inhaler; *Neb*, nebulizer; *PO*, by mouth; *subcut*, subcutaneous.

is masking chronic CO_2 retention. If the Pa_{CO_2} has been chronically elevated, it is important that the hypercarbia not be corrected too quickly. Sudden decreases in Pa_{CO_2} can result in alkalemia because the kidneys cannot instantly excrete the excess bicarbonate.

Anesthetic Management

There is no standard recipe of anesthetic management of the patient with COPD, but some general principles should guide anesthetic planning. It is crucial to realize that COPD patients are susceptible to the development of acute respiratory failure during the postoperative period. Therefore, continued intubation of the trachea and mechanical ventilation of the lungs may be necessary, particularly after thoracic and upper abdominal surgery. Postoperative ventilation is more likely to be needed in those patients with low Pa_{O_2} and dyspnea at rest. Assessment of respiratory function can be performed effectively and inexpensively by considering relevant factors, such as the BODE score (see Table 26-10). In initial

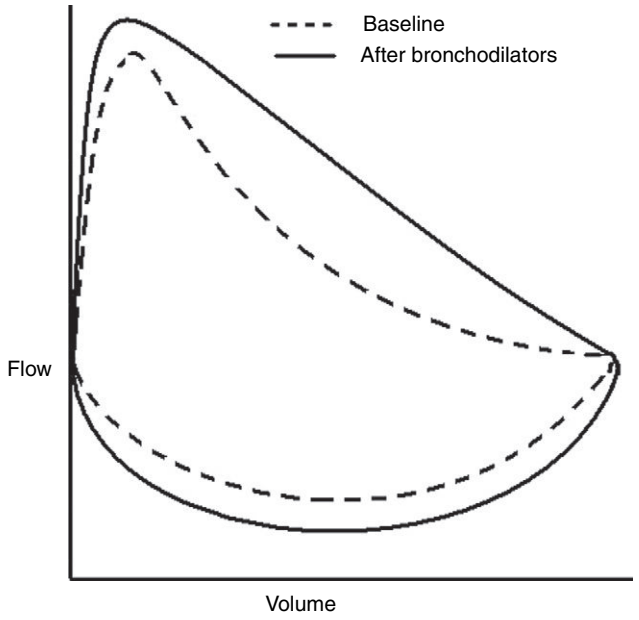

FIGURE **26-19** Flow-volume loop, demonstrating expected improvement after bronchodilator therapy.

study, the BODE score was lower among survivors than among those who died from any cause up to 52 months postoperatively (3.7 ± 2.2 vs. 5.9 ± 2.6, P <0.005).[80] When categorized into four quartiles (BODE indices of 0 to 2, 3 to 4, 5 to 6, and 7 to 10, respectively), there was significant correlation in the mortality rates among patients in higher-scored quartiles.[85]

Regional Anesthesia

Regional anesthesia is useful if sedation is not needed, and it may be less challenging than general anesthesia, to avoid manipulation of the airway and ventilation. However, anesthetists must nonetheless maintain a high level of vigilant monitoring if regional rather than general anesthesia is used. Complications such as pneumothorax and impaired respiratory muscle function (from phrenic nerve block or high spinal block) can lead to respiratory embarrassment quickly in the compromised patient. Neuraxial anesthetic techniques that produce sensory anesthesia above T6 are not recommended. The potential for decreasing expiratory reserve volume, impairing cough effort, and creating anxiety-provoking weakness is too great.[86]

General Anesthesia

General anesthesia often is provided with a volatile anesthetic (to facilitate bronchodilation) and humidification (to prevent drying of secretions). Maintaining adequate anesthesia in patients with significant lung disease presents a challenge. General anesthesia is often associated with an increase in the alveolar-arterial difference in P_{O_2} ($P_{AO_2} - Pa_{O_2}$). Causes include a fairly consistent 20% decrease in FRC when neuromuscular relaxants are used, as well as small airway closure and atelectasis. Atelectasis normally occurs after induction of general anesthesia and has been found to worsen with muscle paralysis and prolonged surgical duration.[87] It is interesting to note that patients with chronic hyperinflation appear to be less likely to develop atelectasis than subjects with healthy lungs, possibly because of airway closure before alveolar collapse or because of resistance to early alveolar collapse from long-standing lung hyperinflation, which prevents prompt formation of atelectasis.[88]

There is some evidence that volatile anesthetics reduce the function of cilia in the respiratory tract.[89] Opioids pose less threat to disrupting ventilation-perfusion matching, and may be an appealing option. However, the residual respiratory depressant effects of opioids must be managed, particularly in the COPD population, which is generally of advanced age. An opioid-heavy technique also requires attention to amnestic coverage. If nitrous oxide (N_2O) is used for this purpose, bullae may enlarge and rupture; therefore, presence of bullous emphysema is a contraindication to use of N_2O. A well-balanced anesthetic, therefore, will minimize many of these concerns.

Ventilation Management

Ventilation strategy should focus on maintaining adequate oxygenation, eliminating CO_2, avoiding barotrauma from excessive inspiratory pressures, avoiding tissue injury from repetitive airway closure and reopening, and avoiding volutrauma from either excessive tidal volumes or from auto-PEEP. Oxygenation is managed first with Fi_{O_2}, but care must be taken to reduce absorptive atelectasis or damaging oxidative effects from overzealous oxygen administration. If concerns about N_2O exist, then oxygen and air provide a useful combination of carrier gases. Attention should be given to adequate hydration to prevent excessive drying of respiratory secretions. In managing CO_2 elimination, providers should avoid correction of a chronic hypercapnia during mechanical ventilation. In the face of long-term renal compensation, doing so may result in an unintended alkalemia and may make ventilator weaning difficult.

Patients with COPD present challenges to both getting gas into the respiratory zone, as well as getting it out again. Airway secretions and bronchial reactivity provide impedance to inspiration. Intermittent vital capacity maneuvers to recruit atelectatic alveoli will help improve oxygenation during surgery,[88] and PEEP will help maintain small airway patency. If the airways are noncompliant, such as with bronchitis, then slower inspiration, perhaps with an inspiratory pause, is helpful to allow time for gas to redistribute from higher compliance areas to less-ventilated areas of lung. Obstructive disease, however, may conflict with those strategies at maximizing oxygenation. With obstructive disease, longer expiratory times are useful (lower inspiration/expiration [I:E] ratio) to allow more time for expiration. The lower I:E ratio is used at the sacrifice of peak pressures, which will rise as higher inspiratory flow is used to deliver the tidal volume in a shorter inspiratory cycle. Leatherman demonstrated that there is no benefit to prolonging expiratory time beyond 4 seconds.[90] With COPD, on expiration, small airway closure and emphysematous loss of elasticity impede full emptying of the tidal breath. As a result, inspiration begins at volumes at which the respiratory system exhibits positive recoil pressure. In other words, pressure builds due to incomplete emptying at the time that the next inspiration begins. This is known as auto-PEEP or intrinsic PEEP (PEEPi).[91,92] In the past, external PEEP (PEEPe) was generally not used in patients with COPD because hypoxemia often is improved with increases in the fraction of inspired O_2 (Fi_{O_2}) and because the risk of barotrauma resulting from further hyperinflation was deemed too great. The risk of PEEP exacerbating incomplete emptying is greater in patients with COPD.[93] However, cyclic closure and reopening of small airways with each breathing cycle is also detrimental, and judicious use of PEEP may avoid this low-volume tissue injury.[93] Research suggests that a PEEPe that is less than the PEEPi in the presence of expiratory flow limitation may assist patients in overcoming the inspiratory mechanical load of PEEPi, ultimately decreasing the work of breathing and eliminating or decreasing atelectatic areas and airway closure.[93-95] Patients whose peak cycling pressures remain

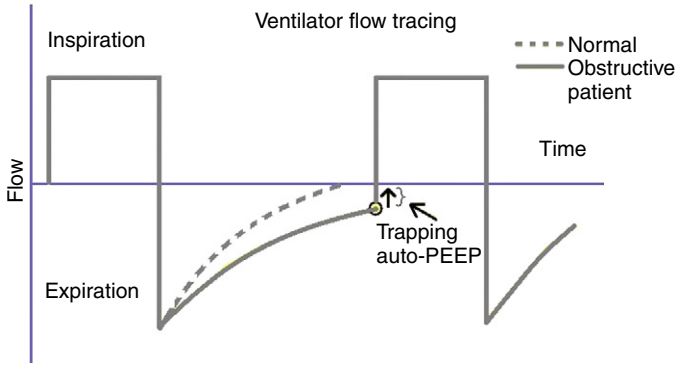

FIGURE **26-20** Development of intrinsic positive end-expiratory pressure (PEEPi) is suspected when the expiratory flow tracing does not reach the zero line before the subsequent inspiration begins. (From García Vicente E, et al. Ventilación mecánica invasiva en EPOC y asma. *Med Intensiva*. 2011; 35[4]:288-298.)

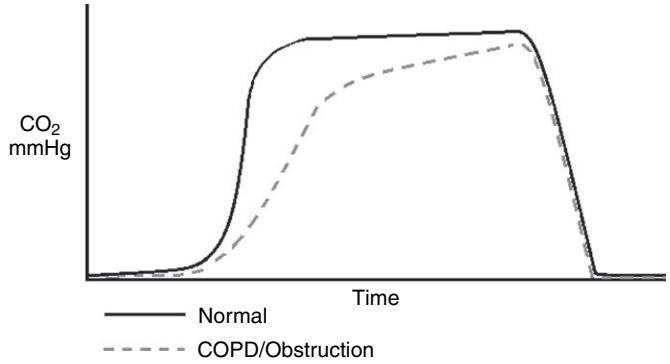

FIGURE **26-21** Capnograph of a patient with expiratory airway obstruction.

essentially unaffected by PEEPe experience the greatest improvement and the least hazard.[96] In the operating room, the clinician can best diagnose PEEPi by assessing whether exhalation is still taking place when the next inhalation starts.[97] This is becoming easier with newer-generation anesthesia machines, which provide dynamic flow and volume tracings of the respiratory cycle (Figure 26-20). Monitoring flow-volume tracings or the capnograph for expiratory airflow obstruction (Figure 26-21) also may help guide decision making about whether incomplete emptying threatens the development of PEEPi. When PEEPe is added, it should be titrated in 2.5- to 5-cm H_2O increments while peak cycling pressures are closely monitored. Because PEEP is intended to avoid closure of small airways and alveoli that would exist at the lower (flat) portion of the compliance curve, the pressure-volume tracing can be used to determine the appropriate amount of PEEP to administer. Research demonstrates that PEEP set just above the lower inflection point of the compliance curve provides optimal oxygenation[98-100] (Figure 26-22). Although it can be difficult to determine this point clinically,[101] the concept is important, because it connects understanding of the physiologic concept of the compliance curve with the clinical intervention of PEEP.

Postoperative Care

Postoperative care of patients with COPD is directed at minimizing the incidence and severity of pulmonary complications, because such patients are at increased risk for the development of acute respiratory failure.[102] Postoperative pulmonary complications are most often characterized by atelectasis followed by

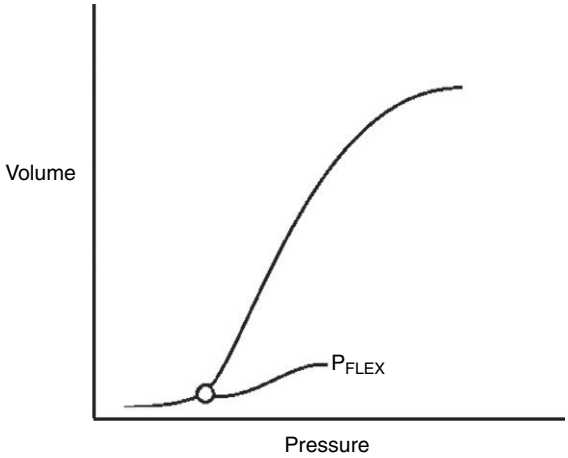

FIGURE **26-22** The lower inflection point (P_{FLEX}) of the pressure-volume curve of the airway suggests an optimal pressure for setting positive end-expiratory pressure (PEEP).

pneumonia and decreases in Pa_{O_2}.[97] These patients require close monitoring; worsening $\dot{V}/\dot{Q}$ mismatch after extubation may not be detected by ABG analysis, possibly because of changes in breathing pattern and cardiovascular function. In fact, minute ventilation may not change, but often respiratory rate increases, and V_T decreases after the termination of mechanical ventilation.[96] The choice of drugs or techniques for producing anesthesia does not seem to predictably alter the incidence of postoperative pulmonary infections. Whether a relationship exists between the duration of anesthesia and the incidence of postoperative pulmonary complications is not clear.

ASTHMA

Definition

The National Asthma Education and Prevention Program Expert Panel Report 3 (EPR-3) defines asthma as "a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role: in particular, mast cells, eosinophils, neutrophils (especially in sudden onset, fatal exacerbations, occupational asthma, and patients who smoke), T lymphocytes, macrophages, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of coughing (particularly at night or in the early morning), wheezing, breathlessness, and chest tightness. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment."[103] Although asthma involves chronic inflammation of the respiratory tract, it is propagated by different mediators of inflammation than in COPD, which is what primarily differentiates the pathogenesis of the two diseases.[67]

Various theories underlie the cause of asthma. The three overarching theories suggest that asthma may result from the following:

1. *Deficiency of acquired immunity*. Lack of exposure to immunologic challenges in early life allows predominance of the Th2-type cytokine response and a general atopy.
2. *Genetics*.
3. *Exposure to respiratory system irritants*. These include airborne allergens (house-dust mite), irritants (tobacco smoke), and viral respiratory infections (respiratory syncytial virus).

A general approach to classification discriminates between extrinsic or intrinsic asthma. Although this system is conceptually helpful, its two groups are not mutually exclusive. Extrinsic asthma (or allergic asthma) most commonly affects children

and young adults and involves exacerbation by infectious, environmental, psychological, or physical factors, whereas intrinsic asthma (or idiosyncratic asthma) usually develops in middle age without specifically identifiable attack-provoking stimuli. It is of significance that the clinical features of idiosyncratic asthma are essentially indistinguishable from the immune-mediated response.

Incidence and Outcome

Up to 22 million persons in the United States have asthma. It is the most common chronic disease of childhood, affecting an estimated 6 million children. The burden of asthma affects the patients, their families, and society in terms of lost work and school, lessened quality of life, and avoidable emergency department (ED) visits, hospitalizations, and deaths.[103]

Pathogenesis and Pathophysiology

Our contemporary understanding of asthma is that it is not a single entity, but rather a heterogeneous clinical syndrome characterized by episodes in which airways are hyperresponsive at times interspersed with symptom-free periods.[104] Bronchoconstriction is a factor long associated with the asthmatic symptom complex, but asthma is much more than bronchoconstriction. Airway inflammation and a nonspecific hyperirritability of the tracheobronchial tree are now recognized as being central to the pathogenesis of even mild cases of asthma. Permanent changes in airway anatomy, referred to as *airway remodeling*, magnify the inflammatory response.[104,105] Some manifestations of airway remodeling include fibrosis, mucus hypersecretion, smooth muscle hypertrophy, and angiogenesis.[103]

Allergic (atopic) asthma is triggered by antigens that provoke a T-lymphocyte–generated, IgE-mediated immune response.[106] It is often associated with a personal or familial history of allergic disease. In susceptible patients, exposure to even minute amounts of an offending agent can cause activation of lymphocytes and cytokine release, setting into motion an immune-mediated inflammatory response. Endobronchial biopsy specimens, even from asymptomatic patients, frequently show an active inflammatory process. Eosinophils, mast cells, neutrophils, and macrophages are prominent features in asthmatic airways, and their activation and degranulation fuel the proinflammatory cascade.

Potent biochemical mediators released from proinflammatory and airway epithelial cells promote vasoconstriction, increased smooth muscle tone, enhanced mucus secretion, submucosal edema, increased vascular permeability, and inflammatory cell chemotaxis. Leukotrienes have been identified as especially potent spasmogenic and proinflammatory substances. Released molecules that are toxic to the airway epithelium cause patchy desquamation, exposing cholinergic nerve endings and compounding the bronchoconstrictive and hyperresponsive response. The asthmatic diathesis creates airways that are inflamed, edematous, and hypersensitive to irritant stimuli, and the degree of airway hyperresponsiveness and bronchoconstriction appears to parallel the extent of inflammation.[107,108] When airway reactivity is high, asthmatic symptoms are generally more severe and unrelenting, and the amount of therapy required to control the episode is greater.[104]

The mechanisms underlying nonimmunologic asthma are less clearly defined. Nonimmunologic asthma occurs in patients with no history of allergy and normal serum IgE. These patients typically develop asthmatic symptoms in response to some provocative or noxious stimulus such as cold air, airway instrumentation or irritation, climate changes, or an upper respiratory illness. Recent upper respiratory infection may precipitate bronchospasm in any patient, but the risk is higher in patients with a history of asthma. The increased bronchomotor tone associated with viral respiratory infections may persist for as long as 5 weeks.[84] Nonasthmatic children with an upper respiratory infection are two to seven times more likely to experience an adverse event perioperatively and are more prone to postoperative desaturation.[109] Asthma itself, however, appears not to be a risk factor for postoperative complications, if it is controlled.[110] Poorly controlled asthma (defined by rescue inhaler use or emergency department visits within 30 days) is associated with an increase in respiratory complications.[111]

Immune mechanisms appear to be causally related or contributory to the development of asthma in more than 50% of cases, but many patients with asthma have disease mechanisms from both categories. Asthma that has its onset in childhood tends to have a strong allergic component, whereas asthma that arises in adults tends to be nonallergic or to have a mixed cause.[104] As a general rule, nonallergic mechanisms of exacerbation are more prevalent in the perioperative period.[112]

IgE-mediated asthma occurs after initial antigen exposure has resulted in IgE antibody formation. On repeat exposure, in the presence of IgE, mast cells release multiple mediators. These mediators directly constrict small and large airways, increase capillary permeability, stimulate vasoconstriction, and increase mucous gland secretion, which contributes to mucus plugging (Figure 26-23).

The mechanism of exercise-induced bronchospasm (EIB) is unknown. One popular theory suggests that a high minute ventilation ($\dot{V}E$) and the low temperature or low H_2O content of inspired gas (which requires greater heat and water transfer from the mucosal surface to the inspired gas) generates a bronchoconstrictive response. Another theory proposes that the evaporation of water from respiratory mucosa and the resultant increase in the osmolarity of the surface-lining fluid induces the degranulation of mast cells. A third theory suggests that reactive hyperemia of the bronchial mucosa occurs with rewarming, resulting in airway narrowing.[113] Regardless of the mechanism, most symptoms last less than 1 hour and are usually very responsive to administration of β_2-adrenergic receptor agonists.[114]

Occupational asthma develops when irritants directly stimulate vagal nerve endings in the airway epithelium. Infection-induced asthma with acute inflammation of the bronchi may be caused by viral, bacterial, or mycoplasmal infections. Aspirin-induced asthma occurs when, in some predisposed persons, cyclooxygenase inhibition drives arachidonic acid metabolism toward the lipooxygenase pathway, resulting in production of leukotrienes, thereby triggering the asthma attack.[115] This peculiar response also can occur with the use of other nonsteroidal antiinflammatory agents. The aspirin-induced asthma variant is not IgE mediated or allergic in nature. It is clinically associated with the presence of nasal polyps.

Clinical Features and Diagnosis

Airflow limitation is caused by a variety of changes in the airway, all influenced by airway inflammation[103]:

- *Bronchoconstriction*—bronchial smooth muscle contraction that quickly narrows the airways in response to exposure to a variety of stimuli, including allergens or irritants
- *Airway hyperresponsiveness*—an exaggerated bronchoconstrictor response to stimuli
- *Airway edema*—As the disease becomes more persistent and inflammation becomes more progressive, edema, mucus hypersecretion, and formation of inspissated mucus plugs further limit airflow

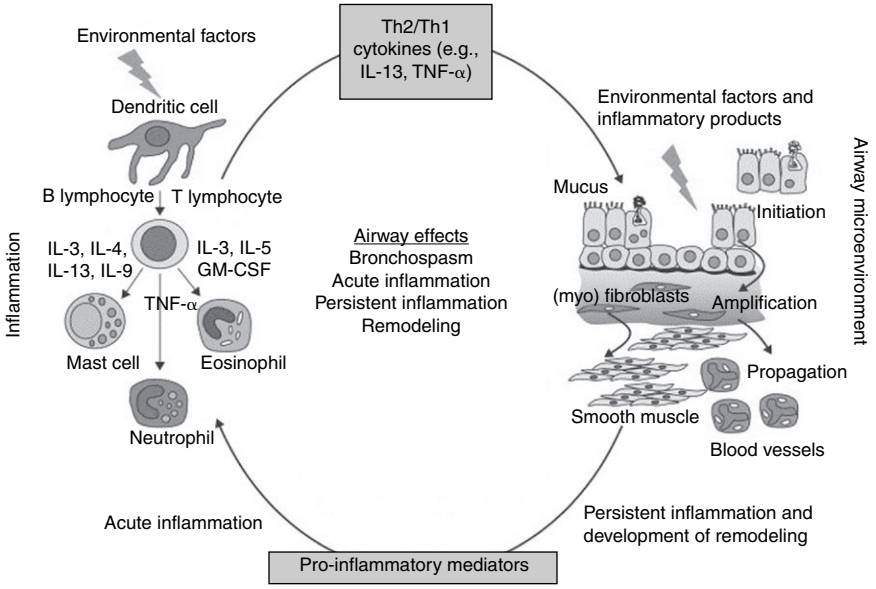

FIGURE **26-23** Factors limiting air flow in acute and persistent asthma. *GM-CSF*, Granulocyte-macrophage colony-stimulating factor; *IgE*, immunoglobulin *E*; *IL-3*, interleukin 3 (and similar); *TNF-α*, tumor necrosis factor-alpha. (Modified and reprinted from Holgate ST, Polosa R. The mechanisms, diagnosis, and management of severe asthma in adults. *Lancet*. 2006;368:780-793.)

Key hallmarks of asthma include[103,107]:

- Recurrent wheezing
- Dyspnea (may parallel the severity of expiratory airflow obstruction)
- Cough (productive or nonproductive; frequently at night or early morning)
- Recurrent labored respirations with accessory muscle use
- Tachypnea (a respiratory rate greater than 30 breaths per minute and a heart rate of 120 suggests severe bronchospasm)
- Recurrent chest tightness
- Prolonged expiratory phase of respiration
- Fatigue
- Symptoms occur or worsen with exercise, viral infection, environmental allergens or irritants, changes in weather, stress, or menstrual cycles

Clinical classification of asthma is noted in Table 26-12, and corresponding treatment protocols are shown in Figure 26-24. Typical attacks are short-lived, lasting minutes to hours. Between attacks the asthmatic patient may be entirely symptom free; however, underlying airway remodeling is still evident.[105,106] Severe obstruction that is refractory to bronchodilator therapy is known as *status asthmaticus*. This variant occurs in persons with a genetic predisposition[116] and requires an escalating approach to therapy for symptoms that may persist over a number of days. Status asthmaticus also can represent an emergency situation. At times, anesthetists are called upon to administer ketamine or volatile anesthetics as part of the treatment for status asthmaticus.[117-119] Use of accessory muscles of respiration and the increased work of breathing associated with a protracted asthmatic episode can result in respiratory muscle fatigue and respiratory failure.

During exacerbations, pulmonary function tests may reflect acute expiratory airflow obstruction (↓ forced expiratory flow [$FEF_{25\%-75\%}$]; ↓ FEV_1/FVC). Viscid mucus secretion may compound the airway narrowing and produce airway collapse.[114] The asthmatic episode produces not only airflow obstruction but also gas exchange abnormalities. The resulting low $\dot{V}/\dot{Q}$ state produces arterial O_2 desaturation.[120] Hypoxemia is common, but in most

TABLE 26-12 Clinical Asthma Classification

Steps	Clinical Characteristics Before Therapy
Step 1—Intermittent asthma	Signs and symptoms occur 0-2 days/week Nighttime symptoms 0-2 days/month SABA use 0-2 days/week No activity limitation Exacerbations 0-1 times/year FEV_1 ≥80% of predicted value; FEV_1/FVC normal
Step 2—Mild persistent asthma	Signs and symptoms 2-6 days per week, but not > 2 times/day Nighttime symptoms 3-4 times/month SABA use 3-6 days/week, but not more than once daily Minor activity limitation Exacerbations ≥ 2 times/year FEV_1 ≥80% of predicted value; FEV_1/FVC normal
Step 3—Moderate persistent asthma	Daily symptoms Nighttime symptoms occur more than once per week but not nightly Daily use of SABA Some activity limitation Exacerbations > 2 times/year FEV_1 60%-80% of predicted value; FEV_1/FVC reduced 5%
Step 4—Severe persistent asthma	Continuous signs and symptoms Often nightly symptoms SABA use several times/day Extremely limited physical activity FEV_1 ≤60% of predicted value; FEV_1/FVC reduced >5%

Modified from National Heart Lung and Blood Institute. *National Asthma Education and Prevention Program, Expert Panel Report 3. Guidelines for the Diagnosis and Management of Asthma*. Bethesda, Md: US Department of Health and Human Services; 2007.
FEV_1, Forced expiratory volume in 1 second; *FEV_1/FVC*, forced expiratory volume in 1 second/forced vital capacity; *SABA*, short-acting β_2-agonist.

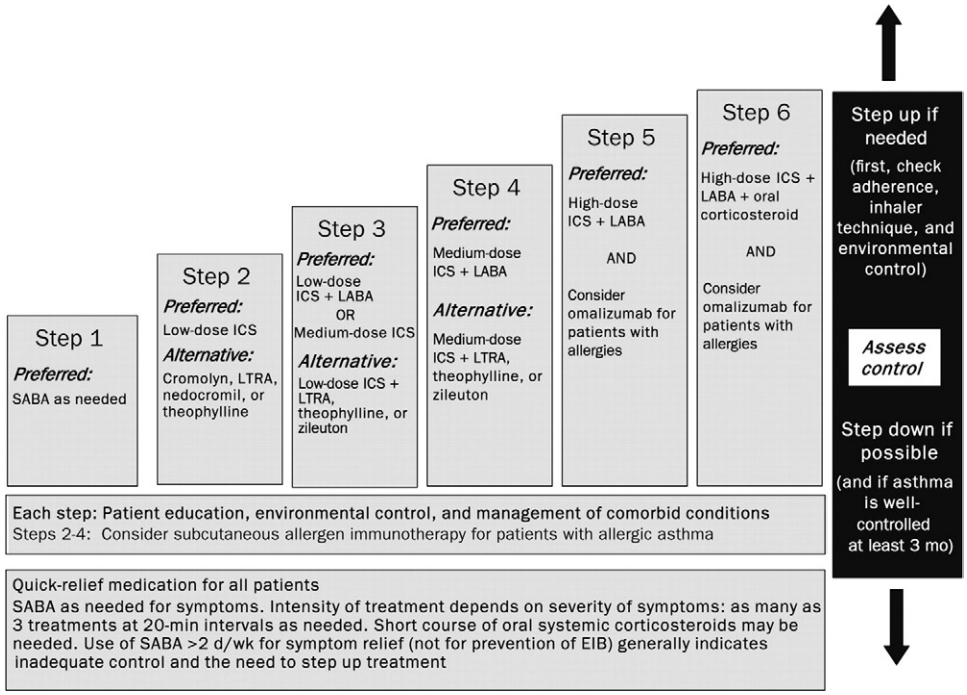

FIGURE **26-24** Stepwise approach to treating asthma in adults. *EIB*, Exercise-induced bronchospasm; *ICS*, inhaled corticosteroid; *LABA*, long-acting β-agonist; *LTRA*, leukotriene receptor antagonist; *SABA*, short-acting β-agonist. NOTES: Zileuton is a less desirable alternative due to limited studies as adjunctive therapy and the need to monitor liver function. Theophylline requires monitoring of serum concentration levels. In *step 6*, before oral corticosteroids are introduced, a trial of high-dose ICS + LABA + either LTRA, theophylline, or zileuton may be considered, although this approach has not been studied in clinical trials. *Steps 1, 2*, and *3* preferred therapies are based on Evidence A; *step 3* alternative therapy is based on Evidence A for LTRA, Evidence B for theophylline, and Evidence D for zileuton. *Step 4* preferred therapy is based on Evidence B, and alternative therapy is based on Evidence B for LTRA and theophylline and Evidence D for zileuton. *Step 5* preferred therapy is based on Evidence B. *Step 6* preferred therapy is based on EPR-2 (1997) and Evidence B for omalizumab. Immunotherapy for steps 2 to 4 is based on Evidence B for house-dust mites, animal danders, and pollens; evidence is weak or lacking for molds and cockroaches. Evidence is strongest for immunotherapy with single allergens. The role of allergy in asthma is greater in children than in adults. Clinicians who administer immunotherapy or omalizumab should be prepared and equipped to identify and treat anaphylaxis that may occur. (From National Heart Lung and Blood Institute. *National Asthma Education and Prevention Program, Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma*. Bethesda, Md US Department of Health and Human Services; 2007.)

patients with acute bronchospasm, CO_2 elimination is relatively well preserved until $\dot{V}/\dot{Q}$ abnormalities are severe. An increased arterial CO_2 tension may indicate impending respiratory failure in the acutely ill asthmatic patient. Chronic asthma may eventually lead to irreversible lung destruction, loss of lung elasticity, pulmonary hypertension (PH), and lung hyperinflation.

Diagnostic Testing

Pulmonary Function Tests. Lung function testing offers limited value to anesthetic risk assessment and should not be performed routinely based solely on the presence of asthma. Although spirometry is used to determine candidacy for lung resection surgery, it has limited value before extrathoracic surgery, even in patients with asthma or other lung disease. Even when spirometry is used to document the degree of airflow limitation, there is not a known threshold that precludes surgery.[110]

When pulmonary function tests are performed, they provide information related to the degree of impairment and the reversibility of airway limitation. RV, FRC, and TLC all increase because of an increase in volume of the gas trapped beyond closed airways, and lung deflation is less because of airway obstruction. Comparison of current and prior pulmonary function test results is useful. Tolerance of activities is used for classifying the degree of dyspnea.[121] The patient in remission may have negative results on all parameters of pulmonary function and may be tested with a cholinergic agonist such as methacholine for bronchial provocation and clarification of the diagnosis of asthma.[122] The hallmark of an incipient exacerbation of asthma is a reduction in the peak expiratory flow rate.[103]

Arterial Blood Gas Analysis. Increased diffusibility of CO_2 (compared with that of O_2) in combination with an often increased respiratory rate generally produces ABG analysis results that reflect the presence of respiratory alkalosis. Even slight hypercapnia may indicate severe air trapping and potential impending respiratory failure.

Chest Radiography. Because nearly 75% of asthma patients have a normal chest radiograph, chest radiography is not helpful in diagnosing or determining the severity of asthma. Hyperinflation with flattening of the diaphragm may be evident. Chest radiography is more helpful in detection of complications.

Electrocardiography. Changes evident on electrocardiography, such as ST-segment changes, right ventricular strain, and right axis deviation, usually manifest only in severe attacks and generally are of little significance with regard to the asthmatic condition.

Sputum Analysis. Eosinophilia, which is common in asthmatic patients, may be manifested as the production of grossly purulent sputum. Microscopic evaluation may reveal Curschmann spirals and Charcot-Leyden crystals, rather than polymorphic neutrophils associated with infection.

Serum Values. Eosinophilia (defined as more than 275 eosinophils per cubic millimeter of blood) is common in asthmatic patients with active IgE-mediated bronchial asthma, but its presence does not serve to differentiate extrinsic from intrinsic asthma. Asymptomatic patients with asthma generally have a total blood eosinophil count that is less than 50/mm^3, with an increasing count often signaling the acceleration of bronchial asthma even before such patients experience symptoms. Determination of an increased eosinophil value in the absence of signs and symptoms of asthma requires that a differential analysis be undertaken. Tests for detection of IgE antibodies are performed only if an identifiable and avoidable substance is suspected. In this instance, consultation with a physician skilled in testing for allergic disease may be indicated.

Anesthetic Management

Several important anesthetic considerations and risk-reduction strategies have been reported. The EPR-3 recommends the following to reduce the risk of complications during surgery[103]:

- Before surgery, review the level of asthma control, medication use (especially oral systemic corticosteroids within the past 6 months), and pulmonary function.
- Provide medications before surgery to improve lung function if lung function is not well controlled. A short course of oral systemic corticosteroids may be necessary.
- For patients receiving oral systemic corticosteroids during the 6 months before surgery, and for selected patients on long-term high-dose inhaled corticosteroids (ICS), give 100 mg hydrocortisone every 8 hours intravenously during the surgical period, and reduce the dose rapidly within 24 hours after surgery.

Preoperative Evaluation

A careful preoperative history and physical examination are essential to discerning the current disease status and medication profile. Frequent nocturnal awakenings due to respiratory difficulty, recent increases in medication use, and signs of viral infection may signal an increased likelihood of intraoperative difficulties.[123] Elective procedures in patients who are exhibiting significant respiratory symptoms should be postponed, and the condition of such patients should be normalized as much as possible.[124]

The predictive value of routine pulmonary function testing does not warrant screening use of this modality, rather, it should be used only when patient condition and surgical procedure cause concern for the patient's pulmonary recovery.[48] FEV and peak expiratory flow rate, which can be measured with inexpensive handheld devices, may be helpful in assessing current respiratory status. Values that fall 30% to 50% below expected baseline values indicate a moderate episode of bronchoconstriction. Values below 50% of normal indicate a severe episode.[123]

Medication management of asthma is similar to that of COPD, with anticholinergics more commonly used in COPD, whereas corticosteroids are slightly better supported for asthma.[125] Pretreatment with systemic corticosteroids has been advocated in asthma patients undergoing surgical procedures. Kabalin et al.[126] studied the administration of corticosteroids in asthmatic surgical patients. Of the 89 subjects in the study, 86 had no postoperative wheezing when given either prednisone or hydrocortisone preoperatively. Complications of steroid therapy such as delayed wound healing, infection, or adrenocortical insufficiency were not noted. Ensuring that a patient who is currently receiving inhaled or systemic steroids receives them immediately before surgery is a prudent course.

Routine preoperative medications should be given to allay anxiety. The anticholinergics atropine and glycopyrrolate exhibit mild bronchodilating effects. As noted earlier, asthmatics experience an increased parasympathetic tone, and these agents are most effective as prophylactic drugs given 20 to 30 minutes preoperatively, rather than for acute therapy.[127] Caution must be exercised when administering narcotics to patients whose respiratory difficulties are evident or when using narcotics associated with histamine release, such as morphine. Fentanyl and the other phenylpiperidine analogs commonly used in anesthesia have been widely used and are safe.[127-129] The use of histamine-2 (H_2)–receptor blocking agents such as cimetidine and ranitidine to reduce gastric volume and acidity should be avoided.[109,129] Bronchospasm after their use has been reported, possibly resulting from loss of inhibitory feedback control via presynaptic H_2-receptor blockade, resulting in increased histamine release. Usual drug therapy for asthma is listed in Table 26-13.

Intraoperative Management

Despite a lack of definitive controlled clinical studies, regional anesthetic techniques are generally considered to be safer than general anesthesia.[130] Spinal or epidural levels to the midthoracic area or higher, however, decrease FRC, expiratory reserve volume, and the ability to cough and should be avoided.

All of the common induction drugs—propofol, etomidate, and ketamine—have been used successfully in asthmatic patients, but some differences exist. Ketamine is the only induction drug with bronchodilating properties, which makes it the agent of choice in patients with active asthmatic symptoms who require emergency surgery. Pizov et al.[131] compared thiopental, thiamylal, methohexital, and propofol in a double-blind randomized study in patients with and without asthma. None of the asthmatic patients who received propofol exhibited wheezing 2 and 5 minutes after intubation. Wheezing after intubation occurred in 26% to 45% of the patients who received one of the three barbiturates. The authors suggested that propofol is advantageous for routine induction in asthmatic patients.

The potent inhalation agents produce bronchial relaxation and have all been successfully used in asthmatic patients after administration of an intravenous induction drug. Isoflurane and desflurane, however, are both mild respiratory irritants, which may be a consideration during emergence. It is common practice to blunt this effect with the administration of opiates. Sevoflurane has been shown to be effective for inhalation induction in children.[132,133] Other anesthesia-related medications that should be avoided in asthmatic patients include atracurium and morphine because of histamine release, and β-receptor blockers, which may produce bronchoconstriction. If a β-blocker is desired, esmolol is a good choice, because of its relative β-1 selectivity and very short half-life. Prostaglandins, such as the F2α subtype that is used to stop obstetric bleeding, should be avoided in asthmatic patients, as should ergonovine and related ergot derivatives because of the risk of bronchospasm. Many practitioners avoid long-acting muscle relaxants and the associated possibility of residual muscle weakness in patients with asthma. Ketorolac and other nonsteroidal

TABLE 26-13 Drug Therapy for Asthma

Medication	Adult Use	Adverse Effects	Comments
Corticosteroids			
Methylprednisolone Prednisolone Prednisone	7.5-60 mg daily in a single dose	*Short-term use*: Reversible Abnormalities in glucose metabolism, hypertension, peptic ulcer, and rarely aseptic necrosis *Long-term use*: Adrenal axis Suppression, hypertension, diabetes, Cushing syndrome, muscle weakness	
Inhaled Long-Acting β_2-Agonists (LABAs)			
Salmeterol DPI 50 mcg/blister Formoterol DPI 12 mcg/single-use capsule	1 dose every 12 hours	Tachycardia, skeletal muscle tremor, hypokalemia, prolongation of QTc interval in overdose	Should not be used for acute symptom relief or exacerbations Use only with ICSs Capsules should be used only with the inhaler and should not be taken orally
Combined Medications			
Fluticasone/salmeterol DPI HFA 45 mcg/21 mcg 115 mcg/21 mcg 230 mcg/21 mcg	1 inhalation bid; dose depends on level of severity or control		
Budesonide/formoterol HFA MDI 80 mcg/4.5 mcg 160 mcg/4.5 mcg	2 puffs bid, dose depends on level of severity or control		
Cromolyn/Nedocromil			
Cromolyn MDI 0.8 mg/puff Nebulizer 20 mg/ampule	2 puffs qid (or 1 ampule of nebulizer) qid	Cough and irritation 15%-20% of patients complain of an unpleasant taste from nedocromil	One dose of cromolyn before potential precipitating event provides effective prophylaxis for 1-2 hours Not as effective as inhaled $beta_2$-agonists for EIB as SABA
Nedocromil MDI 1.75 mg/puff			
Immunomodulators			
Omalizumab (Anti IgE) Subcutaneous injection	150-375 mg subcut every 2-4 weeks, depending on body weight and serum IgE level	Pain and bruising of injection sites in 5%-20% of patients Anaphylaxis has been reported in 0.2% of treated patients Malignant neoplasms were reported in 0.5% of patients compared with 0.2% receiving placebo; relationship to drug is unclear	Monitor patients after injections Be prepared and equipped to identify and treat anaphylaxis that may occur
Leukotriene Modifiers			
Leukotriene receptor antagonists (LTRAs) Montelukast	10 mg nightly	No specific adverse effects have been identified	Long-term, may attenuate exercise-induced bronchospasm in some patients, but less effective than ICS
Zafirlukast	40 mg daily	Infrequent cases of reversible hepatitis and, rarely, irreversible hepatic failure resulting in death and liver transplantation	Zarfirlukast is a microsomal P450 enzyme inhibitor that can inhibit the metabolism of warfarin; doses of these drugs should be monitored accordingly
5-Lipoxygenase inhibitor Zileuton 600-mg tablet	2400 mg daily (give tablets qid)	Elevation of liver enzymes has been reported; limited case reports of reversible hepatitis and hyperbilirubinemia; monitor hepatic enzymes (ALT)	Zileuton inhibits P450 enzymes and can inhibit the metabolism of warfarin and theophylline Doses of these drugs should be monitored accordingly

TABLE 26-13 Drug Therapy for Asthma—cont'd

Medication	Adult Use	Adverse Effects	Comments
Methylxanthines			
Theophylline Liquids, sustained-release tablets, and capsules	Starting dose: 10 mg/kg/day up to 300 mg maximum; usual maximum 800 mg/day	Dose-related acute toxicities include tachycardia, nausea and vomiting, tachyarrhythmias (SVT), central nervous system stimulation, headache, seizures, hematemesis, hyperglycemia, and hypokalemia Adverse effects at usual therapeutic doses include insomnia, gastric upset, aggravation of ulcer or reflux, increase in hyperactivity in some children, difficulty in urination in elderly males who have prostatism	Adjust dosage to achieve serum concentration of 5-15 mcg/mL at steady state (at least 48 hours on same dosage) Due to wide interpatient variability in theophylline metabolic clearance, routine serum theophylline level monitoring is essential Various factors (diet, food, febrile illness, age, smoking, and other medications) can affect serum concentrations.

From National Heart Lung and Blood Institute. *National Asthma Education and Prevention Program, Expert Panel Report 3. Guidelines for the Diagnosis and Management of Asthma.* Bethesda, Md: US Department of Health and Human Services; 2007; Drugs for asthma. *Treat Guidel Med Lett,* 2012;114:11-18.

DPI, Dry powder inhaler; *EIB*, exercise-induced bronchospasm; *HFA*, hydrofluoroalkane; *ICS*, inhaled corticosteroids; IgE, immunoglobulin E; *MDI*, metered-dose inhaler; *NA*, not available (either not approved, no data available, or safety and efficacy not established for this age group); *SABA*, short-acting β_2-agonist.

inflammatory agents should be avoided in patients with aspirin-intolerant asthma.[134]

A strategy for mechanical ventilation that avoids lung hyperinflation and barotrauma while allowing for longer expiratory times should be chosen. A reduction in $\dot{V}_E$, by limiting inspiratory times and prolonging expiratory times, and moderate permissive hypercapnia have been suggested.[135-137]

Intraoperative Bronchospasm

The onset of an asthmatic episode may occur abruptly in surgical patients. Airway manipulation, acute exposure to allergens, or the stress of surgery can provoke wheezing in a patient who was previously asymptomatic. The lability of the disease makes assiduous observation crucial. Wheezing often suggests potentially reversible bronchoconstriction, but the extent or degree of wheezing is a notoriously poor indicator of the degree of airway obstruction.[121] In addition, care must be taken to differentiate wheezing of asthmatic origin from other causes of wheezing, such as pneumothorax, endotracheal tube obstruction, endobronchial intubation, anaphylaxis, pulmonary edema, and pulmonary aspiration.[138]

In anesthetized patients, prominent manifestations of the asthmatic episode are wheezing, mucus hypersecretion, high inspiratory pressures, a blunted expiratory CO_2 waveform, and hypoxemia. Mechanical ventilation and positive airway pressure are associated with a higher incidence of air trapping and lung hyperinflation, and the associated inflammation can result in a pneumothorax.[120] Additionally, alveolar overdistention may lead to decreased venous return and diminution of cardiac output. The combination of impaired ventilation and hypoxemia can precipitate increased pulmonary vascular resistance, enhanced right ventricular afterload, and finally hemodynamic collapse.

If an episode of bronchospasm occurs during anesthesia, the following steps are recommended:

1. Deepen the level of anesthesia with a volatile agent, ketamine, propofol, lidocaine, or a combination that rapidly increases anesthetic depth.
2. Administer 100% O_2.
3. Administer a short-acting β_2-agonist (SABA).
4. In severe cases, administer epinephrine intravenously or subcutaneously (in doses of 10 mcg/kg).
5. Administer intravenous corticosteroids—hydrocortisone 2 to 4 mg/kg.
6. Consider intravenous aminophylline if long-term postoperative mechanical ventilation is planned.

Theophylline has little efficacy for the treatment of acute bronchoconstrictive episodes.[139] Episodes of severe airway obstruction may not respond to bronchodilator treatment, and cessation of wheezing may occur with the worsening of obstruction (i.e., the "ominously silent chest").

In treating bronchospasm, SABAs may be administered by metered-dose inhaler or nebulizer, without a clear outcome advantage of either. Multiple doses may be necessary, but it should be noted that these drugs do exhibit a plateau in efficacy. Therefore extremely high does or intravenous β-agonist do not confer additional advantage. Anticholinergic agents such as ipratropium bromide (0.25-0.5 mg nebulizer every 20 minutes × 3) should be used in moderate to severe cases as a second-line therapy to SABA. Because inflammation is central to asthma exacerbation, corticosteroids are becoming more acceptable for acute usage, to prevent the need for longer-term therapy.[140,141] In cases refractory to other bronchodilators, magnesium sulfate (2 gm IV over 20 minutes) has been demonstrated to be safe and effective. Magnesium is effective both as a direct smooth muscle relaxant, and also as an antiinflammatory.[142] Research attention is turning to traditionally chronic-acute medications such as montelukast for their contribution to acute therapy.[140] In severe cases, use of helium-oxygen and noninvasive ventilation may promote gas flow and prevent intubation in cases of impending respiratory failure.[103]

Emergence

The primary issue during emergence is when to extubate. Some authors suggest deep extubation to avoid the mechanical stimulation from the endotracheal tube on awakening. Others fear that the loss of a secure airway before patient awakening may present a greater difficulty than the presence of the endotracheal tube. Either way, a judgment must be made as to when to extubate the patient, with the understanding that the earliest possible time is advantageous for prevention of mechanical bronchial stimulation. Administration of lidocaine and opiates may help diminish airway sensitivity.

The use of anticholinesterase reversal agents also has been an area of concern. The anticholinesterase should be administered in the minimum adequate dose. To ensure a more complete anticholinergic effect, a small increase in the coadministered dose of atropine or glycopyrrolate is suggested.

Asthma and the Pregnant Surgical Patient

Maintaining asthma control during pregnancy is important for the health and well-being of both mother and baby and for ensuring adequate oxygen supply to the fetus. Uncontrolled asthma increases the risk of perinatal mortality, preeclampsia, preterm birth, and low-birth-weight infants. It is safer for pregnant women to be treated with asthma medications than to have asthma symptoms and exacerbations. The EPR-3 report recommends the following general strategies when caring for the pregnant patient[103]:

- The course of asthma improves in one third of women and worsens for one third of women during pregnancy.
- Albuterol is the preferred short-acting β-agonist, (SABA). The most data related to safety during human pregnancy are available for albuterol.
- Inhaled corticosteroids are the preferred long-term control medication. Budesonide is the preferred ICS, because more data are available on using budesonide in pregnant women than are available on other ICSs, and the data are reassuring. However, no data indicate that the other ICS preparations are unsafe during pregnancy.
- Around the time of delivery, note that β-agonists, which promote bronchodilation, also relax the uterus and may impede the progress of labor or encourage postpartum bleeding. Conversely, prostaglandin preparations and ergot alkaloids, which reduce uterine bleeding, can lead to bronchoconstriction.

PULMONARY HYPERTENSION

Definition

Pulmonary hypertension (PH) is defined by a mean pulmonary artery pressure at least 25 mmHg with a pulmonary capillary occlusion pressure of no more than 15 mmHg.[143] Pulmonary arterial hypertension (PAH) is a subgroup of pulmonary hypertension characterized by vascular cell proliferation and cellular changes in low-resistance pulmonary arteries that increase the pulmonary vascular resistance.[144] PAH represents an advanced stage of a large number of cardiovascular diseases.[145]

Although patients with severe PAH would not be considered candidates for nonessential surgical procedures, an anesthetist may encounter patients with PAH presenting for lung transplant or balloon atrial septostomy as treatment.[146,147]

Incidence and Outcome

PAH is a rare disorder, and its true incidence is unknown; however, it is estimated to affect approximately 15 million people.[145] PAH is characterized by a rapidly progressive course with a 79% mortality rate within 5 years of clinical diagnosis.[148] The degree of increase in pressure in the pulmonary circulation has an important influence on the patient's life expectancy,[149] and prognosis is largely determined by right ventricular integrity.[150] Factors that predict perioperative complications include emergency surgery, major surgery, long operative time, use of general anesthesia, and worse New York Heart Association functional class.[144] Pulmonary hypertension carries an increased risk of respiratory failure (approximately 25%), heart failure, and death following noncardiac surgery.[151,152] The perioperative mortality rate associated with PAH is high, even in mild to moderate disease.[145] Recent reviews of outcomes among patients with PAH demonstrated perioperative death rates of 7%,[144] and 18%.[153] The mortality rate among obstetric patients with PAH undergoing surgery is 25%.[154]

Etiology

PAH may be caused by many associated conditions including drug effects, connective tissue disorders, COPD, sarcoidosis, and idiopathic/genetic causes. Five main categories describe the type of pulmonary hypertension: pulmonary arterial hypertension (PAH); pulmonary hypertension due to left heart disease; pulmonary hypertension due to lung diseases and/or hypoxia; chronic thromboembolic pulmonary hypertension; and causes with unclear mechanisms.[154]

Pathophysiology

The normal pulmonary circulation is mostly passive, of low resistance, and highly distensible.[155] PAH is characterized by an increase in vascular tone and the growth and proliferation of pulmonary vascular smooth muscle. Initial reversible vasoconstriction may progress to muscle hypertrophy and irreversible degeneration.[156] Overload of the right ventricle can lead to cor pulmonale and inhibition of coronary perfusion.

Clinical Features and Diagnosis

PAH may be either acute or chronic. In almost all patients with PAH, dyspnea and exercise intolerance usually are the first complaints.[150,157] Patients also may have angina. Right atrial hypertrophy or right ventricular hypertrophy (or both) may be evident on electrocardiogram (ECG). Chest radiography may demonstrate an enlarged pulmonary artery.[158] Cardiac catheterization combined with pulmonary angiography is most informative in assessment of PAH, cardiac reserve, and the effects of pulmonary vasodilator therapy.[156] Vasodilator therapy is attempted when a vasoconstrictor component is identified. Vasodilator challenge may be performed with cardiac catheterization using a rapid and effective pulmonary vasodilator such as nitroglycerin, isoproterenol, nifedipine, prostaglandin E_1, prostacyclin, prostaglandin E_2, hydralazine, nitroprusside, or adenosine for evaluation of the reversibility of PAH.[159] Frequently, open-lung biopsy is performed for assessment of the histopathologic composition of small pulmonary arteries.[160] Noninvasive evaluation includes Doppler echocardiography for measurement of the velocity of tricuspid regurgitation (which correlates well with invasive PAP measurements) and pulmonic peak flow velocity.[161,162]

Attempts to alleviate pulmonary hypertensive disease states have had varied success. Vasodilator agents are used most commonly and may be helpful in patients with reversible vasoconstriction (Table 26-14). Alpha- and beta-adrenergic antagonists have shown the least benefit, whereas prostacyclin has shown the best, and new drugs such as rho-kinase inhibitors show good promise.[146] Possible beneficial effects of pulmonary arterial dilation are preservation of lung function, prevention of right ventricle deterioration, and improved survival.

Anesthetic Management

The principal objectives during anesthesia in patients with PAH are preventing increases in PAH and avoiding major hemodynamic changes.[157] Preoperative evaluation should include ECG, echocardiogram, chest x-ray, and arterial blood gas. Underlying medical conditions (such as COPD) should be optimized. Chronic therapy for PAH should not be discontinued for fear of its hypotensive effect. Instead, intraoperative hypotension should be treated with vasopressors.[145]

TABLE 26-14 Medication Treatment Options for Patients with Pulmonary Hypertension

Drug or Drug Class	Rationale	Potentially Responsive Types of Pulmonary Hypertension	Limitations
Anticoagulants	Reduce risk of pulmonary thromboembolism	Primary PAH and PAH secondary to acute pulmonary thromboembolism, chronic pulmonary thromboembolism, and anorectic drugs	For primary hypertension, concomitant vasodilator treatment also required
Vasodilators			
Calcium channel blockers	Inhibit influx of calcium into smooth muscle cells with elevated vasomotor tone; preferentially act on pulmonary vasculature	Primary PAH and PAH secondary to connective tissue vascular disease and COPD	Initial treatment in specialized centers recommended to avoid severe adverse outcomes such as negative inotropic effects
Epoprostenol (Flolan)—prostacyclin	May replace deficiencies in endogenous prostacyclin; also inhibits smooth muscle proliferation and platelet aggregation	Primary, persistent PAH of the neonate and PAH secondary to ARDS, crises after heart surgery in infants, and connective tissue disease in adults	Peripheral adverse effects occur when administered by continuous IV infusion
Nitric oxide	Interferes with endogenous vasoconstrictor mechanisms	Primary, persistent PAH of the neonate and PAH secondary to corrective cardiac surgery in children, lung or lung-heart transplant surgery in adults, and COPD	Potential adverse effects include increased bleeding times, negative inotropic effects, and formation of potentially toxic products (e.g., nitrogen dioxide, methemoglobin)
Alprostadil (prostaglandin E_1)	Interferes with endogenous vasoconstrictor mechanisms	Secondary to ARDS	Impaired pulmonary metabolism may result in systemic hypotension
Bosentan (Tracleer)	Oral endothelin receptor antagonist	Severe PAH	Hepatotoxicity
Treprostinil (Remodulin) Ambrisentan (Letairis) Sildenafil (Revatio) Tadalafil Iloprost (Ventavis)	Prostacyclin analog Selective endothelin type A (ET_A) receptor antagonist Inhibits phosphodiesterase type 5 Synthetic analog of prostacyclin PGI2	Primary PAH; classes II-IV Treatment of symptomatic patients (WHO class II or III) with pulmonary arterial hypertension (PAH) Treatment for PAH along with anticoagulant and a diuretic Treatment of PAH in patients with NYHA class III or IV symptoms	Given by continuous infusion via wearable infusion pump; peripheral edema, nasal congestion, and serious birth defects may occur Headaches, dyspepsia, and transient color vision Requires inhalation administration 6-9 times a day
Inhibitors of Vasoconstriction			
α-Adrenergic receptor antagonists	Direct vasodilation; inhibit vasopressin release from pituitary	Persistent PAH of the neonate (especially preterm infants) and PAH secondary to COPD	Can cause severe systemic adverse effects
ACE inhibitors	Inhibit formation of the vasoconstrictor angiotensin II	Secondary to connective tissue disease, effects of high altitude, and congestive heart failure	Prolonged treatment required to obtain an effect

Modified from Treprostinil (Remodulin) for pulmonary arterial hypertension. *Med Lett.* 2002;44(1139):80-82; Sildenafil (Revatio) for pulmonary arterial hypertension. *Med Lett.* 2005;47(1215/1216):65-66,165-167; Ambrisentan (Letairis) for pulmonary arterial hypertension. *Med Lett.* 2007;49(1272):87-90.

ACE, Angiotensin-converting enzyme; *ARDS*, acute respiratory distress syndrome; *COPD*, chronic obstructive pulmonary disease; *IV*, intravenous; *NYHA*, New York Heart Association; *PAH*, pulmonary hypertension.

The anesthetic plan should be based upon maintaining cardiovascular homeostasis, particularly related to the pulmonary vasculature. General or regional anesthesia may be used, but a slight tendency toward more frequent complications has been observed in patients receiving general versus regional anesthesia.[144] In that same review, invasive monitoring with pulmonary artery catheter or transesophageal echocardiography did not reduce complications, but that may have been due to those procedures being used in more complicated patients. Neuraxial anesthesia should be considered because it is appropriate for aortic stenosis—striving for slow, gentle onset and avoiding rapid or extensive changes in SVR. For induction of general anesthesia, etomidate is a likely choice, whereas ketamine, which causes an increase in PVR, should be avoided. A balanced technique will avoid unnecessary vasodilation from volatile agents, and an opioid-heavy technique should rely upon volatile agents for amnesia instead of high concentrations of nitrous oxide. Sympathetic stimulation from desflurane should be avoided. Conditions that increase the PVR (hypoxemia, hypercarbia, acidosis, pain, hypothermia) also should be avoided.[144]

Hypotension during surgery should be treated aggressively, and for this reason, invasive arterial pressure monitoring should be used with few exceptions. Hypotension can begin a downward spiral from which it is difficult to recover, but the anesthetist must also discriminate between a drop in SVR or right ventricular failure as the cause of hypotension. In the former case, vasopressors are indicated, whereas in the latter, inhaled nitric oxide or iloprost would be used.[163,164]

COR PULMONALE

Definition

The term *cor pulmonale* refers to right heart failure secondary to pulmonary pathology. Typically this results from pulmonary hypertension that leads to progressive right ventricular hypertrophy,

BOX 26-5

Classification of Pulmonary Hypertension

1. Pulmonary arterial hypertension (PAH)
   - Idiopathic PAH
   - Familial PAH
   - PAH related to:
     - Connective tissue disease
     - Human immunodeficiency virus infection
     - Portal hypertension
     - Drug/toxins
     - Congenital heart disease
     - Persistent pulmonary hypertension of the newborn
   - PAH with venular/capillary involvement (pulmonary venoocclusive disease, pulmonary capillary hemangiomatosis)
2. Pulmonary hypertension with left heart disease
   - Arterial or ventricular
   - Valvular
3. Pulmonary hypertension with lung disease/hypoxemia
   - Chronic obstructive pulmonary disease
   - Interstitial lung disease
   - Sleep-disordered breathing
   - Developmental abnormalities
4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease
   - Thromboembolic obstruction of proximal pulmonary arteries
   - Thromboembolic obstruction of distal pulmonary arteries
   - Nonthrombotic pulmonary emboli
5. Miscellaneous

From Murray JF, Nadel JA. *Textbook of Respiratory Medicine*. 5th ed. Philadelphia: Saunders; 2010.

dilation, and eventual cardiac decompensation. This situation arises from a variety of disorders that affect the structure and function of the lungs (Box 26-5). COPD is the leading cause of cor pulmonale.[165]

Incidence and Outcome

In individuals older than 50 years of age, cor pulmonale is the third most common cardiac disorder (after ischemic heart disease and hypertensive cardiac disease). The male-to-female ratio of incidence of the disease is 5:1, and 10% to 30% of patients admitted to the hospital with coronary heart failure exhibit cor pulmonale.[166] The incidence of pulmonary hypertension among patients with advanced COPD is estimated to be 50%.[167]

Prognosis is determined by the pulmonary disease responsible for the increased PVR. In patients with COPD in whom P_{AO_2} can be maintained at near-normal levels, the prognosis is favorable. However, cor pulmonale associated with hypoxic lung disease is associated with a 70% rate of mortality within 5 years after onset of associated peripheral edema.[168] Prognosis is poor for those patients in whom cor pulmonale is the result of gradual obstruction of pulmonary vessels by intrinsic pulmonary vascular disease or pulmonary fibrosis. These anatomic changes cause irreversible alterations in the pulmonary vasculature, resulting in fixed elevations of PVR.

Etiology

COPD is associated with the functional loss of pulmonary capillaries and subsequent arterial hypoxemia; these events initiate pulmonary vasoconstriction, which is the leading cause of chronic cor pulmonale. The World Health Organization has proposed a classification of conditions associated with cor pulmonale. Diseases associated with hypoxic pulmonary vasoconstriction include the following:

- COPD
- Bronchiectasis
- Chronic mountain sickness
- Cystic fibrosis
- Idiopathic alveolar hypoventilation
- Obesity-related hypoventilation syndrome
- Neuromuscular disease
- Kyphoscoliosis
- Pleuropulmonary fibrosis
- Upper airway obstruction

Diseases that produce obstruction or obliteration of the pulmonary vasculature include the following:

- Pulmonary embolism (PE)
- Pulmonary fibrosis
- Pulmonary lymphangitic carcinomatosis
- Idiopathic PAH
- Progressive systemic sclerosis
- Sarcoidosis
- Intravenous drug abuse
- Pulmonary vasculitis
- Pulmonary venoocclusive disease

Pathophysiology

Pulmonary hypertension is always an underlying pathology of cor pulmonale. In COPD, polycythemia, hypoxic pulmonary vasoconstriction, hyperinflation, and the reduction in size of the pulmonary vascular bed lead to pulmonary hypertension.[169] Sustained pulmonary hypertension produces hypertrophy of the smooth muscle in the tunica media, and remodeling of the vascular smooth muscle leads to irreversible increases in PVR. Also contributory is an imbalance in nitric oxide and endothelin, with the balance tipped toward the vasoconstrictive effects of endothelin.[169] The rate at which right ventricular dysfunction develops depends on the magnitude of pressure increase in the pulmonary circulation and on the rapidity with which this increase occurs. For example, pulmonary embolism may lead to right ventricular failure in the presence of a mean PAP as low as 30 mmHg. By contrast, when PAH occurs gradually, as it does in COPD, right ventricular compensation occurs; congestive heart failure (CHF) rarely occurs before mean PAP exceeds 50 mmHg.

The normal pulmonary circulation can accommodate a maximal right ventricular output with minimal increase in pulmonary pressure via distention of existing vessels or recruitment of unused vessels. The compensatory mechanism for pressure overload on the right ventricle involves enhancement of contractility and an increase in preload, which result in an increase in right ventricular end-diastolic volume.[170] In response to chronic pressure overload imposed by the PAH, right ventricular hypertrophy occurs (chronic leads to hypertrophy). Brain natriuretic peptide shows a positive correlation to ventricular stretch, which occurs in cor pulmonale.[169] Cor pulmonale can be precipitated acutely. For example, patients with COPD have larger than normal increases in PAP when executing maneuvers that increase pulmonary blood flow (e.g., exercise, even if resting hemodynamic status is normal).[171] Cor pulmonale can be produced acutely by sudden increases in PVR, such as from exercise, pulmonary embolism, or ARDS.[172]

Clinical Features and Diagnosis

Clinical manifestations of cor pulmonale often are nonspecific and obscured by coexisting COPD. Echocardiography may be useful,[172] but right-sided heart catheterization usually is required

for diagnosis. Cardiac catheterization combined with pulmonary angiography provides the most definitive information on the degree of PAH, cardiac reserve, and the effects of pulmonary vasodilator treatment.[156]

Symptoms of cor pulmonale are retrosternal pain, cough, dyspnea on exertion, weakness, fatigue, early exhaustion, and hemoptysis.[156] Occasionally hoarseness secondary to left recurrent laryngeal nerve compression by the enlarged pulmonary artery is present.[166] Syncope on effort may occur, reflecting the inability of the right ventricular stroke volume to increase in the presence of a fixed elevation of PVR.

Physical signs of cor pulmonale include the following:

- Elevation of jugular venous pressure
- Cardiac heave or thrust along the left sternal border and S_3 gallop
- Presence of an S_4 heart sound secondary to significant right ventricular hypertrophy
- A widely split S_2 heart sound
- Possible murmur of pulmonic and tricuspid insufficiency
- Hepatomegaly, ascites, and lower-extremity edema (late signs)

Diagnostic Testing

Electrocardiography. Right atrial displacement, right ventricular hypertrophy, right atrial hypertrophy, and right atrial enlargement may be observed. *P pulmonale* (tall, peaked p-waves) are a characteristic sign. Patients may develop concomitant supraventricular tachycardic arrhythmias (i.e., tachycardic atrial fibrillation, sinus tachycardia, and paroxysmal atrial tachycardia).

Imaging Studies. On chest radiography, enlargement of the pulmonary arteries is observed, followed by right ventricular hypertrophy. Meeting criteria for pulmonary artery dilation has 98% sensitivity for diagnosing pulmonary hypertension.[169] Echocardiography may be helpful to demonstrate enlargement, dilation, or thickening of the right ventricle, with or without tricuspid valve regurgitation, and elevated pulmonary artery systolic pressure. All of these findings suggest that at least acute or possibly chronic PAH is present. Shifting of the intraventricular septum as a result of increased right ventricular end-diastolic volume is another characteristic finding.[169] Although more expensive, magnetic resonance imaging provides better evaluation of the ventricular wall thickness than does echocardiography.

Treatment

The three major drug classes for treatment of PAH are prostanoids, endothelin receptor antagonists, and phosphodiesterase inhibitors. The goals of treatment are decreasing the workload of the right ventricle, reducing PVR, preventing increases in PAP, and avoiding major hemodynamic changes. Diuretics may be used to reduce cardiac workload, but caution must be employed to avoid causing inadequate preload.[169] Improvement of gas exchange is the primary focus of treatment in COPD patients with cor pulmonale.[156,173] Treatment includes supplemental administration of O_2 to maintain a Pa_{O_2} of greater than 60 mmHg or an arterial O_2 saturation of greater than 90%. O_2 is the only vasodilator with a selective effect on pulmonary vessels that is not associated with a risk of worsening hypoxemia.[174] Ventilation under anesthesia should focus on maintaining low airway pressures and avoiding PEEPi.[172]

Heart-Lung Transplantation

A heart-lung transplantation may ultimately be needed when cor pulmonale progresses despite the provision of maximal medical therapy.

In general, preoperative preparation of the patient with cor pulmonale includes the following:

- Elimination and control of acute or chronic pulmonary infections
- Reversal of bronchospasm
- Improvement in clearance of secretions
- Expansion of collapsed or poorly ventilated alveoli
- Hydration
- Correction of any electrolyte imbalance

Anesthetic Management

Regional anesthesia technique may be appropriate as long as a high sensory level of anesthesia is not required, because any decrease in systemic vascular resistance in the presence of a fixed PVR may produce undesirable degrees of systemic hypotension.[175]

General Anesthesia

Volatile agents decrease PVR. Studies have demonstrated that PAP is decreased by isoflurane. N_2O has been shown to increase PVR in patients with PPH. Intravenous agents, with the exception of ketamine, appear to have little effect on PVR. During all stages of anesthesia, manipulations that increase PAP must be avoided. Five key principles should be followed[156]:

- Maintain good oxygenation.
- Avoid acidosis.
- Avoid the use of exogenous and endogenous vasoconstrictors.
- Avoid presenting stimuli that increase sympathetic tone.
- Avoid hypothermia.

PULMONARY EMBOLISM

Definition

Pulmonary embolism (PE) is the impaction of a dislodged thrombus into the pulmonary vascular bed. A significant thrombus obstructs blood flow and causes forward ischemia and rearward cardiac overload.

Incidence and Outcome

Being a major source of morbidity and mortality, PE affects between 300,000 and 600,000 people in the United States annually. One-third of them develop post-thrombotic syndrome (long-term complications such as swelling, pain, and discoloration in the affected limb), one-third of people with PE die within 1 month of diagnosis, and one-fourth of them present with sudden death as the first symptom.[176] Pulmonary emboli originate from deep vein thrombosis (DVT) of the iliofemoral vessels in approximately 90% of patients, although other sites of thrombus formation include the pelvic veins, the renal and hepatic veins, the axillary veins in the upper extremities, and the right atrium.[177] PE occurs in approximately 1% of surgical patients overall,[178] but the incidence is as high as 30% among high-risk orthopedic procedures.[179] Mortality from perioperative PE is approximately 10%.[178,180]

Etiology

PE is considered by some to be a clinical manifestation of DVT rather than a separate entity, because almost all incidents of PE result from an embolized vein thrombosis. The incidence of symptoms from DVT is greater with more proximal sites of thrombosis. Three major factors promote the formation of venous thrombi: stasis of blood flow, venous injury, and hypercoagulable states. These three components are described as the Virchow triad and underlie the risk factors for venous thrombosis (Box 26-6). Smoking and obesity have been shown to be independent risk factors for PE in women,[181] and malignancies are a particularly high risk for

BOX **26-6**

Risk Factors for Venous Thrombosis, Based Upon Virchow's Triad

Stasis
- Congestive heart failure or cor pulmonale
- General anesthesia
- Immobility
- Obesity
- Prior venous thrombosis
- Varicose veins

Hypercoagulability
- Disseminated intravascular coagulation
- Estrogen therapy/oral contraceptive use
- Infection
- Malignancy
- Nephrotic syndrome
- Pregnancy
- Thrombophilias:
  - Anticardiolipin antibody
  - Factor V Leiden mutation
  - Protein C and S deficiencies
  - Antithrombin III deficiency

Vascular injury
- Trauma
- Surgery

Modified from Ozsu S, et al. The role of risk factors in delayed diagnosis of pulmonary embolism. *Am J Emerg Med*. 2011;29(1):26-32; Epley D. Pulmonary emboli risk reduction. *J Vasc Nurs*. 2000; 18(2):61-8;69-70; Dijk FN, et al. Pulmonary embolism in children. *Paediatr Respir Rev*. 2012;13[2]:112-122.

PE. Cancer patients are found to have over twice the incidence of venous thromboembolism as that in the general population, and this risk is heightened further when indwelling central venous catheters are in place.[182] Other, less common causes of PE include air, tumor, bone, fat, catheter fragments, and amniotic fluid. Fillers used in illicit drug preparations by intravenous drug abusers also may cause PE. Of particular concern to anesthesia providers are air emboli caused by the opening of venous structures during surgery or by disconnected intravenous lines.

Most pulmonary emboli resolve within 8 to 21 days of the initial presentation; 10% to 20% are estimated to develop into unresolved emboli, and 0.5% to 4% lead to the development of chronic PAH. Chronically unresolved emboli that lodge in major pulmonary arteries may become incorporated into the vascular walls and obstruct blood flow. Patients with such emboli are surgical candidates, representing approximately 1000 cases in the United States each year.[183]

Pathophysiology

Once a thrombus has formed, it rarely remains static. It can be dissolved through fibrinolysis, become "organized" into a vessel wall, or be released into the circulation. Because thrombi are most friable early in their development, it is then that the greatest risk for embolization exists.

If the fragment is released from its site of formation, it can be rapidly swept into one of the pulmonary arteries. It may pass through the vasculature completely, disintegrate, and block several smaller pulmonary vessels; or if the thrombus is sufficiently large, it may impact against one or both pulmonary arteries and cause pulmonary collapse, massive infarction, and ultimately cardiac arrest.[184]

Within the pulmonary capillaries, hemorrhage is frequently seen distal to the site of the embolism. The alveolar structures in this area can remain viable for a period of time.[184] However, if the clot does not dissolve or if it is not quickly squeezed through the vasculature, the alveolar structure will be permanently damaged. Bronchial circulation limits this consequence of pulmonary infarction, and substantial damage is unusual unless an embolus completely blocks a large artery or preexisting lung disease is present.[185] In fact, less than 10% of emboli actually cause any type of infarction.[186]

Mechanism

When a pulmonary artery is occluded, ventilation distal to the obstruction is decreased. This is a result of the direct effect of alveolar P_{CO_2} (P_{ACO_2}) on the smooth muscle of the local small airways, which is bronchoconstriction. The reduction of airflow to the unperfused lung reduces the amount of wasted ventilation. This mechanism is very short lived, with distribution of ventilation returning to normal within several hours.[184,186] The elastic properties of the embolized region may change some hours after the event; localized atelectasis is believed to result from a loss of pulmonary surfactant, the rapid turnover of which requires adequate blood flow.[186]

Pulmonary Function

Pulmonary Circulation. Normally the pulmonary circulation has a very large reserve capacity. However, when PAPs increase, previously unfilled capillaries are recruited, and distention occurs. This allows for obstruction of at least half of the pulmonary circulation before a substantial increase in PAP becomes manifest.[184] Obstruction of perfusion begins a damaging cycle, as blood flow is further reduced by serotonin and platelet-activating factor from platelets of the embolus, vasoactive peptides from plasma, and histamine from mast cells.[187] Occlusion of approximately 70% of the pulmonary vascular bed results in PAH with subsequent right ventricular failure, increased end-diastolic pressures, and development of arrhythmias and possibly of tricuspid valve incompetence.[185] Pulmonary edema may follow, because blood flow is diverted to alternate areas of lung.[184,188] Acute pulmonary edema develops when hyperperfusion from intact circulation to the perfused lung results in extravasation of fluid into the alveoli. If the clot breaks up and passes quickly or if the affected area is minimal, the PAPs gradually decrease with embolus resolution by fibrinolysis or transformation onto the vessel wall as a scar.[185]

The right ventricle will initially increase stroke volume through adrenergic activation. Eventually, though, the increased ventricular volume shifts the intraventricular septum and reduces left heart output. The reduction in left ventricular output can compromise coronary filling, and lead to ischemia, which further degrades contractility.[187]

Gas Exchange. An embolus can have a significant effect on gas exchange. Moderate hypoxemia without CO_2 retention is often seen after PE as both physiologic shunt and dead space increase. In spontaneously breathing patients, P_{aCO_2} is maintained at the normal level after PE by increasing the respiratory rate. The resultant increase in ventilation may be substantial because of the large physiologic dead space. Because the anesthetized patient who is not spontaneously breathing cannot increase his or her ventilation, the P_{aCO_2} rises and O_2 saturation decreases more quickly.[186,189]

BOX 26-7

Differential Diagnosis of Acute Intraoperative Pulmonary Embolism

- Anaphylactic reaction
- Aortic dissection
- Aortic stenosis
- Brainstem stroke
- Bronchospasm
- Heart failure
- Hypertrophic cardiomyopathy
- Myocardial infarction
- Pulmonary hypertension
- Tension pneumothorax

The difference between Pa_{CO_2} and end-tidal P_{CO_2} ($P_{ET}CO_2$) is a very useful indicator in PE, with high sensitivity and specificity.[186] The mixed $P_{ET}CO_2$ tends to be low because of the high $\dot{V}/\dot{Q}$ ratio in the embolized region. Particularly if underlying ventilation and perfusion prior to embolization were well matched, the $P_{ET}CO_2$ is an accurate and immediate indicator of the status of pulmonary gas exchange. In anesthetized patients, the Pa_{CO_2} continues to increase more quickly because of this increase in dead space without ventilatory compensation. If the embolus does not completely occlude the vessel, the discrepancy between $P_{ET}CO_2$ and Pa_{CO_2} may not be as great.[184]

Clinical Features and Diagnosis

The patient's clinical presentation depends largely on the size of the embolus. Signs and symptoms of PE vary and are common to a number of disorders. Therefore, the differential diagnosis may be difficult (Box 26-7). Dyspnea of sudden onset appears to be the only common historic complaint. Sudden hypotension and tachycardia, wheezing, tachypnea, and signs of right ventricular overload are common. Hypoxemia is a constant feature of PE, possibly owing to intrapulmonary shunting. Because PE often occurs without premonitory signs and the symptoms are not highly specific, in the acute setting, diagnosis is often presumptive and by exclusion. Table 26-15 outlines common clinical findings (history and symptoms) in patients who developed pulmonary embolism.

Small emboli often go unrecognized; however, multiple small emboli can produce extensive obstruction of the pulmonary capillary bed, possibly causing PAH and cardiac failure. Generally, however, small thromboemboli are incorporated into the arterial wall and have little effect on either parenchyma or the circulation. Patients may complain of dyspnea on exertion that may lead to syncope; sometimes, a right ventricular "heave" or a split-second heart sound can be detected on examination. Patients with medium-sized emboli may present with pleuritic pain accompanied by dyspnea, a slight fever, and a productive cough that yields blood-streaked sputum. These patients usually are tachycardic. A small pleural effusion can develop and mimic the appearance of pneumonia.

Massive emboli can produce sudden cardiac collapse. Preceding symptoms range from pallor, shock, and central chest pain to sudden loss of consciousness. In patients with cardiac collapse, the pulse becomes rapid and weak, blood pressure decreases, neck veins become engorged, and cardiogenic shock may be present or impending. Also, a decrease in $P_{ET}CO_2$ and an increase in Pa_{CO_2} occur, with the difference between the values increasing as conditions worsen. If a pulmonary artery catheter is in place, pulmonary artery pressures (PAPs) are observed to increase rapidly. The ECG may begin to show right ventricular strain. The prognosis for these patients is very poor.[184]

TABLE 26-15 Associated Factors in Patients with Pulmonary Embolism*

Finding	Incidence
Dyspnea	96%
Tachycardia	71%
Acute onset of symptoms (<48 hr)	70%
Syncope	35%
Arterial hypotension (SBP <90 mmHg)	34%
Congestive heart failure	32%
History of venous thrombosis	29%
Recent major operation (within 10 days)	27%
Cancer	12%
Major trauma or fracture within 10 days	11%
Chronic pulmonary disease	11%
Stroke	2%

From Kasper W, et al. Management strategies and determinants of outcome in acute major pulmonary embolism: results of a multicenter registry. *J Am Coll Cardiol.* 1997;30(5):1165-1171.
*Data from 1001 patients with pulmonary embolism.
SBP, Systolic blood pressure.

Diagnostic Testing

Few of the common preoperative tests indicate the presence of PE. A number of imaging and laboratory tests are available for diagnosis (Table 26-16). The most common electrocardiographic signs are noted in Box 26-8. In addition, echocardiography may demonstrate right ventricular dilation or dyskinesis, septal shift, tricuspid regurgitation, or dilation of the pulmonary artery. In the patient with PE, ABG analysis generally reveals hypoxemia and increased differences between Pa_{CO_2} and $P_{ET}CO_2$, which result from ventilation of unperfused alveoli.[189] Massive PE is associated with severe hypoxemia and hypocapnia. An initial difference between Pa_{CO_2} and $P_{ET}CO_2$ is common early during the embolic event.[186] Some common conditions associated with an increased risk for deep vein thrombosis are given in Box 26-9.

There are limited laboratory analyses useful to support the diagnosis of PE. The d-dimer assay cannot rule in PE, but a normal result makes diagnosis of PE very unlikely. Troponin I and troponin T levels are elevated in less than one half of cases of significant PE. Therefore, their presence is not useful for diagnosis, but elevation of troponins is associated with adverse outcomes including death and the need for aggressive resuscitation.[190]

Prevention

Aggressive efforts at prevention have been successful in reducing the incidence of DVT in surgical patients. Use of compression stockings, intermittent pneumatic compression devices, administration of various anticoagulants and thrombolytics, and ambulation are typical measures for preventing embolus formation. Because surgery is a risk factor for venous thromboembolism, care should be taken to reduce risk for every surgical patient. Anesthesia for patients at risk for PE is aimed at avoiding venous stasis, hypercoagulability, and vessel injury. This involves ensuring administration of lower extremity circulatory aids or anticoagulants before anesthetic induction. Anesthetic planning also may contribute to

TABLE 26-16 Diagnostic Tests for Suspected Pulmonary Embolism

Test	Comments
Oxygen saturation	Nonspecific, but suspect PE if there is a sudden otherwise unexplained decrement
Electrocardiogram	May be normal, especially in younger, previously healthy individuals; may provide alternative diagnosis, such as myocardial infarction or pericarditis
Echocardiography	Best used as a prognostic test in patients with established PE, rather than as a diagnostic test; many patients with larger PE will have normal echocardiograms
Lung scanning	Usually provides ambiguous results, used in lieu of chest CT for patients with anaphylaxis to contrast agent, renal insufficiency, or pregnancy
Chest CT	Most accurate diagnostic imaging test for PE; beware if CT result and clinical likelihood are discordant
Pulmonary angiography	Invasive, costly, uncomfortable; used primarily when local catheter intervention is planned
D-dimer	An excellent "rule out" test if normal, especially if accompanied by non-high clinical suspicion
Venous ultrasonography	Excellent for diagnosing acute symptomatic proximal DVT, but a negative test does not rule out PE, because a recent leg DVT may have embolized completely; calf vein imaging is operator dependent
Magnetic resonance imaging	Reliable only for imaging proximal segmental pulmonary arteries; requires gadolinium but does not require iodinated contrast agents

From Goldhaber SZ. Pulmonary embolism. In: Bonow RO, et al. *Braunwald's Heart Disease*. 9th ed. Philadelphia: Saunders; 2012:1686.
PE, pulmonary embolism; *CT*, computed tomography; *DVT*, deep venous thrombosis.

BOX 26-8

Electrocardiographic Signs Associated with Pulmonary Embolism

- Negative T wave in leads V1-V5
- Right axis deviation greater than 90 degrees
- Negative T wave in leads II, III, aVF
- Pulmonary P wave
- R greater than S or Q in aVR
- Complete or incomplete right bundle branch block (RBBB)

From Lewczuk J, et al. Electrocardiographic signs of right ventricular overload in patients who underwent pulmonary embolism event(s). Are they useful in diagnosis of chronic thromboembolic pulmonary hypertension? *J Electrocardiol.* 2004;37(3):219-25.

risk reduction. For example, the use of neuraxial anesthesia, which causes vasodilation in the lower extremities, reduces the incidence of DVT by 50% in comparison to general anesthesia.[191,192]

Medical and Surgical Treatment

Guidelines for treatment of PE are summarized in Box 26-10. Anticoagulation is the most common intervention, aimed at preventing further insult. Clot removal is most often accomplished with thrombolytic agents. Surgical intervention is indicated for patients who are unresponsive to other measures; however, this represents only around 1% of patients.[193] Currently the most common surgical procedure for patients with PE is placement of an umbrella filter, which traps thromboemboli. Vena cava filters are usually indicated for patients with bleeding disorders who are not able to tolerate standard anticoagulant therapy, or for those who are refractory to anticoagulant therapy. The filter is placed in the inferior vena cava under fluoroscopic guidance, usually below the renal veins at the level of the L2 to L3. Suprarenal placement is required when a thrombus directly involves the renal veins or has propagated above the level of the renal veins. The presence of an infrarenal filter in a pregnant woman may place her and her fetus at risk because of the possibility that the filter will come in to contact with the gravid uterus. Suprarenal placement prevents this risk.

Thromboendarterectomy is the treatment of choice for chronic large vessel thromboembolic PAH.[194] Desired results include decreased pulmonary vascular resistance (PVR), improved CO, restoration of exercise tolerance, and resolution of hypoxemia. Improvements in RV function and hemodynamics may be prompt, whereas improvements in gas exchange occur over weeks to months. Although the role of pulmonary embolectomy remains controversial, in the few patients who do not benefit from optimal medical therapy, it remains an acceptable procedure.[195]

Anesthetic Management

Anesthetic management of a patient presenting with a pulmonary embolus is primarily aimed at preventing further embolism and providing respiratory and cardiovascular support.[196] Table 26-17 outlines preventative prophylactic medications for patients at risk of PE. The use of a high F_iO_2 supports pulmonary vasodilation. If PAP is monitored, the anesthesia provider will have additional information to optimize right-sided heart function and assess the effects of anesthetic management on PVR.[188] However, the risk-benefit ratio of a pulmonary artery catheter should consider the possibility that these catheters may dislodge clots in the right side of the heart. Induction is often performed with etomidate. Ketamine may appear to be a compelling choice in the face of cardiovascular compromise, but ketamine may increase PVR.[186] The use of N_2O is generally believed to be acceptable. However, the use of N_2O may be limited by the desire to administer high F_iO_2 and concerns for increasing the PVR. The use of N_2O is contraindicated in patients with venous air embolism, because of the potential for N_2O to rapidly expand the volume of the embolism.[185] Patients with moderate to severe PE often are experiencing acute right-sided heart failure. Cardiac function can be optimized by the use of minimally depressing cardiac agents such as opioids.

Persistent, severe hypotension, such as that accompanying a massive PE, may necessitate the use of a cardiotonic agent or partial or full cardiopulmonary bypass. The goal is preservation of perfusion to the brain and heart until cardiopulmonary bypass is started and surgical removal of the clot attempted.[188] Patients with PE are extremely sensitive to any anesthetic agent. It is critical to have heparin ready to support initiation of bypass if necessary. Although separation from bypass is beyond the scope of this chapter, the anesthetist should anticipate that difficulties may be encountered. Reports of operative mortality during pulmonary embolectomy range from 11% to 55%, with much higher rates among patients experiencing cardiac arrest.[197]

BOX **26-9**

Conditions Associated with Increased Risk for Deep Vein Thrombosis

- Advancing age
- Obesity
- Previous venous thromboembolism
- Surgery
- Trauma
- Active cancer
- Acute medical illnesses—e.g., acute myocardial infarction, heart failure, respiratory failure, infection
- Inflammatory bowel disease
- Antiphospholipid syndrome
- Dyslipoproteinemia
- Nephrotic syndrome
- Paroxysmal nocturnal hemoglobinuria
- Myeloproliferative diseases
- Behçet's syndrome
- Varicose veins
- Superficial vein thrombosis
- Congenital venous malformation
- Long-distance travel
- Prolonged bed rest
- Immobilization
- Limb paresis
- Chronic care facility stay
- Pregnancy/puerperium
- Oral contraceptives
- Hormone replacement therapy
- Heparin-induced thrombocytopenia
- Other drugs
- Chemotherapy
- Tamoxifen
- Thalidomide
- Antipsychotics
- Central venous catheter
- Vena cava filter
- Intravenous drug abuse

BOX **26-10**

Guidelines for the Treatment of Pulmonary Embolism

1. Treat DVT or PE with therapeutic levels of unfractionated intravenous heparin, adjusted subcutaneous heparin, or low-molecular-weight heparin for at least 5 days and overlap with oral anticoagulation for at least 4 to 5 days. Consider a longer course of heparin (approximately 10 days) for massive PE or severe iliofemoral DVT. Enoxaparin, tinzaparin, or fondaparinux also may be used depending on renal function and indications.
2. For most patients, heparin and oral anticoagulation can be started together and heparin discontinued on day 5 or 6 if the INR has been therapeutic for 2 consecutive days.
3. Patients with reversible or time-limited risk factors can be treated for at least 3 months. Patients with a first episode of idiopathic DVT should be treated indefinitely. Approved regimen is warfarin, target INR of 2.0 to 3.0 for 6 months, followed by low-intensity warfarin, target INR of 1.5 to 2.0.
4. The use of thrombolytic agents continues to be highly individualized, and clinicians should have some latitude in using these agents. Patients with hemodynamically unstable PE or massive iliofemoral thrombosis are the best candidates.
5. Inferior vena caval filter placement is recommended when there is a contraindication to or failure of anticoagulation, for chronic recurrent embolism with pulmonary hypertension, and with concurrent performance of surgical pulmonary embolectomy or pulmonary endarterectomy.

Modified from Goldhaber SZ. Deep vein thrombosis and pulmonary thromboembolism. In: Longo DL, et al, eds. *Harrison's Principles of Internal Medicine*. 18th ed. Vol. 2. New York: McGraw-Hill; 2012: 2170-2177.
DVT, Deep vein thrombosis; *INR*, international normalized ratio; *PE*, pulmonary embolism.

Detection of Pulmonary Embolism During Anesthesia

In the intubated patient under general anesthesia, clinical presentation is limited to objective signs. A decreasing PET_{CO_2} and tachycardia usually are the first signs of PE.[188,189] These can be followed by a decrease in Sa_{O_2} and the generation of ABG values that indicate unexplained arterial hypoxemia. In the case of massive PE, abrupt, unexplained hypotension and tachycardia are the classic (albeit, nonspecific) signs. Increased PAP and central venous pressure (CVP) are observed in combination with a decrease in systolic and diastolic blood pressures.[189] Bronchospasm may occur.[183] Finally, ECG changes that indicate right axis deviation, incomplete or complete right bundle branch block, or peaked T waves may be observed in the presence or absence of an accompanying systolic ejection murmur.[184,189]

Intraoperative Management of Acute PE

In the case of suspected PE in the anesthetized patient, treatment requires rapid intervention because cardiovascular decompensation can occur quickly. First and most importantly, an airway must be established by intubation if the patient is not already intubated. Second, delivery of the anesthetic agent must be discontinued, and administration of a 100% Fi_{O_2} initiated.[188] Next, the circulatory system should be supported with the infusion of intravenous fluids or blood (or both) as needed, and sympathomimetics initiated if necessary. Norepinephrine may be the vasopressor of choice, because of its ability to support contractility as well as improve brain perfusion through vasoconstriction.[187] Epinephrine, dopamine, or dobutamine + norepinephrine may also be helpful. Ventricular dysrhythmias should be treated with

TABLE 26-17 Prevention of Venous Thromboembolism

Condition	Strategy
Total hip or knee replacement; hip or pelvis fracture	Warfarin (Coumadin) (target INR 2.5) × 4-6 weeks LMWH/subcut (e.g., fondaparinux 2.5 mg subcut [except for total knee replacement]) or rivaroxaban 10 mg daily or dalteparin 2500-5000 units daily subcut where available IPC ± warfarin
Gynecologic cancer surgery	LMWH consider 1 month of prophylaxis
Thoracic surgery	IPC *or* GCS *plus* unfractionated heparin, 5000 units bid or tid
High-risk general surgery (e.g., prior VTE, current cancer, or obesity)	IPC *or* GCS *plus* unfractionated heparin, 5000 units bid tid or LMWH
General, gynecologic, or urologic surgery (without prior VTE) for noncancerous conditions	GCS *plus* unfractionated heparin 5000 units bid or tid Dalteparin 2500 units subcut once daily Enoxaparin 40 mg subcut once daily
Neurosurgery, eye surgery, or other surgery when prophylactic anticoagulation is contraindicated	GCS ± IPC
Neurosurgery	Unfractionated heparin 5000 units bid or tid Enoxaparin 40 mg subcut once daily GPC *or* IPC Consider surveillance of lower extremity by ultrasonography
Orthopedic surgery	Enoxaparin 30 mg twice daily Enoxaparin 40 mg once daily* Dalteparin 5000 units once daily* Fondaparinux 2.5 mg subcut daily Warfarin (target INR = 2-3) GCS *plus* IPC
General surgery	Unfractionated heparin 5000 units bid or tid Enoxaparin 40 mg daily Dalteparin 2500 or 5000 units once daily GCS *plus* IPC
Pregnancy	Enoxaparin 40 mg daily Dalteparin 5000 units daily
Medical patients	Unfractionated heparin 5000 units bid or tid Enoxaparin 40 mg daily Dalteparin 5000 units once daily Fondaparinux 2.5 mg subcut daily in patient who cannot tolerate heparin Consider surveillance of lower extremity by ultrasonography GCS *plus* IPC
Long distance air travel	LMWH for high-risk patients

Modified from Goldhaber SZ. Deep vein thrombosis and pulmonary thromboembolism. In: Longo DL, et al, eds. *Harrison's Principles of Internal Medicine*. 18th ed. Vol. 2. New York: McGraw-Hill; 2012:2177; Goldhaber SZ. Pulmonary embolism. In: Bonow RO, et al, eds. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*. 9th ed. Philadelphia: Saunders; 2012:1692.
*Approved only for total hip replacement prophylaxis.
GCS, Graduated compression stockings; *INR*, international normalized ratio; *IPC*, intermittent pneumatic compression; *LMHW*, low-molecular weight heparin; *subcut*, subcutaneous; *VTE*, venous thromboembolism.

intravenous administration of lidocaine or amiodarone, and the patient should receive PEEP for optimization of oxygenation.[185] If symptoms are refractory to treatment, thrombolysis or pulmonary embolectomy may be necessary. Severe hemodynamic difficulty should be anticipated and resuscitative efforts continued. In severe cases, cardiopulmonary bypass may be necessary until the obstruction can be relieved.

Patients with PE present particular management challenges in their postoperative course, including reperfusion edema, persistent hypoxemia, pericardial effusion, psychiatric disorders, and pulmonary blood flow steal. The areas of the lung to which pulmonary artery flow has been restored are subject to development of reperfusion pulmonary edema, presumably as a manifestation of oxidant- and protease-mediated acute lung injury. Other possible causes are extracorporeal circulation, anticoagulation, and an increase in perfusion pressure in a previously obstructed pulmonary artery. Complications include immediate pulmonary hemorrhage and respiratory disturbance, and death may occur.[197] This syndrome may develop 3 to 5 days after surgery.[198] Olman et al.[199] have observed that after pulmonary thromboendarterectomy for relief of chronic thromboembolic PAH, perfusion lung scans often reveal new perfusion defects in segments served by undissected pulmonary arteries. This phenomenon has been labeled *pulmonary blood flow steal* and is believed to be caused by

TABLE 26-18 Common Causes of Restrictive Lung Disease

Cause	Example
Interstitium	
Interstitial fibrosis, infiltration	Asbestosis
Pulmonary edema	Left ventricular failure
Pleura	
Pleural disease	Fibrothorax
Thoracic Cage and Abdomen	
Neuromuscular disease	Poliomyelitis
Skeletal abnormalities	Severe kyphoscoliosis
Marked obesity	Gross obesity

Modified from Taichman DB, Fishman AP. Approach to the patient with respiratory symptoms. In: Fishman AP, et al, eds. *Fishman's Pulmonary Diseases and Disorders*. 4th ed. New York: McGraw-Hill; 2008:400.

postoperative redistribution of regional PVR due to the altered (widened) architecture of the dissected vessels that received arterectomy. No evidence of embolism was found in the previously normal areas.

RESTRICTIVE PULMONARY DISEASES

Definition

Restrictive pulmonary disease is defined as any condition that interferes with normal lung expansion during inspiration, and it is characterized by a TLC below the 5th percentile.[44] Typically, it includes disorders that increase the inward elastic recoil of the lungs or chest wall (Table 26-18). Consequently, the alteration in pulmonary dynamics results in decreases in lung volumes and capacities and in lung or chest-wall compliance. Some restrictive diseases produce ventilation abnormalities and $\dot{V}/\dot{Q}$ mismatching, whereas others lead to impairment of diffusion. FEV_1 and FVC are both decreased, owing to a reduction in TLC or a decrease in chest-wall compliance or muscle strength However, the FEV_1/FVC ratio is normal or elevated.

Impairment-producing restrictive pulmonary diseases can be classified as: (1) acute intrinsic, (2) chronic intrinsic, or (3) chronic extrinsic. Acute intrinsic disorders are primarily caused by the abnormal movement of intravascular fluid into the interstitium of the lung and alveoli secondary to the increase in pulmonary vascular pressures occurring with left ventricular failure, fluid overload, or an increase in pulmonary capillary permeability. Examples of acute intrinsic disorders include pulmonary edema, aspiration pneumonia, and acute respiratory distress syndrome (ARDS). Chronic intrinsic diseases are characterized by pulmonary fibrosis. Conditions that produce fibrosis of the lung include idiopathic pulmonary fibrosis (IPF), radiation injury, cytotoxic and noncytotoxic drug exposure, O_2 toxicity, autoimmune diseases, and sarcoidosis. Chronic extrinsic diseases can be defined as disorders that inhibit the normal lung excursion. They include flail chest, pneumothorax, and pleural effusions. They also include conditions that interfere with chest-wall expansion, such as ascites, obesity, pregnancy, and skeletal and neuromuscular disorders.

The pulmonary system and its functions are directly manipulated by the administration of anesthesia. The effect of intraoperative pulmonary insult or preexisting pulmonary disease on respiratory function during anesthesia and the postoperative period is predictable: greater degrees of pulmonary impairment lead to marked alterations in intraoperative respiratory status and higher rates of occurrence of postoperative pulmonary complications. This section illustrates the pathophysiologic changes involved in these clinical disorders and discusses their clinical presentation, diagnosis, treatment, and anesthetic implications.

Pulmonary Edema

Pulmonary edema is not itself an independent disease entity, but rather the result of a variety of disease processes. Simply stated, pulmonary edema is the accumulation of excess fluid in the interstitial and air-filled spaces of the lung. The mechanisms responsible for its development include an increase in hydrostatic pressure within the pulmonary capillary system, an increase in the permeability of the alveolocapillary membrane, and a decrease in intravascular colloid oncotic pressure.[200]

To understand the etiology and pathophysiology of pulmonary edema, Starling's law of transcapillary fluid exchange must be clearly understood. The pulmonary capillary endothelium is semipermeable. Pulmonary interstitial fluid pressures, both hydrostatic (peak inspiratory flow [Pif]) and osmotic (πif), along with the hydrostatic pressure in the pulmonary capillaries (Pc) and the osmotic pressure of the plasma (πp), are the primary determinants that balance fluid exchange across this semipermeable barrier.[201] These factors, which ultimately determine the amount of fluid that actually leaves the pulmonary vascular space, are incorporated into what is known as the *Starling equation*. A simplified version of this equation is as follows:

$$\dot{Q} = k[(Pc - Pif) - (\pi p - \pi if)]$$

where $\dot{Q}$ is the total amount of fluid that traverses the endothelial membrane and *k* is the fluid filtration coefficient, which describes quantitatively the permeability of the membrane.[200,201]

The Pc, the force favoring fluid movement out of the vessel wall, is in direct opposition to the Pif. The Pif, when positive, tends to force fluid inward through the capillary membrane; when it is negative, it tends to force fluid outward.[4] The πp and Pif also oppose each other, with the πif keeping fluid within the capillary and the Pif pulling it outward into the interstitium. Overall, the balance of forces shown in the Starling equation favors fluid filtration into the interstitial space. Fluid filtered out into the alveolar interstitial space does not enter the alveoli, because under normal conditions, the alveolar epithelium is composed of very tight junctions that prevent fluid and protein from entering the alveolar air spaces. The fluid moves to the extravascular interstitial space, where the lymphatic vessels remove all of the filtered fluid and return it to the systemic circulation.[202]

Pulmonary edema can occur if any variable in the Starling equation is altered in the direction favoring increased fluid filtration. High pressure (Pc) and increased permeability (k) are the two most important components of the Starling equation that are altered in states of pulmonary edema. Because of this, pulmonary edema is classified as being either cardiogenic (high pressure, hydrostatic) or noncardiogenic (permeability is increased).

Cardiogenic pulmonary edema occurs whenever the Pc is increased. Increased Pc is the most common form of pulmonary edema. Cardiogenic pulmonary edema is initiated by some type of left-sided heart incompetence or failure. The term *left ventricular failure* implies that a decrease has occurred in left ventricular contractility, which ultimately leads to a reduction in both stroke volume and CO. Incomplete left ventricular emptying elevates left ventricular end-diastolic volume, which in turn elevates left ventricular end-diastolic pressure. Increased left ventricular end-diastolic pressure is "reflected back," causing elevation of the

left atrial, pulmonary venous, and pulmonary capillary pressures. When pulmonary capillary pressure reaches levels of 20 to 25 mmHg (normal range, 10 to 16 mmHg), the rate of fluid transudation often exceeds lymphatic drainage capacity, and alveolar flooding occurs.

Coronary artery disease, hypertension, cardiomyopathies, mitral regurgitation, and mitral stenosis are a few of the cardiac conditions that may increase pulmonary intravascular hydrostatic pressure (Pc) and predispose a patient to the development of pulmonary edema. Although an elevated left ventricular end-diastolic pressure is the major cause of an increase in Pc, and therefore pulmonary edema, it is important to realize that several noncardiac problems also may increase Pc. These include pulmonary venoocclusive disease, fibrosing mediastinitis, head trauma, cerebrovascular accident, exposure to high altitudes, and overhydration.

Noncardiogenic pulmonary edema is associated with an increase in endothelial permeability caused by an insult that disrupts the barrier function of the blood-tissue interface. Unlike cardiogenic pulmonary edema, in which the capillary endothelium remains intact and no leakage of protein is noted, noncardiogenic pulmonary edema is associated with leakage of both fluid and protein from the vascular space.[201] Because this respiratory membrane disruption cannot be easily or directly measured, noncardiogenic pulmonary edema is said to exist when suspicious chest radiographic evidence coexists with insufficient hemodynamic basis. The presence of a pulmonary wedge pressure less than 12 mmHg and the absence of a significant history of cardiac disease generally suffice for exclusion of a hemodynamic mechanism.

Although a multitude of disorders are associated with noncardiogenic pulmonary edema, the most commonly encountered cause is systemic sepsis that leads to ARDS. Other clinical conditions associated with noncardiogenic pulmonary edema include the aspiration syndromes, inhalation of toxic fumes and gases, and the embolization phenomena (Box 26-11).

Pulmonary edema is nearly always associated with some type of preexisting disease state or insult. If a patient with pulmonary edema has a history of CHF, hypertension, or ischemic heart disease, the presence of cardiogenic pulmonary edema can be assumed. In addition to systemic sepsis, anaphylaxis, pancreatitis, disseminated intravascular coagulation, trauma, multiple transfusions, and near-drowning can all result in noncardiogenic pulmonary edema.

Neurogenic Pulmonary Edema

Neurogenic pulmonary edema begins with a massive outpouring of sympathetic nervous system stimulation triggered by central nervous system insult. This centrally mediated central nervous system overactivity typically occurs in the hypothalamic area.[201] Excessive sympathetic activation induces remarkable hemodynamic alterations—primarily systemic and pulmonary vasoconstriction. The left ventricle fails because of the inordinate pressure work imposed by the systemic hypertension, and pulmonary blood volume increases because of the functional imbalance between the failing left ventricle and the normal right ventricle.[201] Although this sequence seems to parallel that of hemodynamic pulmonary edema, a permeability component exists, as evidenced by the high protein concentration found in the pulmonary secretions of affected patients.

Uremic Pulmonary Edema

Uremic pulmonary edema is seen in those patients with renal insufficiency or failure. Overhydration and expansion of the circulating blood volume lead to increases in pulmonary capillary pressures. Again, a "leaky" component exists because of the metabolic abnormalities associated with uremia. Reducing the circulating blood volume of these patients via hemodialysis promotes resolution of this type of pulmonary edema.[201]

BOX 26-11

Clinical Disorders Associated with Acute Respiratory Distress Syndrome

Sepsis Trauma
- Fat emboli
- Lung contusion
- Nonthoracic trauma

Liquid Aspiration
- Gastric contents
- Fresh and salt water (drowning)
- Hydrocarbon fluids

Drug Associated
- Heroin
- Methadone
- Barbiturates
- Colchicine
- Aspirin
- Hydrochlorothiazide

Inhaled Toxins
- Smoke
- Oxygen (high concentration)
- Corrosive chemicals (NO_2, Cl_2, NH_3, phosgene)

Shock from Any Cause
- Hematologic disorders
- Massive blood transfusion
- Disseminated intravascular coagulation

Metabolic
- Acute pancreatitis
- Uremia

Miscellaneous
- Lymphangiography
- Reexpansion pulmonary edema
- Increased intracranial pressure
- After cardiopulmonary bypass
- Eclampsia
- Air emboli
- Amniotic fluid embolism
- Ascent to high altitude

Primary Pneumonias
- Viral
- Bacterial
- Mycobacteria
- Tuberculosis
- Fungal

From Ware LB, Matthay MA. Pulmonary edema and acute lung injury. In George RB, et al, eds. *Chest Medicine: Essentials of Pulmonary and Critical Care Medicine*. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2005:555.

High-Altitude–Related Pulmonary Edema

High-altitude–related pulmonary edema can occur in the absence of left ventricular failure whenever an individual overexerts before acclimating to a high altitude. The pathogenesis of this form of pulmonary edema is unclear, but it may be the result of intense hypoxic pulmonary arterial vasoconstriction or massive sympathetic discharge triggered by cerebral hypoxia.[202]

Pulmonary Edema Due to Upper Airway Obstruction

Pulmonary edema caused by upper airway obstruction results from prolonged, forced inspiratory effort against an obstructed upper airway. The most common cause of this type of pulmonary edema in adults is laryngospasm after extubation and general anesthesia. In children, pulmonary edema after obstruction caused by croup, epiglottitis, and laryngospasm also is well documented. Vigorous inspiration against obstruction creates high negative intrathoracic, transpleural, and alveolar pressures, enlarging the pulmonary vascular volume and subsequently the interstitial fluid volume. The capacity of the lymphatics becomes overwhelmed, and interstitial fluid transudes into the pulmonary alveoli. Hypoxia causes a

massive sympathetic discharge that results in systemic vasoconstriction and a translocation of fluid from the systemic circulation to the already expanding pulmonary vascular and interstitial spaces. Hypoxia also increases pulmonary capillary pressures. Because hypoxia alters myocardial activity, left atrial function and left ventricular function are reduced.

During obstruction, vigorous inspiratory efforts are unsuccessful because of the airway obstruction. Unsuccessful expiration produces an increase in intrathoracic and alveolar pressures. Intrinsic PEEP also is produced during this stage. Relief of the obstruction results in cessation of intrinsic PEEP.

The consequence of these events is the sudden massive transudation of fluid from the pulmonary interstitium into the alveoli, which results in pulmonary edema. The malignity of pulmonary edema is determined by the extent of prior alveolar and capillary damage and the immensity of hemodynamic and cardiovascular alterations.

Not all of those who experience an acute airway obstruction develop pulmonary edema, and no specific risk factors for its occurrence have been identified. Factors that may predispose to its formation after obstruction include youth, male gender, long periods of obstruction, overzealous perioperative fluid administration, and the presence of preexisting cardiac and pulmonary disease.

Treatment includes prompt recognition of the condition, securing a patent airway, supportive therapy with oxygenation, and administering diuretics. Although the onset of pulmonary edema after laryngospasm usually is immediate, cases have been reported of the occurrence of pulmonary edema several hours after laryngospasm. Therefore, it is recommended that patients who develop laryngospasm be observed postoperatively longer than the typical 60 to 90 minutes. The diagnosis of pulmonary edema and its differentiation into cardiogenic and noncardiac categories necessitates taking a detailed medical history and performing a physical examination, chest radiography, and ABG analysis.

Physical examination reveals increased respiratory effort. As water accumulates, the lungs become heavy and noncompliant, and a decrease in FRC occurs. This increase in the volume of extravascular lung fluid provides a potent stimulus for surrounding interstitial stretch receptors (J-receptors), the activation of which results in tachypnea. Tachypnea is not relieved by the administration of O_2 and the return of Pa_{O_2} to normal. Intercostal retractions and use of accessory muscles are apparent on physical examination. Signs of sympathetic stress stimulation, such as hypertension, diaphoresis, and tachycardia, often are noted. The expectoration of pink, frothy sputum signals that alveoli have been flooded.[201]

The detection of basilar crackles on auscultation is the traditional hallmark of early pulmonary edema. In reality, by the time these crackles become audible, excess water has already flooded the alveoli and overflowed into the terminal bronchioles.[199] It is in the bronchioles, not in the alveoli, that the crackles of pulmonary edema are generated. The earliest and most often disregarded clinical sign is rapid, shallow breathing.

In cardiogenic pulmonary edema, heart size may be increased. High CVPs, an S_3 or S_4 gallop, and jugular venous distention often are observed.[200] Chest radiography is still the most reliable and expedient tool for early detection of pulmonary edema. In cardiogenic pulmonary edema, the cardiac silhouette may appear abnormal or enlarged; in noncardiogenic pulmonary edema, it can be enlarged or remain normal. Interstitial edema can be observed before the alveoli flood and the onset of clinical signs occurs. Pleural effusions are common, and a "whited-out" or "butterfly" appearance may be noted.[201]

ABG analysis reveals hypoxemia secondary to $\dot{V}/\dot{Q}$ abnormalities. When right-to-left shunting is great, the Pa_{O_2} can be affected by any change in the central venous O_2 content. Increases in O_2 consumption or decreases in CO further reduce the Pa_{O_2}. The Pa_{CO_2} may be low, normal, or elevated. The initial hypocarbia is related to tachypnea and high minute volumes (MVs); at later stages, hypercarbia is frequently secondary to muscle fatigue and exhaustion. Changes in pH usually reflect changes in Pa_{CO_2}, but metabolic or lactic acidosis or both may occur from tissue O_2 deficiency, low CO, or sepsis.

Anesthetic Management

Pulmonary edema is considered a medical emergency, and immediate intervention is required for treatment of the underlying disease, support of other failing organ systems, and optimization of O_2 delivery.[200] O_2 should be administered either by nasal cannula, facemask, or endotracheal tube. If oxygenation does not improve with the administration of high Fi_{O_2}, positive-pressure ventilation with either PEEP or CPAP must be initiated. Institution of positive-pressure mechanical ventilation in patients with acute pulmonary edema usually results in a prompt increase in oxygenation and, in some cases, in CO. Improvement occurs because of superior inflation and $\dot{V}/\dot{Q}$ matching. Improvement in left ventricular function (CO) may occur secondary to four possible mechanisms: (1) improvement in arterial oxygenation and therefore improvement of myocardial O_2 supply; (2) reduction in the extreme pleural pressure swings present with spontaneous ventilation and hence reduction in afterload on the left ventricle; (3) decrease in the workload of the failing heart because of a reduction in work of breathing (and therefore a reduction in O_2 requirement) effected by a mechanical ventilator; and (4) decrease in preload (and a subsequent reduction in venous return) occurring secondary to the use of positive-pressure ventilation.

Pharmacologic therapy includes the use of vasodilators, inotropes, steroids, and diuretics. For more than 50 years, morphine sulfate has been used in the treatment of cardiogenic pulmonary edema because of its venodilatory and preload-reducing properties.[201] Nitroprusside is a very effective preload and afterload reducer. By reducing systemic blood pressure, nitroprusside decreases the afterload on the left ventricle; this may result in better cardiac function, with a subsequent lowering of left atrial pressures. Inotropic agents such as dopamine or dobutamine improve myocardial contractility and lower cardiac filling pressures. In patients with chronic CHF and pulmonary congestion, digitalis augments contractility and promotes decreases in left atrial and ventricular filling pressures. (The use of steroids is discussed later in this chapter in the section on ARDS.)

Fluid balance is managed with both fluid restriction and diuresis. This therapy helps achieve a "negative" fluid balance in hydrostatic pulmonary edema, in which Pc is high. Even in permeability pulmonary edema, in which Pc is thought to be low, any decrease in the hydrostatic pressure further reduces the net movement of pulmonary microvascular fluid outward.[200] Potent diuretics such as furosemide not only lower left atrial filling pressure by decreasing systemic venous tone but also induce diuresis of the expanded extravascular volume.

The type of fluid, whether crystalloid or colloid, that should be used in the presence of pulmonary edema remains controversial. Regardless of type used, it is generally agreed that administration should proceed slowly.

ASPIRATION PNEUMONITIS

Definition

Aspiration is a rare yet serious complication of general anesthesia. Much effort is expended to prevent this untoward occurrence and minimize sequelae if it does occur. It can occur at any time during

the course of anesthesia administration, and if it is severe, a multitude of serious complications may follow. Pneumonitis adds an average of 15 hospital days' stay and over $20,000 to the course of care of a patient who suffers this complication.[203]

Pneumonitis from perioperative aspiration ("Mendelson's syndrome") was described by Curtis Mendelson in 1946 after he observed a number of deaths among obstetric patients.[204] Mendelson's laboratory investigations led him to the conclusion that two entirely separate clinical aspiration disorders existed. One followed the aspiration of solid food and produced a picture of laryngeal or bronchial obstruction, whereas the other resulted from direct acid injury to the lung and produced the "asthma-like" syndrome that now carries his name.[205] Aspiration pneumonitis in anesthetic patients results from the intersection of three components: First, gastric contents escape from the stomach into the pharynx; second, those contents enter the lungs; and third, they are of a caustic nature, which results in tissue injury. This results from preexisting disease, airway manipulation, and the inevitable compromise in protective reflexes that accompany the anesthetized state. Aspirates may be categorized as contaminated, acidic, alkaline, particulate, and nonparticulate. Pneumonitis is a chemical injury and is not synonymous with pneumonia. Less than half of all aspirations lead to pneumonia, which occurs most often in patients who aspirate infected material or who are immunocompromised. Ingestion of highly acidic or particulate aspirate may cause severe respiratory damage without an infectious component. Patients who initially show no signs of infection, however, may develop pneumonia over time because of the severity of the lung injury and prolonged respiratory support.[206]

Incidence and Outcome

Although the incidence of regurgitation is estimated to be frequent (as high as 15%, according to some authors), pulmonary aspiration complicates only about 1 out of 3000 anesthetics.[207] This incidence is roughly doubled for cesarean section surgery[208] and emergency surgery.[209] Fortunately, the majority of aspiration incidents require little or no treatment. Warner et al.[210] reviewed 215,488 general anesthetics and studied the outcomes of pulmonary aspiration. They noted that approximately 60% of episodes were asymptomatic, 20% were symptomatic but required only conservative treatment or short-term ventilation, 15% required mechanical ventilation for more than 6 hours, and 5% of episodes led to death (Figure 26-25). The overall mortality was 1 in 71,829 anesthetic procedures. Several of their findings were interesting. Complications developed in equal percentages among those who received and those who did not receive pharmacologic acid aspiration prophylaxis. Patients who aspirated but did not develop symptoms within 2 hours could be discharged. If signs or symptoms did not emerge in that timeframe, they would not occur subsequently. Not surprisingly, the largest number of aspirations occur during induction and intubation or on emergence within 5 minutes of extubation. They found no serious morbidity from pulmonary aspiration in nearly 120,000 elective procedures in ASA class I or II.

In a later study, the same group reported on the incidence of aspiration in infants and children.[211] Although pediatric patients are often reported as having a higher incidence of aspiration than adults,[209] the researchers found no increase in the incidence among young patients. They noted 24 aspirations in a series of 63,180 general anesthetic procedures. Fifteen of the 24 children did not develop symptoms within 2 hours, and no treatment was required. Five children required respiratory support, three for more than 48 hours. No deaths occurred. Common risk factors for aspiration are given in Box 26-12.

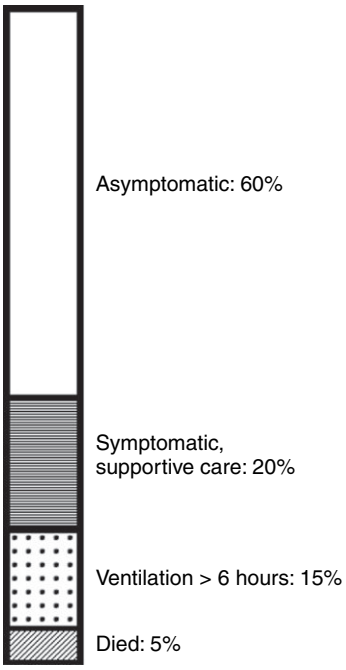

FIGURE **26-25** Outcomes of patients with perioperative aspiration. (Percentages approximate.) (Data from Warner MA, et al. Clinical significance of pulmonary aspiration during the perioperative period. *Anesthesiology.* 1993;78[1]:56-62.)

The Anesthetic Incidence Monitoring Study database in New Zealand noted 133 cases of aspiration out of 5000 reported anesthesia incidents.[212] Five deaths occurred. Aspiration was confirmed by clinical signs or radiography. Predisposing factors included abdominal pathology, obesity, diabetes, neurologic deficit, lithotomy position, difficult intubation, reflux disease, hiatal hernia, and inadequate anesthesia leading to straining and bucking.

In an interesting study, researchers examined general anesthesia by mask in obstetric patients who required surgery immediately after vaginal delivery.[213] Procedures included placental extraction; repair of vaginal, cervical, and perineal tears; and uterine manipulation. This database in Israel involved 1705 anesthetic procedures with only one case of mild pneumonitis.

Etiology

Although vomiting and gastroesophageal reflux are common clinical events, aspiration usually occurs only when normal protective reflexes (swallowing, coughing, gagging) fail.[210] Reflex responses to aspiration are automatically blunted with depression of consciousness. The most common setting for depression of reflex protection occurs during anesthesia induction and emergence.[210]

Three aspiration syndromes have been identified: (1) chemical pneumonitis (Mendelson's syndrome); (2) mechanical obstruction; and (3) bacterial infection. Because acute chemical pneumonitis poses the greatest difficulty to anesthesia providers, the pathophysiology, presentation, and anesthetic implications of Mendelson's syndrome are discussed.

The etiology of aspiration pneumonia often is characterized according to the pH, volume, and type of gastric material aspirated. It has long been considered that gastric fluid volume (GFV) greater than 0.4 mL/kg (25 mL/70 kg) and a pH less than 2.5

BOX **26-12**

Risk Factors for Aspiration

- Emergency surgery
- Full stomach
- Obstetrics
- Gastrointestinal obstruction
- Ascites
- Diabetic gastroparesis
- Gastroesophageal reflux
- Hiatal hernia
- Peptic ulcer disease
- Difficult airway management
- High gastric pressure or reduced lower esophageal sphincter tone
- Impaired airway reflexes
- Head injury
- Depressed level of consciousness
- Seizures
- Obesity
- Scleroderma, CREST, or other connective tissue disorders affecting the esophagus
- Trauma or stress
- Nausea and vomiting
- Opioid administration
- Cricoid pressure
- Residual neuromuscular relaxation
- Cardiac arrest, severe hypotension

CREST, Calcinosis, Raynaud phenomenon, Esophageal dysmotility, Sclerodactyly, and Telangiectasia.

are significant indicators of risk for aspiration sequelae. In 1974, Roberts and Shirley[214] published a classic article advocating these arbitrarily defined surrogate end-points in patients undergoing cesarean section. These markers became widely accepted in clinical practice, and efforts to reach these levels preoperatively in many patient groups included insertion of nasogastric tubes, as well as multidrug pharmacologic intervention. Unfortunately, the experiment by Roberts and Shirley by far lacked adequate scientific design to derive recommendations on assessing risk or administering prophylaxis to patients to reduce aspiration. Questions have therefore been raised as to the validity of the data behind these recommendations, with the suggestion that a reappraisal is in order.[215]

GFVs greater than 0.4 mL/kg are more common, even in fasting individuals, than the overall incidence of aspiration would suggest, if this were a major risk factor for aspiration. In a recent report comparing gastric content differences in healthy obese versus lean patients, GFV greater than 25 mL and pH less than 2.5 were noted in 26.6% of obese and 42% of lean patients.[216] These data suggest that healthy obese patients do not exhibit delayed gastric emptying and that many patients routinely fall into the arbitrary range of GFV greater than 25 mL and pH less than 2.5 without experiencing aspiration. Although the volume *aspirated* correlates with the severity of pulmonary damage, there is less correlation between the volume in the stomach and the risk of pneumonitis. A review of the value of routine nasogastric tube use after abdominal surgery demonstrated a slight *increase* in pulmonary complications among patients nonselectively treated with a nasogastric tube.[217] The applicability of this to short-term use under anesthesia is unknown, but it should be noted that gastric tubes not only provide evacuation but also may provide a conduit for regurgitation. Their value in patients not at risk for aspiration is not clear.[217]

Acidity plays a role in aspiration-induced lung damage; however, preoperative pharmacologic manipulation of gastric pH has not been proven to be clinically effective.[210,211,218] It is time to shift the focus away from GFV and pH and toward patient characteristics, patient condition, and anesthetic practices that place the patient at risk for pulmonary aspiration. Attention to the presence of factors listed in Box 26-12 and in particular to the presence of *multiple* factors from that list will prove more fruitful to the anesthetist's ability to predict aspiration risk than will over-attention to the questionable and nonspecific factors of gastric fluid volume and gastric pH.

Pathophysiology

The pathophysiology of aspiration pneumonitis is typically characterized by four stages: (1) The aspirated substance causes immediate damage to the lung parenchyma, resulting in tissue damage. (2) Atelectasis results within minutes, owing to a parasympathetic response that leads to airway closure and a decrease in lung compliance. (3) One to two hours after the injury, an intense inflammatory reaction occurs, characterized by pulmonary edema and hemorrhage. Inflammatory cytokines, including interleukin-8 and tumor necrosis factor-alpha released by alveolar macrophages, play a central role. The attracted neutrophils also play a key role in this phase by releasing oxygen radicals and proteases. (4) By 24 hours after the insult, secondary injuries result from fibrin deposits and necrosis of alveolar cells.

When aspiration is severe, damage to the entire alveolar-capillary barrier, including the basement membranes and capillary endothelial cells, may occur. It is important to note that physical damage is done to the lung endothelium instantly on contact with caustic aspirate. Therefore, there is no benefit in performing bronchoscopy or deep tracheal suctioning with the intent of halting the damage. Unless the patient has aspirated a particulate substance that can be retrieved, deep suctioning after aspiration will probably cause more irritation than any benefit from reversing the process. Suctioning the mouth and pharynx to prevent further aspiration is helpful.

Hypoxemia occurs secondary to a shunting effect due to atelectasis. Initially, Pa_{CO_2} tends to be low because of hyperventilation from hypoxic drive and because of the mechanical and irritative stimuli to the large airways and parenchyma. Hypercarbia associated with hypoventilation is a negative prognostic sign. Because atelectasis is common, PEEP is commonly a useful treatment modality for patients who require mechanical ventilation. Damage to the lung parenchyma causes an increase in the permeability of the pulmonary blood vessels followed by a profound capillary leak syndrome. This capillary leak produces flooding of the interstitium and alveolar spaces with a protein-rich fluid (permeability pulmonary edema). Mucus rapidly buffers the acidic fluid entering the lungs. Despite this, initial contact with highly acidic material has still been shown

to increase the vascular permeability in a very predictable fashion. In addition to the inactivation of surfactant by the gastric aspirate itself, the loss of protein through the impaired capillary wall can cause changes in surfactant production and, in turn, can contribute to a loss of lung compliance. Hemodynamic changes may include hypotension and reduction in CO from hypoxemia-induced myocardial ischemia, pulmonary hypertension, and acidosis.

In the inflammatory stage, there is a release of various phagocyte-derived substances such as reactive oxygen metabolites, nitric oxide, and proteases. This stage is characterized by neutrophil infiltration, which has been found to be an important negative factor in the eventual outcome after aspiration. Recent research has demonstrated that inhibition of alveolar macrophages will decrease the levels of inflammatory mediators and neutrophil recruitment to the area of injury.[219] Direct inhibition of neutrophils with neutrophil aggregation inhibitors, such as pentoxifylline and lidocaine, are gaining research interest for their potential to improve outcomes of pneumonitis. Lidocaine has been demonstrated to inhibit neutrophil chemotaxis,[209] suppress superoxide production,[220] reduce reperfusion injury,[221] and improve outcomes following acid aspiration.[222]

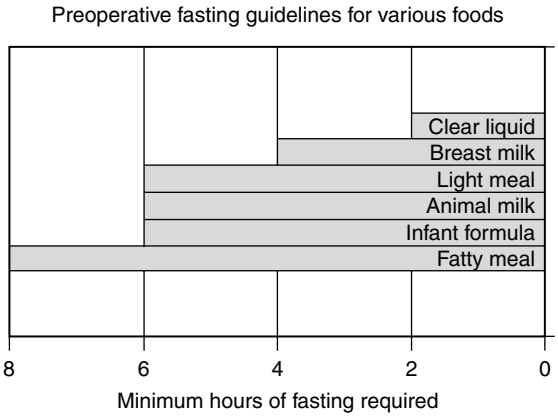

FIGURE **26-26** Preoperative fasting guidelines. (Data from American Society of Anesthesiologists Committee on Standards and Practice Parameters. Practice guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration: application to healthy patients undergoing elective surgery. *Anesthesiology.* 2011;114:495-511.)

Clinical Features and Diagnosis

Arterial hypoxemia, the hallmark sign of aspiration pneumonitis, is frequently the first sign of aspiration. Because the majority of aspiration incidents are asymptomatic or mildly symptomatic, unexplained hypoxemia occurring in otherwise healthy patients postoperatively often may be a vague sign of silent aspiration. Other signs to alert the anesthetist to the possibility of aspiration include tachypnea, dyspnea, tachycardia, hypertension, and cyanosis.

Diagnosis may be difficult to establish unless the aspiration is witnessed or gastric contents are visualized directly in the airway or suctioned from an endotracheal tube. ABG analysis and chest radiography are needed for evaluation. Infiltrates in perihilar and dependent regions along with pulmonary edema are the most common findings on radiography.

Anesthetic Management

Preoperative Management

When dealing with aspiration, "an ounce of prevention is worth a pound of cure." Recognizing risk factors and employing risk mitigation (including avoidance of general anesthesia) are important steps in preventing aspiration. When the use of general anesthesia is unavoidable in at-risk patients, taking the following steps may help minimize the risk of aspiration, or at least limit its consequences.

Nil per os (NPO) policy has been a mainstay of prophylaxis against aspiration, by aiming to reduce patients' intragastric volume by the time they undergo anesthesia. The suggestion by Roberts and Shirley that a gastric fluid volume greater than 0.4 mL/kg would predispose to aspiration gave credence to this approach. Following this concept, practitioners have instructed patients to refrain from oral intake for 8, 12, and sometimes as much as 16 hours (e.g., afternoon-scheduled surgeries, for which the patient is told to remain "NPO after midnight"). However, these long NPO periods are unnecessarily long to ensure stomach emptying of most low-fat foods, and the prolonged NPO periods contribute more to patient discomfort, dehydration, and insulin resistance than to ensuring an empty stomach.[223] It has become evident that clear liquids leave the stomach within 2 hours of ingestion, but gastric acid secretion continues, even in the absence of food intake. Therefore, in the absence of prokinetic stimulation by oral intake, a fasting patient may have a higher gastric volume and acidity than one who was allowed clear fluids closer to the time of surgery. The effects of gastrin and cholecystokinin on stimulating gastric emptying in response to clear liquid ingestion are greater than the effect of the migrating motor complex in emptying the stomach in the absence of food or liquid intake. As a result, patients who are allowed liberal intake (without upper limit of volume) of clear fluids up to 2 hours before a procedure have higher gastric pH and lower volume than those who fasted for more than 4 hours.[224,225] Contemporary understanding of this concept has led to revision of blanket NPO guidelines in favor of food-specific guidelines, particularly a much more liberal approach to clear liquid ingestion preoperatively (Figure 26-26).

Pharmacologic prophylaxis for aspiration may be considered to reduce risk factors for pneumonitis. Agents such as gastrokinetics, histamine blockers, anticholinergics, antacids, proton pump inhibitors, and antiemetics are all used alone or in various combinations to raise gastric pH, lower gastric volume, and reduce the incidence of emesis (Table 26-19). Although research evidence does not support routine use of prophylactic agents, practitioners may administer them when indicated for patients at risk. While previously used to inhibit gastrointestinal activity, anticholinergic agents are no longer supported for prophylactic use, and they may even antagonize other useful agents. For example, metoclopramide raises barrier pressure (which opposes gastric regurgitation) by increasing the tone of the lower esophageal sphincter; however, anticholinergics inhibit this effect. Metoclopramide stimulates gastric emptying and acts as an antiemetic.

Clear, nonparticulate antacids such as sodium citrate or sodium citrate with citric acid ("bicitra") have been shown to be clinically effective in increasing the pH of gastric contents. Desired onset of action occurs within 15 minutes, and duration of action is 1 to 3 hours. Although citrate preparations may last up to 6 to 7 hours, some patients will also experience a rebound increase in gastric acid production, so if surgery is delayed more than 1 hour after citrate administration, it may be prudent to repeat the dose.[226]

Intravenous administration of the H_2-receptor blockers cimetidine, ranitidine, or famotidine 45 to 60 minutes before surgery can raise gastric pH. Of the H_2 blockers, famotidine provides the best profile of duration of action and low incidence of side effects.[227] Although the H_2 blockers reduce gastrin-induced acid production, they are less effective against vagal or muscarinic influence. In contrast, proton pump inhibitors irreversibly bind to H^+/K^+ ATPase, blocking the final pathway for acid production. They are therefore more effective in reducing acid production, but for maximal effectiveness, they must be administered as a dose the night before surgery and then repeated preoperatively. In emergency cases or where the prior-night dose was not performed, H_2-receptor blockers may provide a better option for single-dose therapy.

Although cricoid pressure has long been considered a foundation of management of aspiration risk, the effectiveness of this technique has recently been called into question.[228-231] Confounding findings include that in a significant number of patients, the esophagus is not aligned directly posteriorly to the trachea,[232,233] so there are numerous reports of aspiration despite application of cricoid pressure.[234] Other suggestions are that cricoid pressure is inconsistently applied, or cricoid pressure itself will reduce lower esophageal sphincter pressure (LESP), thereby increasing the gradient for gastric regurgitation.[235,236] This LESP reduction appears to be a reflex mechanism in response to cricoid pressure and can be blunted by remifentanil.[237] Other nonpharmacologic mechanisms such as elevating the patient's head may offer limited benefit. In a small study of non-obese, awake, non-fasted patients, Jeske et al.[238] found no difference in gastric regurgitation, regardless of 20-degree head elevation or depression. Proponents of cricoid pressure posit that while the procedure may not exactly compress the esophagus as Sellick envisioned, it may nonetheless provide a barrier against regurgitation.[239,240] Although the overall benefit of cricoid pressure is questionable, it is still widely considered a standard of care.[241]

TABLE 26-19 Drug Prophylaxis for Aspiration Risk*

Medication Type	Common Examples
Gastrointestinal stimulants	Metoclopramide
Histamine-2 antagonists	Cimetidine Famotidine
Proton pump inhibitors	Omeprazole Lansoprazole
Antacids	Sodium citrate Sodium bicarbonate Magnesium trisilicate
Antiemetics	Droperidol Ondansetron
Anticholinergics†	Atropine Scopolamine Glycopyrrolate

Data from American Society of Anesthesiologists Committee on Standards and Practice Parameters. Practice guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration: application to healthy patients undergoing elective surgery. *Anesthesiology.* 2011;114:495-511.
*The routine preoperative use of these medications to decrease aspiration risk in patients with no apparent increased risk is not recommended.
†The use of anticholinergics to decrease aspiration risk is not recommended.

Intraoperative Management

If intubation is not expected to be difficult, a rapid-sequence induction (rather than awake endotracheal intubation) is acceptable in the patient with aspiration risk. There is little evidence that "modified" rapid sequence technique (which allows for gentle mask ventilation) worsens aspiration incidence, and this approach may be preferable in patients at risk for rapid oxygen desaturation.[242] Because difficult intubation itself is a risk factor for aspiration, there should be a low threshold for performing awake intubation in a patient with aspiration risk who may also pose airway challenges. Endotracheal intubation is considered the optimal approach for airway isolation, but regurgitated material can seep around the endotracheal tube (ETT) cuff, particularly if it is not lubricated.[243,244] Preventive measures in the anesthetic plan include ensuring that the patient is fully awake before extubation and manifesting protective reflexes, residual neuromuscular blockade is minimized to the extent possible, the degree of narcosis does not impair the level of consciousness postoperatively, and that the stomach has been evacuated.

If vomiting or aspiration occurs during induction, immediate treatment includes tilting of the patient's head downward or to the side, rapid suctioning of the mouth and pharynx, and intubation. There is little benefit in performing tracheal or bronchial suctioning in most cases, and bronchoscopy should be reserved for those patients suspected of having aspirated solid material. If aspiration is severe, surgery may be postponed. ABG analysis should be performed for determination of the extent of hypoxemia. Early application of PEEP is recommended for improving pulmonary function and combating atelectasis.[215]

Oxygenation should be supported with supplemental oxygen only to the minimum extent necessary. The damage to pulmonary parenchyma from caustic aspiration predisposes the tissue to oxygen toxicity. Indiscriminate administration of oxygen may worsen tissue damage.[245] For pharmacologic treatment of aspiration pneumonitis, the use of steroids is controversial. Long considered a mainstay of treatment, steroid therapy is associated with more rapid resolution of radiologic evidence of pneumonitis but also with longer intensive care unit (ICU) stays for some patients. Lidocaine 1.5 mg/kg is probably not harmful, but may be helpful as a neutrophil aggregation for improving long-term outcome after aspiration.[222] Although most aspirations are of sterile material (such as typical gastric acid), leukocytosis, fever, and infiltrate on x-ray are common findings in aspiration pneumonitis. The clinical findings resemble but do not indicate bacterial colonization (i.e., pneumonia). For this reason, the routine use of antibiotics is not recommended. Antibiotics are indicated only if the fever does not resolve within 48 hours, or there is risk for bacterial colonization (e.g., a patient on high-pH gastric tube feedings) or protected-sample bronchial or blood cultures indicate infection. Box 26-13 gives standard treatment protocol for aspiration pneumonitis.

The common time course of symptoms after aspiration has been characterized. Warner et al.[210] noted that the condition of the patient at 2 hours after the aspiration was prognostic of the patient's eventual course. Patients could be discharged if they did not manifest significant symptoms within 2 hours of the incident. Their criteria were as follows: (1) patients did not develop symptoms that included a new cough or a wheeze; (2) no decrease in Spo_2 of greater than or equal to 10% of preoperative levels occurred while the patient was breathing room air; (3) patients did not exhibit an A-a gradient of greater than or equal to 300 mmHg; and (4) no radiographic evidence of pulmonary aspiration was present.

ACUTE RESPIRATORY DISTRESS SYNDROME

Definition

The term *acute respiratory failure* is often used synonymously with *acute* (formerly *adult*) *respiratory distress syndrome* (ARDS). Although ARDS may be caused by or associated with a variety of clinical conditions, most patients with this disease demonstrate similar clinical and pathologic features, regardless of the cause of lung injury. Common features include a history of a preceding noxious event that served as a trigger for the subsequent development of ARDS and insult to the alveolar–capillary membrane that results in increased permeability and subsequent interstitial and alveolar edema.[246] Clinical presentation is characterized by dyspnea, severe hypoxemia, diffuse bilateral pulmonary infiltration, and stiffening and noncompliance of the lungs.[247] The consensus definition is given in Table 26-20.

Incidence and Outcome

Risk factors for the development of ARDS appear to be additive. Taylor[248] reported the incidence of occurrence to be 25% with the presence of one risk factor, 42% with the presence of two, and 85% with the presence of three. The mortality rate for ARDS remains high, around 50%.[249] However, the mortality rate often exceeds 90% when gram-negative septic shock precedes ARDS development.[250]

Etiology

The most common events and risk factors associated with the development of ARDS include: (1) sepsis; (2) bacterial pneumonia; (3) trauma; and (4) aspiration pneumonitis.[251] Other causes include diseases of the central nervous system, metabolic events (e.g., pancreatitis and uremia), disease states that result in the release of inflammatory mediators (e.g., extrapulmonary infections, disseminated intravascular coagulation, anaphylaxis, coronary bypass grafting, and transfusion reactions), and other forms of shock (cardiogenic, or hypovolemic) (see Box 26-11).[247]

BOX 26-13

Treatment of Aspiration Pneumonitis

- Suction mouth and pharynx
- Deeper suctioning only for particulate material
- Administer oxygen; only to extent needed
- Lidocaine to inhibit neutrophil response
- Steroids of questionable benefit
- Intubate as needed to support oxygenation
- Bronchodilator, PEEP to support ventilation
- Antibiotics only if indicated or for fever or ↑ WBC count >48 hours

PEEP, Positive end-expiratory pressure; *WBC*, white blood cell count.

Pathophysiology

The pathophysiology of ARDS is centered on severe damage and inflammation to the alveolar-capillary membrane. Research has focused on the release of cytokines and membrane-bound phospholipids from the capillary endothelium and the activation of leukocytes and macrophages (via the complement system) within the lungs.[252] As in pneumonitis, neutrophils play a role in the pathology of ARDS, and IL-8 (interleukin-8) has been identified as the main chemotactic factor for neutrophils.[253]

Phospholipids are converted into prostaglandins and leukotrienes by the enzymes cyclooxygenase and lipoxygenase, respectively. It is believed that prostaglandin metabolites mediate pulmonary vasoconstriction, alter vascular reactivity (i.e., decrease hypoxic pulmonary vasoconstriction), and cause airway constriction.

In addition, microembolus formation is a common manifestation of ARDS. Complement system activation and the release of thromboplastin from soft-tissue injury can trigger the coagulation system. Damage to the alveolar-capillary membrane impairs oxygenation, and loss of lung compliance leads to challenges in effectively ventilating patients. The effect of microemboli, prolonged alveolar hypoxia and hypercapnia, and injury to the alveolar tissue leads to increases in pulmonary vascular resistance. High alveolar pressures from aggressive positive pressure ventilation further contribute to high afterload on the right ventricle. This afterload leads to cor pulmonale in 25% of cases,[254] and shunting across a patent foramen ovale occurs in 20%.[255] Associated right ventricular dysfunction increases the associated mortality from ARDS,[256] particularly when plateau pressures are high.[257]

Clinical Features and Diagnosis

The clinical presentation of ARDS resembles that of pulmonary edema and aspiration pneumonitis. Patients are dyspneic, hypoxemic, and hypovolemic and often require intubation and mechanical ventilation. Noncardiogenic pulmonary edema is a hallmark finding. Findings on histologic examination are similar to those of aspiration pneumonitis, with the exception that fibrosis of lung is more pronounced. Recovery of lung function is unpredictable. Milder cases resolve quickly, whereas others progress to fibrosis and death.

Treatment

Treatment is supportive and includes correction of hypoxemia, afterload reduction, and inotropic support as indicated. Maintaining tissue oxygenation and reducing further lung damage are the main goals of therapy. Preserving end-organ perfusion is of utmost importance. There is no definitive treatment for ARDS, but some approaches to reducing the inflammatory reaction and improving

TABLE 26-20 American-European Consensus Conference on ARDS: Recommended Criteria for Acute Lung Injury and Acute Respiratory Distress Syndrome

Criteria	Timing	Oxygenation	Chest Radiography	Pulmonary Capillary Wedge Pressure
Acute lung injury	Acute onset	Pa_{O_2}/Fi_{O_2} ≤ 300 mmHg (regardless of PEEP level)	Bilateral infiltrates	<18 mmHg or no clinical evidence of left atrial hypertension
Acute respiratory distress syndrome	Acute onset	Pa_{O_2}/Fi_{O_2} ≤ 200 mmHg (regardless of PEEP level)	Bilateral infiltrates	<18 mmHg or no clinical evidence of left atrial hypertension

From Bernard GR, et al. The American-European Consensus Conference on ARDS: definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med.* 1994;149:818-824.

Fi_{O_2}, Fraction of inspired oxygen; Pa_{O_2}, partial pressure of oxygen in arterial blood; *PEEP*, positive end-expiratory pressure.

oxygenation include corticosteroids, inhaled nitric oxide, exogenous surfactant, and extracorporeal gas exchange.[258,259]

Anesthetic Management

Anesthetic preparation includes evaluation of the patient's respiratory, cardiac, and renal status. The anesthetist should carefully manage vascular volume to avoid transudation of water into the lungs and give meticulous attention to avoiding air in vascular lines, due to the potential for right-to-left shunting. Useful monitoring will likely include cardiac filling pressures, cardiac output, invasive blood pressure, and a urinary catheter.

Ventilator settings should be noted and special attention devoted to peak inspiratory pressures and PEEP levels. Considering the prominence of cor pulmonale, the ventilation strategy must balance the need for alveolar recruitment with the potential for overloading the right ventricle. As PEEP is added, alveoli are recruited, improving oxygenation and reducing afterload on the right ventricle. However, at a point, alveolar overdistention will tip the balance beyond benefit and into detrimental effects, as the intrapulmonary pressure provides impedance to cardiac output.[260] The concept of "permissive hypercapnia" offers license to limit aggressiveness of ventilation in the interest of minimizing mean airway pressures; however, the effects of hypercapnia on increasing the PVR are varied. Some report a significant reduction (20%) in right ventricular ejection,[261] whereas others have found the hemodynamic effects temporary and nondetrimental.[262] In any case, right ventricular function should be monitored along with blood gas results as outcome goals for any ventilation strategy used in ARDS. Rising central venous pressures as well as chamber dilation, reduced ejection fraction, and septal deviation or paradoxical motion by echocardiography are means of identifying RV dysfunction.[263]

A protective ventilation strategy is often used, aimed at minimizing airway pressures and avoiding barotrauma and volutrauma in the face of severely reduced compliance. Some approaches are referred to as "open lung" strategies, inferring a primary goal of preventing atelectasis and airway closure. Open lung approaches have tended toward use of high levels of PEEP, but there is growing evidence that more modest levels may be equally effective.[260,264] Protective ventilation strategies vary in their details. In some cases, very unconventional ventilation approaches such as high-frequency oscillation must be used. Oscillation has been demonstrated to reduce mortality and improve gas exchange over conventional ventilation.[265,266] Strategies focused on supporting right ventricular performance may include prone positioning.[263] Prone positioning improves airway pressures, gas exchange, and reduces the indicators of cor pulmonale.[267-269] Some common modes of ventilation are shown in Table 26-21; however, Table 26-22 provides a sampling of some protective ventilation protocols that have been used in ARDS research or as guidelines.

TABLE 26-21 Common Modes of Positive Pressure Ventilation

	Trigger (signals the beginning of inspiration)	Control Variable (what is guaranteed in each breath)	Notes
Controlled Mandatory Ventilation (CMV)			
Traditional mode of anesthesia ventilators without patient responsiveness. Most suitable for unconscious, apneic patients.			
Machine-initiated breath	Time (set *f*)	V_T (6-8 mL/kg)	Spontaneous breaths not augmented; variable, based on underlying flow present in circuit
Assist Control (AC)			
Machine-initiated breath	Time (set *f*)	V_T (6-8 mL/kg)	High peak pressures may result if lung compliance is low; pressure limit should be set
Patient-initiated breath	Pressure drop or initiation of inspiratory flow	V_T (6-8 mL/kg)	Spontaneous breaths receive full tidal volume; can lead to hyperventilation if tachypneic
Intermittent Mandatory Ventilation (IMV)			
Traditional weaning mode			
Machine-initiated breath	Time (set *f*)	V_T (6-8 mL/kg)	
Patient-initiated breath	No trigger; spontaneous breaths without augmentation	No limit; flow and volume are patient-driven	
Synchronized Intermittent Mandatory Ventilation (SIMV)			
Promotes better patient-ventilator synchrony than IMV.			
Machine-initiated breath	Time (set *f*), but slight variability built in, to correspond with patient effort	V_T (6-8 mL/kg)	
Patient-initiated breath	Pressure drop or initiation of inspiratory flow initiates some breaths	Flow and volume are patient-driven, except for machine-synchronized breaths	Some spontaneous breath efforts will be augmented by regular machine breath
Pressure Control Ventilation (PCV)			
Prevents excessive peak pressure in low compliance, but V_T varies with changes in compliance.			
Machine-initiated breath	Time (set *f*)	Pressure (≈20 cm H_2O; adjusted to obtain V_T 6-8 mL/kg)	

Continued

TABLE 26-21 Common Modes of Positive Pressure Ventilation—cont'd

	Trigger (signals the beginning of inspiration)	Control Variable (what is guaranteed in each breath)	Notes
Patient-initiated breath	Pressure drop or initiation of inspiratory flow	Pressure (≈20 cm H_2O; adjusted to obtain V_T 6-8 mL/kg)	
Pressure Support Ventilation (PSV)			
Useful with SIMV during weaning or for spontaneous breathing under anesthesia (as when using a LMA).			
Machine-initiated breath	N/A, except for devices that incorporate an apneic backup and provide an "escape" rate in the absence of patient effort		
Patient-initiated breath	Pressure drop or initiation of inspiratory flow	Pressure (usually set at 5-20 cm H_2O to achieve desired V_T)	Each spontaneous breath is augmented by generation of the set amount of pressure
Continuous Positive Airway Pressure (CPAP)			
Useful for spontaneously breathing patients.			
Patient-initiated breath	N/A	Pressure (usually set at 5-10 cm H_2O)	A continuous amount of pressure in the breathing circuit both augments inspiration and prevents airway collapse on expiration
Biphasic Positive Airway Pressure (BiPAP)			
Resembles a combination of PS and CPAP.			
Patient-initiated breath	Pressure drop or initiation of inspiratory flow	Two levels of pressure (10-15 cm H_2O, 0-5 cm H_2O): inspiratory and expiratory	Two levels of pressure set, provide (higher) inspiratory augmentation like PS, and continuous (lower) pressure during expiration, like CPAP or PEEP; useful as noninvasive ventilation, such as to avoid intubation in COPD
Airway Pressure Release Ventilation (APRV)			
Like BiPAP, but held at high pressure level most of time, with brief drops to lower level.			
Patient-initiated breath	Time; inspiratory time (high pressure) set ≈5 seconds, expiratory time (low pressure) set ≈0.5 seconds	Two levels of pressure (high level 20-30 cm H_2O; low level 0-5 cm H_2O); pressures should ideally correspond to high and low inflection points on pressure-volume (lung compliance) curve	Patient breathes spontaneously at high level of pressure, which augments inspiration and retards full expiration; low pressure phases help turnover lung volume to promote CO_2 removal; similar to pressure-control, inverse-ratio ventilation

COPD, Chronic obstructive pulmonary disease; *f*, frequency (respiratory rate); *PEEP*, positive end-expiratory pressure; *PS*, pulmonary stenosis; *VT*, tidal volume; *LMA*, laryngeal mask airway.

NOTE: Inspiratory cycles can be determined by pressure, volume, flow, or time for most modes, with wide variability between devices. Intermittent modes determine end-of-inspiration signaling time by the set respiratory rate and I:E ratio. The prototype settings for each mode are presented here. PEEP can be added to most modes.

TRANSFUSION-RELATED PULMONARY DISEASE

With increasing awareness of a host of complications related to blood transfusion, the connection to pulmonary complications has become a significant area of concern. The primary transfusion-related pulmonary complication is transfusion-related acute lung injury (TRALI).

Definition

TRALI is a form of acute lung injury that is associated with blood transfusion and that is characterized by pulmonary infiltrates and hypoxemia. TRALI is defined as acute onset hypoxemia, bilateral lung infiltrations on the chest radiograph, and no evidence of circulatory overload, which occurs during or within 6 hours of blood transfusion in a patient with no other risk factor for acute lung injury (ALI).[270] TRALI resembles ARDS in clinical presentation, but unlike ARDS, it has a lower mortality and is self-limiting with spontaneous resolution usually occurring within 96 hours.[270]

Incidence and Outcome

TRALI was the leading cause of transfusion-related fatalities in years 2005 to 2009, and it is the most common cause of major morbidity and death after transfusion;[271-274] 5% to 10% of cases are fatal.[275,276] Although the incidence is often stated as being one in 5000 blood transfusions, there is a prevailing sense that TRALI is underdiagnosed, and so the incidence may be much higher than that stated figure.[270,274]

Etiology

TRALI is thought to occur because of an interaction between transfused blood products and the recipient's white blood cells.

TABLE 26-22 Ventilation Strategies for ARDS

Name	Description	Notes
ARDSnet ventilator protocol (a)	Any ventilator mode. V_T initially 8 mL/kg PBW; reduce V_T by 1 mL/kg at intervals until V_T = 6 mL/kg PBW; I:E: 1:1 or lower; set initial rate to approximate baseline minute ventilation and adjust to maintain pH > 7.30 or $Paco_2$ < 25 (but not > 35 bpm); adjust V_T and RR to maintain pH > 7.3, Pplat ≤ 30 cmH_2O; use a minimum PEEP of 5 cmH_2O; set Fio_2/PEEP to maintain Pao_2 55-80 mmHg or Spo_2 88%-95%	Acute Respiratory Distress Syndrome Network (ARDSnet) is a clinical network formed by the National Heart, Lung, and Blood Institute, National Institutes of Health to carry out multicenter clinical trials of ARDS treatments
Open lung strategy with staircase recruitment (b)	PCV. Fio_2 adjusted until SpO_2 = 90%-92%; Pplat < 30 cmH_2O, V_T 6 mL/kg IBW; *staircase recruitment maneuver:* pressure set to 15 cmH_2O above the PEEP, and then increased in a stepwise manner to 20, then 30, and then 40 cmH_2O every 2 min, and then reduced incrementally to an absolute minimum of 15 cmH_2O every 3 min until a decrease in Sao_2 ≥ 1% from maximum Sao_2 is observed (derecruitment point); PEEP is then increased to 40 cmH_2O for 1 min and returned to a level 2.5 cmH_2O above the derecruitment point	Greater reduction in some systemic cytokines (IL-8 and TNF-α), improved oxygenation and lung compliance over 7 days in comparison to ARDSnet protocol
Open lung approach (c)	VCV. Fio_2 0.7, RR: 20-40 to achieve pH >7.30 V_T: 6 mL/kg, I:E: 1:1, PEEP set at 20 cmH_2O and a recruitment maneuver with a continuous airway pressure of 50 cmH_2O for 30 sec is performed; after that, PEEP is reduced in decrements of 2 cmH_2O and set at P_{FLEX} (mean PEEP was 15 cmH_2O)	Improved oxygenation and redistributed pulmonary perfusion when compared with the ARDSnet protocol, without differences in lung inflammatory response
Decremental open lung positive end-expiratory pressure titration (d)	PCV. V_T 5-8 mL/kg IBW, I:E: 1:1, RR set to keep arterial pH > 7.20; PEEP is set at 20 cmH_2O and the lungs are recruited by stepwise increases of the driving pressure up to 30 cmH_2O; PEEP is reduced in steps of 2 cmH_2O while measuring the dynamic compliance; PEEP is set 2 cmH_2O over the level that yielded the highest dynamic compliance measurement	Increased oxygenation and improved respiratory system compliance over standard ventilation; evidence of right ventricular stress and strain during recruitment maneuver; otherwise, right ventricular function was significantly improved

(a) from National Heart Lung and Blood Institute. *Mechanical Ventilation Protocol Summary*, 2008. Accessed July 20, 2012, at http://www.ardsnet.org/system/files/6mlcardsmall_2008update_final_JULY2008.pdf; (b) from Hodgson CL, et al. A randomised controlled trial of an open lung strategy with staircase recruitment, titrated PEEP and targeted low airway pressures in patients with acute respiratory distress syndrome. *Crit Care*. 2011;15(3):R133; (c) from Spieth PM, et al. Open lung approach vs acute respiratory distress syndrome network ventilation in experimental acute lung injury. *Br J Anaesth*. 2011;107(3):388-397; (d) from Gernoth C, et al. Respiratory and haemodynamic changes during decremental open lung positive end-expiratory pressure titration in patients with acute respiratory distress syndrome. *Crit Care*. 2009;13(2):R59. *PCV*, Pressure control ventilation; *VCV*, volume control ventilation; *IBW*, ideal body weight; *Pplat*, plateau pressure; *Spo_2*, arterial oxygen saturation; *I:E*, inspiratory to expiratory ratio; *V_T*, tidal volume; *RR*, respiratory rate; *P_{FLEX}*, lower inflection point on the pressure-volume curve. *PBW*, patient body weight; *$Paco_2$*, arterial partial pressure of carbon dioxide; *RR*, respiratory rate; *PEEP*, positive end expiratory pressure; *PaO_2*, blood partial pressure of oxygen; *FiO_2*, fraction of oxygen inspired; *SaO_2*, oxygen saturation.

Attention first focused on an immune mechanism, particularly surrounding the human leukocyte antigens (HLAs) and human neutrophil alloantigens (HNAs) in the recipient. The finding that some victims did not demonstrate elevated antibody titers, and that TRALI could be induced in excised lungs indicated that there is at least one other mechanism. In cases of nonimmune TRALI, reactive lipid products released from the donor blood cells may act as the trigger. In either form of TRALI, neutrophils play an important role. Theories often entertain a "two hit" hypothesis, assuming that a preexisting factor is present in victims and leads to the abnormal reaction to the allograft blood.[277,278] This hypothesis helps explain why TRALI occurs only in some individuals.

Predisposing factors for TRALI seem to surround events that may "prime" the immune system—recent surgery, malignancy, and sepsis, as well as alcoholism and liver disease. Increased levels of HLA and previous ALI as a risk factor point to immunologic predisposition as another factor.[279] Donor risk factors also play an important role in development of TRALI. For example, pregnancy causes an elevation in HLA in many women and a high proportion of TRALI cases arise in individuals who receive blood products donated by women with leukocyte antibodies. For this reason, the United Kingdom halted use of plasma from female donors in 2003, and a significant reduction in the incidence of TRALI ensued. The U.S. Food and Drug Administration is considering methods to implement a similar policy.[274] Although TRALI has occurred in association with a wide variety of blood products, the greatest incidence follows platelet transfusion.[270]

Pathophysiology

Upon activation, neutrophils become trapped within the pulmonary microvasculature, causing congestion and leading to noncardiogenic pulmonary edema. Complement activation and release of oxygen free radicals and proteases then cause damage to the capillary endothelium, which also promotes fluid leak into the alveoli. Platelets also play an important role in TRALI, because they are activated and then sequestered in the lungs through some interaction with neutrophils.[280]

Clinical Features and Diagnosis

TRALI, by definition, is associated with blood transfusion, so symptoms begin during or up to 6 hours after transfusion of any blood product. Acute onset and hypoxemia are key findings, with Pao_2/Fio_2 ratio less than 300. Bilateral infiltrates are found on chest radiography. Clinical symptoms include fever, chills, and dyspnea. Hypertension and hypotension occur with equal frequency.

It is important to distinguish TRALI from other causes of lung dysfunction; therefore diagnosis must exclude any other precipitating factor for acute lung injury. Cardiogenic causes and acute

hypersensitivity reactions or ABO incompatibility reactions must also be excluded. TRALI appears with similar symptomatology as transfusion-related circulatory overload (TACO). TACO usually presents with tachycardia, dyspnea, and pulmonary edema. The key differentiating factor is that signs of circulatory overload or predisposition to circulatory overload (e.g., CHF) exist in TACO but not in TRALI. For patients with coronary artery disease, congestive heart failure, or who are status post lung resection (particularly with peripheral edema, jugular vein distension, S3 heart sound), circulatory overload should be ruled out before presuming a diagnosis of TRALI. Patients who develop TACO often show signs of circulatory overload prior to the blood infusion.

Treatment

Treatment is largely supportive, as is the treatment for ARDS. A lung-protective ventilation strategy is used for patients requiring mechanical ventilation.

Anesthetic Management

Management of the patient who develops TRALI requires immediate cessation of the transfusion. IV fluids are used to support blood pressure if the patient is hypotensive, and diuretics are not indicated, because the respiratory distress is due to microvascular injury rather than fluid overload; 70% of cases require mechanical ventilation, but resolution occurs more quickly than does ARDS.

Appropriate attribution of cause is important to guide the correct treatment. Finding of anti-HLA or HNA antibodies in plasma support the diagnosis of TRALI, whereas signs of fluid overload (clinical signs or elevated brain natriuretic peptide) support the diagnosis of TACO.[281,282]

DRUG-INDUCED PULMONARY DISEASE

Currently, more than 100 pharmacologic agents are known to produce adverse effects on the lung parenchyma, the pleura, and the airway. Drug-induced pulmonary injury occurs in several hundred thousand people each year in the United States. Knowledge of doses and the potential adverse effects of the prescribed medications may prevent or minimize drug-induced damage. The rapid development of nanotechnology also lends concern for new forms of pulmonary toxicity. Nanoparticles, because of their extremely small size, can gain access to physiologic areas that traditional molecules cannot. In particular, in the respiratory tract, carbon nanotubes cause damage to alveolar cells, form granulomas, and led to fibrosis. This damage leads to release of proinflammatory cytokines and generation of oxygen free radicals.[283-285] With the growing use of nanotubes in medications, cosmetics, disease treatment, and other applications, it is likely that new forms of pulmonary toxicity will grow in incidence.

Mechanism

The mechanism of drug-induced pulmonary injury is not well defined. It has been shown that cytotoxic drugs used in the treatment of cancer cause pulmonary insult by a combination of the direct toxic effects of a drug or its metabolite and of their indirect effects—that is, the enhancement of inflammation or immune processes. The clinical features produced by different cytotoxic agents are similar, but chronic pneumonitis and fibrosis are the most commonly associated clinical syndromes. Box 26-14 lists various chemotherapeutic agents that may produce pulmonary toxicity. The pathogenesis of pulmonary toxicity is uncertain but has been found to include disruption of the endothelial cells and changes in calcium homeostasis that lead to toxic injury. The mechanisms of drug-induced pulmonary injury associated with noncytotoxic drugs are less well defined but may involve changes in pulmonary homeostasis. Noncytotoxic agents can induce the development of numerous clinical syndromes. Several commonly implicated agents are discussed in the following sections.

BOX 26-14

Classification of Drug-Induced and Related Pulmonary Diseases by Type of Medication

Chemotherapeutic

Cytotoxic
- Azathioprine inhibitors
- Bleomycin*
- Busulfan
- Chlorambucil
- Cyclophosphamide
- Etoposide
- Interleukin-2
- Melphalan
- Mitomycin C*
- Nitrosamines
- Procarbazine
- Tumor necrosis factor
- Vinblastine
- Zinostatin

Noncytotoxic
- Bleomycin*
- Cytosine arabinoside*
- Gemcitabine
- Methotrexate*
- Procarbazine*

Antibiotic
- Amphotericin B*
- Nitrofurantoin
  - Acute*
  - Chronic
- Sulfasalazine

Antiinflammatory
- Acetylsalicylic acid*
- Gold
- Interferons
- Leukotriene antagonists
- Methotrexate
- Nonsteroidal antiinflammatory agents
- Penicillamine

Analgesic
- Heroin*
- Methadone*
- Naloxone*
- Placidyl*
- Propoxyphene*
- Salicylates*

Cardiovascular
- Amiodarone*
- Angiotensin-converting enzyme
- Anticoagulants
- β-Blockers*
- Dipyridamole
- Flecainide
- Protamine*
- Tocainide

Inhalant
- Aspirated oil
- Oxygen

Intravenous
- Blood*
- Ethanolamide maolate (sodium morrhuate)*
- Ethiodized oil (lymphangiogram)
- Talc

Miscellaneous
- Appetite suppressants
- Bromocriptine
- Dantrolene
- Complement-mediated leukostasis*
- Hydrochlorothiazide*
- Methysergide
- Radiation
- Systemic lupus erythematosus (drug induced)
- Tocolytic agents*
- Tricyclics*
- l-Tryptophan

From Murray JF, Nadel JA. *Textbook of Respiratory Medicine*. 5th ed. Philadelphia: Saunders; 2010.
*Typically manifests as acute or subacute respiratory insufficiency.

Noncytotoxic Drug-Induced Pulmonary Disease

Amiodarone

Amiodarone is one of the most frequently prescribed medications for ventricular dysrhythmias. Pulmonary disease from amiodarone occurs with 5% to 15% prevalence and takes the form of chronic interstitial pneumonitis, organizing pneumonia, ARDS, or a solitary mass of fibrosis.[286] Toxicity may be related to direct toxicity,

immunologic mechanisms, or related to activation of the renin-angiotensin system.[287]

Clinical diagnosis of amiodarone-induced pulmonary toxicity is based on the presence of two or more of the following signs and symptoms[288]:

1. New onset of pulmonary symptoms such as dyspnea, cough, or pleuritic chest pain
2. Detection of new chest radiographic abnormalities such as an interstitial or alveolar infiltrate
3. A decrease in DLCO of 20% from the pretreatment value; if no pretreatment values are available, then a value equal to less than 80% of the predicted value
4. Abnormal gallium-67 uptake by the lungs
5. Characteristic histologic changes of lung tissue obtained by bronchoscopic or open-lung biopsy

Amiodarone-induced pulmonary toxicity is commonly characterized by an insidious onset with nonproductive cough, hypoxemia, progressive dyspnea, weight loss, pleuretic chest pain, pleural effusion, and occasional fever.[286,289] Some patients present with a rapidly progressive dyspnea, high fever, and hypoxemia. Chest radiographs demonstrate parenchymal infiltrates with a predominant diffuse alveolar, interstitial, or mixed pattern that may progress to fibrosis.[290] Pleural thickening and effusions also have been reported. Pulmonary function tests performed at the onset of pulmonary toxicity reveal abnormalities typical of restrictive lung disease. Onset usually occurs after 2 months and is dose-related, occurring most commonly if doses greater than 400 mg/day are used.[286] Toxicity is rare when given acutely. Therapeutic options are limited. In cases where drug withdrawal is not desirable, corticosteroids are helpful at ameliorating the disease.[291] When the drug is discontinued, resolution of toxic signs is gradual due to the drug's half-life of approximately 40 to 70 days. Fibrosis, when it occurs, is not reversible.[286]

Cytotoxic Drug-Induced Pulmonary Disease

Three clinical syndromes are associated with cytotoxic drug-induced pulmonary injury: (1) chronic pneumonitis and fibrosis, (2) acute hypersensitivity lung disease, and (3) noncardiogenic pulmonary edema.[292] These syndromes may coexist.

Chronic Pneumonitis and Fibrosis

Interstitial pneumonitis and fibrosis is the most frequently encountered pattern in drug-induced pulmonary injury. The mechanism of injury is a direct cytotoxic effect of a drug or its metabolites on the endothelial, interstitial, or alveolar epithelial cells. On lung parenchyma, the cytotoxic effect elicits an inflammatory response characterized by the proliferation of macrophages, lymphocytes, and other inflammatory cells. This inflammatory response leads to the deposition of fibrin within the alveoli, which produces interstitial inflammation and fibrosis.

Interstitial pneumonitis can be classified as acute, subacute, or chronic; the chronic form is the most frequently encountered. Common manifestations of these subgroups include dyspnea, dry cough, low-grade fever, fatigue, and malaise that develop over several weeks to months. Chest radiography demonstrates diffuse interstitial infiltrates. Bleomycin is the causative agent most often implicated in interstitial pneumonitis. Treatment includes discontinuation of the offending agent with or without institution of corticosteroid therapy; prognosis is variable. Other antineoplastics implicated in pneumonitis and fibrosis are trastuzumab, gemcitabine, temsirolimus, everolimus, paclitaxel, docetaxel, irinotecan, gefitinib, oxaliplatin, tubotecan, and imatinib.[293]

Syndrome of Hypersensitivity Lung Disease

Hypersensitivity lung disease has been associated with the cytotoxic agents bleomycin, methotrexate, L-asparaginase, procarbazine, etoposide, teniposide, and mitoxantrone.[293] Common pulmonary manifestations include a nonproductive cough, dyspnea, and chest pain. The systemic allergic response is manifested as fever, urticaria, arthralgias, hypotension, and eosinophilia. Chest radiography may reveal pneumonitis, pleuritis, and pleural effusion. Corticosteroid use may or may not be indicated, and prognosis is generally favorable.

Drug-Induced Pulmonary Edema

The development of noncardiogenic pulmonary edema is an acute but rare phenomenon that occurs after the administration of some antineoplastic agents. Cytotoxic drugs that contribute to its development include methotrexate, cytosine arabinoside (cytarabine), gemcitabine, imatinib, and cyclophosphamide.

Numerous pharmacologic agents used in the treatment of cancer have been implicated in the development of toxic pulmonary side effects. The agents most commonly implicated in pulmonary insult include bleomycin, busulfan, carmustine, and methotrexate. Pulmonary toxicity in the use of antineoplastic agents is defined as the development of clinical signs and symptoms of pulmonary distress that were not present during the pretreatment studies. The prevalence of diffuse pulmonary infiltration occurring as a result of drug toxicity is reported to be as high as 20%.

Prototype Agents Implicated in Pulmonary Insult

Bleomycin. Bleomycin, an antitumor antibiotic, is the most common chemotherapeutically induced potentiator of pulmonary injury. Despite the benefits of bleomycin therapy, the development of pulmonary toxicity is the limiting factor of its use.[294] The most common adverse effect of bleomycin is the development of interstitial fibrosis. The incidence of pulmonary fibrosis is approximately 20%, with a 1% mortality rate. Anesthesia-related problems occur postoperatively and are associated with exposure to high O_2 concentrations. Symptoms of toxicity initially include a dry hacking cough and dyspnea on exertion. Progression of lung disease is associated with dyspnea at rest, tachypnea, fever, and cyanosis. Changes on chest radiography usually occur later and manifest as bibasilar reticular infiltrates that may progress to frank consolidation.

Several investigators have suggested that patients undergoing general anesthesia who have a concurrent history of bleomycin therapy should receive the lowest possible O_2 concentrations that allow maintenance of adequate Pa_{O_2}.[295,296] The use of steroids has been effective in some patients.

Anesthetic Management of Bleomycin-Treated Patients. Although universally accepted guidelines for the management of a bleomycin-treated patient undergoing general anesthesia are lacking, the following suggestions have been made:

- O_2 saturation should be monitored continuously and ABG analysis performed intermittently.
- Immediately before anesthesia, 100% O_2 should be administered for 1 to 4 minutes.
- After induction, a target Pa_{O_2} should be chosen and the Fi_{O_2} maintained at the lowest level that allows adequate oxygenation.
- The use of PEEP should be considered.
- Crystalloid solutions should be administered carefully and the use of colloid solutions considered if large fluid volumes are required.

- The patient should be informed of the possible need for postoperative ventilation.
- Postoperatively the Fi_{O_2} should be kept at the lowest possible setting that maintains the target Pa_{O_2}.

The choice of anesthetic technique varies, but as with all surgical procedures, careful evaluation and management are essential. There are no reports suggesting the superiority of regional anesthesia in patients treated with bleomycin.

Methotrexate. Methotrexate is an analog of folic acid that inhibits cellular reproduction by causing an acute intracellular deficiency of folate coenzymes. Methotrexate is used in the treatment of malignant and benign conditions, including leukemia, osteogenic sarcoma, choriocarcinoma, polymyositis, psoriasis, and connective tissue disorders (particularly rheumatoid arthritis). Regardless of the route of administration, pulmonary toxicity has been reported to occur with all forms of delivery, with an incidence of 7.6%. Clinically, the onset of pulmonary dysfunction may be chronic, but more commonly it is acute. The syndrome often develops over 7 to 14 days and is characterized by fever, dry cough, dyspnea, hypoxemia, and bilateral pulmonary infiltrates. Improvement may begin 10 to 14 days after onset.

PULMONARY OXYGEN TOXICITY

Etiology

As with all prescribed drugs, the risks of the adverse effects of O_2 administration must be considered, despite its beneficial effects. The prolonged use of high concentrations of O_2 (greater than 50% for longer than 24 hours) is potentially toxic and may result in irreversible lung damage.[295] The rate of development of O_2 toxicity is directly related to the exposure: partial pressure of inspired O_2[297] and duration of administration. Deleterious effects have been reported with more brief administrations.[297]

Normobaric hyperoxia can result in four clinical syndromes: (1) acute tracheobronchitis, (2) absorption atelectasis, (3) acute alveolar lung injury (ARDS), and (4) bronchopulmonary dysplasia. When nitrogen is replaced with O_2, absorption atelectasis occurs in the alveoli that are poorly ventilated. The loss of the so-called "nitrogen splint" promotes alveolar collapse.

Pathophysiology

The pathogenesis of pulmonary O_2 toxicity is linked to the excessive production of free O_2 radicals.[298] Free radicals are molecules that contain one or more unpaired electrons. Free radicals are highly reactive metabolites of O_2 (e.g., superoxide anion, hydrogen peroxide, and hydroxyl radical) that overwhelm antioxidant systems, including cellular enzymatic defenses (superoxide dismutase, catalase, glutathione peroxidase) and nonenzymatic scavengers (α-tocopherol acetate). Free radicals exert their toxic effect on cell and organelle membranes; they interfere with vital cellular functions, causing inactivation of enzymes and transport proteins, membrane lipid peroxidation, and inhibition of cell growth and division. Factors predisposing to oxygen toxicity are increased exposure (concentration × duration), advanced age, and radiation therapy to the thorax and use of chemotherapeutic agents that alter antioxidant defense mechanisms or generate oxidants.

Clinical Features and Diagnosis

The earliest manifestations are related to the effects on the tracheobronchial mucosa. Symptoms may occur after 6 hours of O_2 exposure and include substernal chest pain that is prominent with inspiration, tachypnea, and a nonproductive cough. By 24 hours, paresthesia, anorexia, nausea, and headache occur. Physiologic changes include a decrease in tracheal mucous velocity, vital capacity (VC), pulmonary compliance, and diffusing capacity and increased $P_{AO_2} - Pa_{O_2}$. Some individuals develop signs of mild airway obstruction. Chest radiography demonstrates an alveolar and interstitial pattern.

Management

Both hyperoxia and hypoxemia have undesirable effects. Therefore, deciding the must judicious administration of O_2 requires astute clinical judgment. The goal is to deliver the lowest level of Fi_{O_2} needed for maintaining adequate arterial O_2 saturation (generally, a Pa_{O_2} of greater than 90 mmHg). Measures such as PEEP should be used for decreasing the need for high Fi_{O_2}. In cases of frank oxygen toxicity, corticosteroid therapy reduces antioxidant enzyme activity and may be useful.

AUTOIMMUNE DISORDERS

Autoimmune diseases, *connective tissue diseases*, *collagenosis*, and *rheumatologic diseases* are terms used interchangeably in clinical medicine. These entities are often characterized by multiple-organ involvement and inflammation. On the whole, these disorders have unknown causes; however, the inflammatory process is immunologically mediated, as evidenced by the presence of autoantibodies, rheumatoid factor, and immune complexes, as well as by elevation of the sedimentation rate and the observation of certain clinical characteristics. Pulmonary manifestations are common and often assume a major role in the disease process. Characteristic restrictive lung changes may result if pulmonary impairment is sufficiently severe. Box 26-15 lists pulmonary manifestations of various collagen vascular diseases.

Sarcoidosis

Sarcoidosis is a multisystemic disorder characterized by the presence of epithelioid-cell granulomata. It is described as an intense interaction of activated lymphocytes and macrophages that results in tissue injury. The disease most often involves the lungs, reticuloendothelial system, skin, eyes, and myocardium. The prevalence of disease globally is 16.5/100,000 men and 19/100,000 women. The disease predominantly occurs in those aged 20 to 40 years.[299] A preponderance of the disease among African Americans and varying phenotypes among other ethnic groups points to a strong genetic influence.[300] The cause of sarcoidosis is unclear; no organic or inorganic causative agent has been consistently found. The route of transmission also is uncertain and may be related to human lymphocyte antigen polymorphisms, which lead to granuloma formation after various interactions of antigens, HLA molecules, and T-cell receptors.[301] Interferon-gamma and cytokines such as tumor necrosis factor-alpha (TNF-α), IL-12, and IL-18 play a critical role in the formation of granulomatous lesions.[302]

Most sarcoid granulomata resolve spontaneously, leaving no scar. Others persist for a longer duration, with little or no fibrosis, and still others become hyalinized, fibrotic areas that cause tissue damage. Pulmonary involvement is primarily in regions rich in lymphatic vessels, such as the subpleural, perivascular, and peribronchial areas. Often, adjacent nonspecific inflammatory changes as well as alveolitis with cellular infiltrates are noted.[303]

Parenchymal infiltration and fibrosis result in a decrease in lung compliance, impairment of diffusing capacity, and a reduction in lung volumes. A restrictive pattern of ventilation is usually observed, but many patients exhibit a reduced FEV_1/FVC and increased airway resistance. $\dot{V}/\dot{Q}$ imbalance and an increase in Pa_{O_2} occur in response to a nonuniform decrease in lung compliance. An obstructive pattern resulting from endobronchial disease or peribronchial fibrosis may occur simultaneously. Pulmonary

BOX **26-15**

Pulmonary Manifestations of Some Collagen Vascular Diseases

Rheumatoid Arthritis
- Pleural disease (effusions)
- Diffuse interstitial pneumonitis
- Necrobiotic nodules
- Caplan syndrome
- Pulmonary hypertension (arteritis)
- Apical fibrobullous disease
- Bronchiolitis obliterans with and without organizing pneumonia
- Cricoarytenoid arthritis

Systemic Lupus Erythematosus
- Pleural disease (pleuritis, effusions)
- Atelectasis
- Acute lupus pneumonitis
- Diffuse interstitial lung disease
- Pulmonary hemorrhage
- Respiratory muscle dysfunction

Progressive Systemic Sclerosis
- Diffuse interstitial fibrosis
- Pulmonary vascular disease
- Aspiration pneumonia
- Chest-wall restrictions secondary to thoracic skin sclerosis
- Pleural disease

Polymyositis—Dermatomyositis
- Interstitial pneumonitis
- Aspiration pneumonia
- Respiratory myositis
- Pulmonary hypertension
- Bronchiolitis obliterans organizing pneumonia

Mixed Connective Tissue Disease
- Diffuse interstitial lung disease
- Pulmonary hypertension (vasculitis)
- Pleural disease
- Diaphragmatic muscle dysfunction

Sjögren Syndrome
- Respiratory mucosal dryness
- Pleurisy
- Chronic airway disease
- Lymphocytic interstitial pneumonia
- Pseudolymphoma
- Lymphoma
- Amyloid
- Pulmonary hypertension (vasculitis)

hypertension occurs in varying percentages, but is reportedly as high as 50% to 70% in some groups (particularly lung transplant patients).[304] Cor pulmonale may develop in the presence of severe pulmonary fibrosis. Inhaled prostacyclin and sildenafil may be used to reduce pulmonary hypertension.

Clinical presentation is varied and may be categorized as asymptomatic (occurring in 20% of individuals investigated and based on the detection of abnormality of chest radiography) or symptomatic (characterized by nonspecific features ranging from fever, fatigue, anorexia, weight loss, chills, and night sweats to dyspnea and blindness). The lung is the most commonly affected organ, with pulmonary involvement occurring in more than 90% of individuals with sarcoidosis.[301] Respiratory symptoms are those typical of interstitial involvement and include dyspnea, dry cough, and retrosternal chest pain (35% to 50% of patients). Less common symptoms include wheezing, hemoptysis, pleural effusion, and clubbing of the fingers. Sarcoidosis is one of the few chest diseases that concurrently involve lymph nodes in the lung (hilar region) and the mediastinum. On radiography, intrathoracic involvement has been classified into three categories. Stage I is characterized by bilateral, symmetric, hilar, and mediastinal adenopathy; stage II by hilar adenopathy and diffuse pulmonary infiltrates; stage III by diffuse pulmonary infiltrates without adenopathy; stage IV by pulmonary fibrosis.[301] Stage I is associated with the most favorable prognosis, and stage IV with the worst.

The diagnosis of sarcoidosis requires evidence of multisystem disease (i.e., multiorgan presence of granulomas). Extrathoracic involvement typically involves lymphatics, skin, liver, eye, spleen, and bone. Salivary glands, heart, nervous system, and larynx involvement occur in small percentages. Although not a common site, laryngeal involvement should cause concern about possible difficulty with airway instrumentation. Laryngeal involvement is signaled by hoarseness, dyspnea, dysphagia, dysphonia, cough, or stridor.[299] When laryngeal involvement exists, it affects the supraglottic area in 80% and the subglottic area in 20%.[299] Tracheotomy, transoral resection, corticosteroids, and laser resection may be used to treat laryngeal granulomas.

The overall prognosis in sarcoidosis is good. The acute onset usually is followed by a self-limiting course of approximately 2 years' duration with spontaneous resolution in approximately 20%.[301] Treatment with corticosteroids (topical, inhaled, enteral, or parenteral) is frequently used and produces relief of symptoms, clinical remissions, and suppression of inflammation and granuloma formation. Conversely, because spontaneous and permanent remissions occur in 50% of patients, the use of corticosteroids in these individuals is controversial. Other therapies include methotrexate, azathioprine, leflunomide, and mycophenolate.[301] Considering a prominent role of tumor necrosis factor, infliximab, a monoclonal antibody to TNF, has been found effective in treating sarcoidosis.[305,306]

The mortality rate for patients with sarcoidosis after 5 years is approximately 4% to 10% and is attributed to respiratory failure, azotemia from renal injury caused by chronic hypercalciuria, cardiac arrest resulting from myocardial involvement, and massive hemoptysis due to colonization of bullae by *Aspergillus fumigatus*.

FLAIL CHEST

Flail chest, a condition that results from chest trauma and multiple rib fractures, is reported to occur in 5% of patients who sustain thoracic injury (Figure 26-27).[307] The hallmark of flail chest is paradoxical movement of the chest wall at the site of the fracture. During inspiration, the chest wall is drawn inward, owing to the negative intrathoracic pressure; and outward during expiration, when the intrathoracic pressure increases above atmospheric pressure (Figure 26-28). Inefficient lung inflation caused by rib fracture and paradoxical breathing limits alveolar ventilation and may progress to hypoventilation, hypercapnia, and progressive alveolar collapse.[308] Treatment includes pain control with measures such as intercostal nerve block with a local anesthetic or insertion of an epidural catheter with a local anesthetic or opioid, and in severe

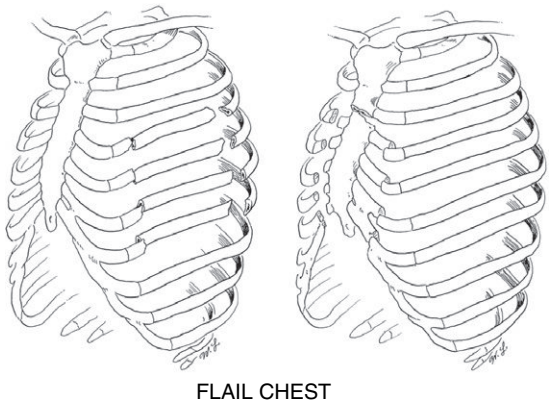

FIGURE **26-27** Fracture of several adjacent ribs in two places with lateral flail or central flail segments. (From Marx JA, et al, eds. *Rosen's Emergency Medicine: Concepts and Clinical Practice*. 7th ed. Philadelphia: Mosby; 2010:389.)

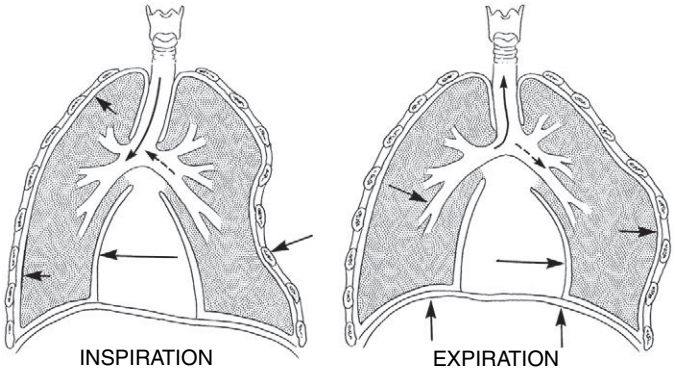

FIGURE **26-28** Flail chest: Paradoxical respiration. On inspiration, flail section sinks in as chest expands, impairing ability to produce negative intrapleural pressure to draw in air. Mediastinum shifts to uninjured side. On expiration, flail segment bulges outward, impairing ability to exhale. Mediastinum shifts to injured side. Air may shift uselessly from side to side in severe flail chest *(broken arrows)*. (Redrawn from Marx JA, et al, eds. *Rosen's Emergency Medicine: Concepts and Clinical Practice*. 7th ed. Philadelphia: Mosby; 2010:394.)

BOX **26-16**

Indications for Treatment of Flail Chest with Mechanical Ventilation

Respiratory Failure Manifested by One or More of the Following Criteria

- Clinical signs of respiratory fatigue
- Respiratory rate >35/min or <8 min
- P_{AO_2} <60 mmHg at Fi_{O_2} ≥0.5
- Pa_{CO_2} <55 mmHg at Fi_{O_2} ≥0.5
- Alveolar-arterial oxygen gradient >450
- Clinical evidence of severe shock
- Associated severe head injury with lack of airway control or need to ventilate
- Severe associated injury necessitating surgery

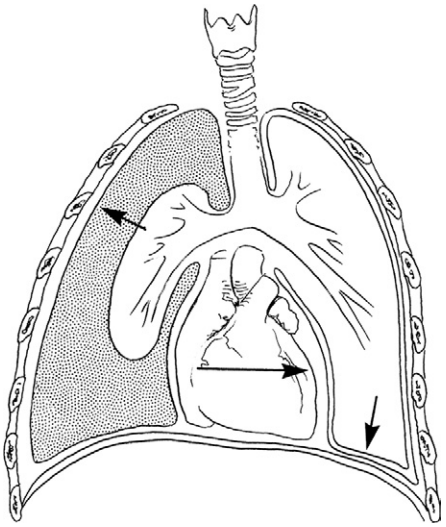

FIGURE **26-29** Closed pneumothorax. Simple pneumothorax is present in the right lung, with air in the pleural cavity and collapse of right lung. (From Marx JA, et al, eds. *Rosen's Emergency Medicine: Concepts and Clinical Practice*. 7th ed. Philadelphia: Mosby; 2010:393.)

cases, tracheal intubation with mechanical ventilation and PEEP (Box 26-16). Ventilator settings are adjusted so that wide swings in pleural pressure are decreased or avoided. Surgical fixation of the rib cage may be indicated in some patients for persistent pain, severe chest wall instability, or a progressive decline in pulmonary function testing in a patient with flail chest.[309] The mortality rate is directly related to the underlying and associated injuries and is reported to be between 8% and 35%.[308]

PNEUMOTHORAX

Pneumothorax can be subdivided into three categories, depending on whether air has direct access to the pleural cavity.

Simple Pneumothorax

In simple pneumothorax, no communication exists with the atmosphere (Figure 26-29). Additionally, no shift of the mediastinum or hemidiaphragm results from the accumulation of air in the intrapleural space. The severity of pneumothorax is graded on the basis of the degree of collapse: collapse of 15% or less is small; collapse of 15% to 60% is moderate; and collapse of greater than 60% is large. Treatment of a simple pneumothorax is determined by the size and cause of injury and may include catheter aspiration or tube thoracostomy; close observation of the patient with simple pneumothorax is essential.

Communicating Pneumothorax

In communicating pneumothorax, air in the pleural cavity exchanges with atmospheric air through a defect in the chest wall (Figure 26-30). Communicating pneumothorax represents a severe ventilatory disturbance because the affected lung collapses on inspiration and expands slightly on expiration. The exchange of air in and out of the wound results in a large functional dead space and a decrease in the efficacy of ventilation.

The wound should be covered with an occlusive dressing immediately. The dressing should prevent influx of air, but should allow egress of air from inside the thorax to avoid development of tension pneumothorax (see next section). Treatment measures include administration of supplemental O_2, tube thoracostomy, and intubation; mechanical ventilation may be indicated.

Tension Pneumothorax

Tension pneumothorax develops when air progressively accumulates under pressure within the pleural cavity (Figure 26-31). If the

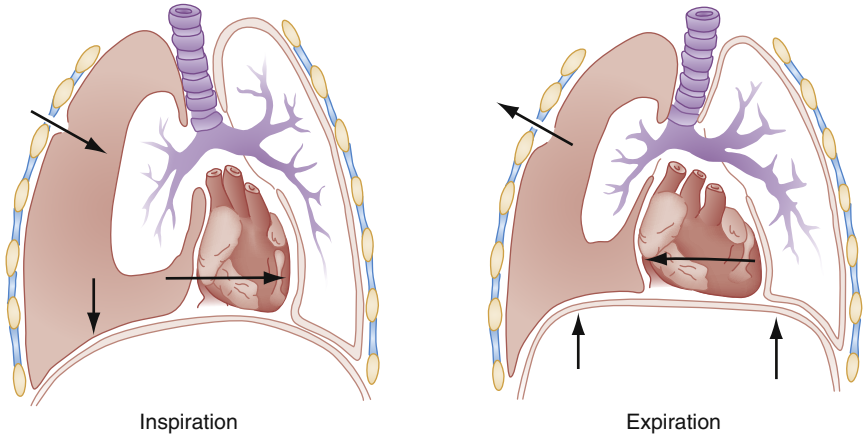

FIGURE **26-30** Communicating pneumothorax. The right lung has collapsed, and air is present in the pleural cavity, with communication to the outside through the defect in the chest wall. In sucking chest wounds, lung volume is greater with expiration. (From Marx JA, et al, eds. *Rosen's Emergency Medicine: Concepts and Clinical Practice*. 7th ed. Philadelphia: Mosby; 2010:394.)

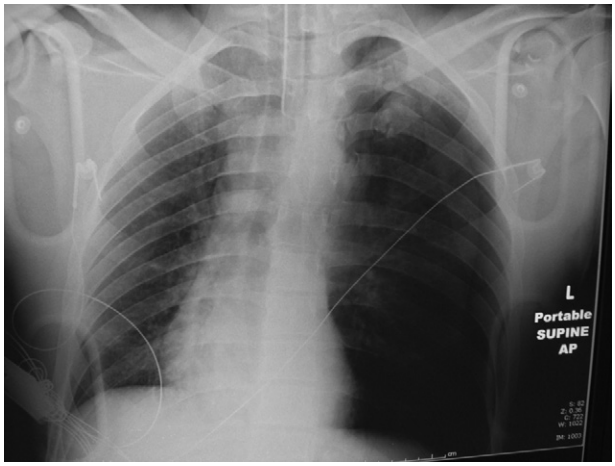

FIGURE **26-31** Tension pneumothorax. Hyperlucency is noted, mostly toward the left lung base, because the x-ray is a supine exposure. Shift of the mediastinum toward the right is noted. (From Marx JA, et al, eds. *Rosen's Emergency Medicine: Concepts and Clinical Practice*. 7th ed. Philadelphia: Mosby; 2010:394.)

pressure becomes too great, the mediastinum shifts to the opposite hemithorax, and this causes compression of the contralateral lung and great vessels. Subsequently, venous return is decreased, and air enters the pleural space but cannot exit. Respiratory and cardiac disturbances ensue, exhibited by a decrease in CO, a decrease in blood pressure, an increase in CVP, and a shunting of blood to nonventilated areas. The hallmark signs of tension pneumothorax are hypotension, hypoxemia, tachycardia, increased CVP, and increased airway pressure. Other findings include absence of breath sounds on the affected side, asymmetric chest wall movement, tracheal shift, displacement of the cardiac impulse, and hyperresonance to percussion in the affected hemithorax. The patient may exhibit extreme anxiety or a feeling of impending doom.

Tension pneumothorax is potentially lethal; therefore, immediate treatment is essential. Decompression of the chest can be performed with the insertion of a 14-gauge angiocatheter into the second or interspace anteriorly or the fourth or fifth interspace laterally. A rush of air is heard when decompression occurs. The angiocatheter converts the tension pneumothorax to a simple pneumothorax.

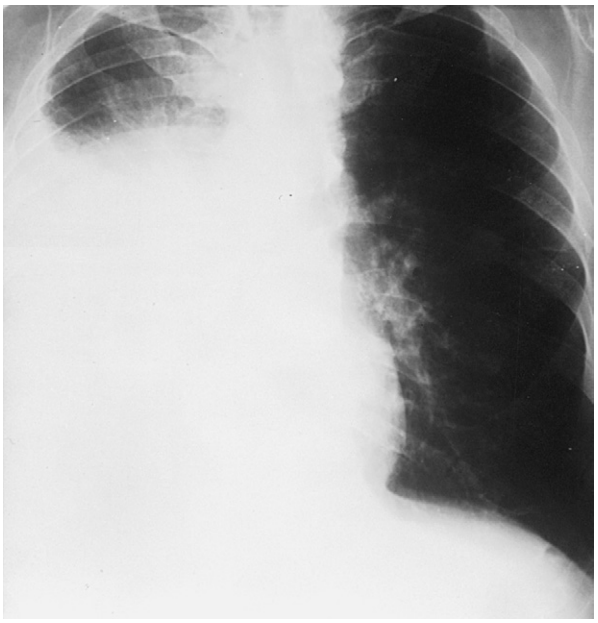

FIGURE **26-32** Dense opacity on the right side with meniscus, indicating hemothorax. (From Townsend CM, et al. *Sabiston Textbook of Surgery*. 18th ed. Philadelphia: Saunders; 2007:499.)

Hemothorax

A hemothorax is the accumulation of blood in the pleural cavity. It usually is a result of trauma (Figure 26-32), but other causes include the rupture of small blood vessels in the presence of inflammation, pneumonia, tuberculosis, or erosion by tumors.

The treatment of hemothorax consists of airway management as necessary, restoration of circulating blood volume, and evacuation of the accumulated blood. Thoracostomy may be indicated if the initial bleeding rate is greater than 20 mL/kg/hr. If bleeding subsides but its rate remains greater than 7 mL/kg/hr, if chest radiograph worsens, or if hypotension persists after initial blood replacement and decompression, thoracostomy is indicated.

Pathogenesis

Different presentations may be distinguished, according to the mechanism of injury.

Spontaneous. Pneumothorax usually is caused by rupture of alveoli near the pleural surface of the lung after a forceful sneeze or cough. This mechanism is most common in individuals with a long narrow chest and in those with emphysema.

Traumatic. Hemothorax, pneumothorax, and flail chest may occur after blunt chest trauma; however, they most often occur after rib fracture. Hemopneumothorax also may occur with penetrating injury.

Iatrogenic. Hemothorax and pneumothorax may occur after any of the following:

- Subclavian central line insertion (incidence 2% to 16%)
- Supraclavicular brachial plexus block (interscalene and intercostal block are possible, but less prevalent causes)
- Barotrauma (resulting from overdistention of the alveoli by PEEP or high peak pressure; abrupt deterioration of Pa_{O_2} and cardiovascular function during mechanical ventilation should arouse suspicion of pulmonary barotrauma, especially pneumothorax)
- Other surgical procedures (e.g., mediastinoscopy, radical neck dissection, mastectomy, axillary lymph node dissection, or nephrectomy)

Nitrous Oxide and Pneumothorax

The blood-gas partition coefficient of N_2O (0.47) is 34 times greater than that of nitrogen (0.014). This differential solubility means than N_2O can leave the blood to enter an air-filled cavity 34 times more rapidly than nitrogen can leave the cavity and enter the blood. As a result, the volume or pressure of the air-filled cavity surrounded by a compliant wall increases. An often-cited study determined that 75% N_2O doubles the volume of a pneumothorax in 10 minutes.[310] If in the presence of pneumothorax the chest tube is patent and functioning, N_2O is theoretically acceptable, because little pleural air should be present, and any accumulation should be evacuated by the chest tube. A closed pneumothorax is a contraindication to the administration of N_2O. Decreased pulmonary compliance (increased pulmonary inspiratory pressure) during administration of anesthesia to patients with a history of chest trauma may reflect the expansion of an unrecognized pneumothorax.

ATELECTASIS

Definition

Atelectasis is an abnormal condition characterized by a collapse of pulmonary tissue that prevents the respiratory exchange of CO_2 and O_2. Atelectasis can involve a small localized area or an entire lung. Atelectasis is common with all general anesthetics. It commonly develops within the first few minutes of induction of anesthesia, regardless of the mode of ventilation used, and persists for hours to days after anesthesia, depending on the extent and location of surgery.[311] Atelectasis commonly forms adjacent to the diaphragm in dependent lung regions. Compression of lung tissue, absence of diaphragmatic-induced negative pressure, impaired surfactant, and absorption of oxygen from nitrogen-free alveoli are common causes of atelectasis. Affecting 90% of patients under general anesthesia, atelectasis and airway closure are responsible for the vast majority of gas exchange impairment observed under anesthesia.[312]

Etiology and Pathophysiology

Atelectasis results from a blockage or obstruction of many small bronchi or of a major bronchus. The loss of diaphragmatic tone and function during general anesthesia is a major contributing factor to atelectasis, which characteristically develops within minutes after anesthesia induction. As small airways close due to maldistribution of ventilation under positive-pressure breathing, or due to the cephalad migration of abdominal contents, the gas within the affected alveoli is absorbed, and there is no further ventilation to reopen those alveoli. Reduction in the Fi_{O_2} can help reduce the degree of atelectasis (as measured by the shunt fraction).[313]

Incidence and Outcome

Atelectasis occurs almost universally under general anesthesia and is the most common cause of postoperative respiratory dysfunction. Postoperatively, it occurs most often after thoracic and upper abdominal procedures, with rates of incidence reaching 80%. In lower-risk surgeries, postoperative atelectasis most often is subclinical and resolves spontaneously within 24 to 48 hours. No recent data support that atelectasis predisposes one to the development of pneumonia.

Treatment

Historically, practitioners used large tidal volumes (10 to 15 mL/kg) to combat atelectasis intraoperatively. Although the concept of injury related to high-pressure barotraumas has been long understood, the understanding of ventilator-associated lung injury (VALI) being related to high ventilating volumes, even in the presence of moderate-peak inspiratory pressures (volutrauma) has changed the approach to establishing ventilator tidal volumes.[273,314] To reduce the deleterious effect of high volumes, smaller tidal volumes of 6 to 10 mL/kg are more beneficial for mechanical ventilation, particularly in cases of respiratory distress syndrome. There is evidence that this reduction in tidal volume does not worsen the degree of atelectasis.[315] Instead, PEEP and various maneuvers to reopen ("recruit") and maintain alveoli have been proposed to reduce atelectasis.[316] Most common of these are vital capacity maneuvers, where the lungs are intermittently expanded to vital capacity or 30 cm H_2O and held in that state for around 10 seconds.[313,317] Such recruitment maneuvers are most effective when combined with other strategies such as reduction in Fi_{O_2} or "open-lung" ventilation approaches.

Open-lung ventilation describes myriad approaches to providing mechanical ventilation with the goal of preventing atelectasis. Pressure-control inverse ratio ventilation (PC-IRV) and, more recently, airway pressure release ventilation (APRV) are approaches designed to maintain a higher mean lung volume and thereby reduce airway closure and atelectasis. Airway pressure release ventilation is analogous to CPAP, with intermittent release phases that allow the lung volume to drop briefly. APRV has an advantage over more "controlled" ventilation modes (such as PC-IRV) in that it is useful in spontaneously breathing patients to reduce neuromuscular blockade, preserve respiratory effort and protective reflexes, and cause less patient-ventilator dyssynchrony.[318]

Standard postoperative measures for improving pulmonary function include incentive spirometry, deep breathing, intermittent positive-pressure breathing, and administration of CPAP, with the last of these offering the greatest superiority in increasing FRC.

PLEURAL EFFUSION

Pleural effusion is the abnormal accumulation of fluid in the pleural space. It usually is an indication of disorders or disease complications in the surrounding structures. Possible causes of effusion are: (1) blockage of lymphatic drainage from the pleural cavity; (2) cardiac failure, which causes an increase in pulmonary capillary pressures and eventual movement of fluid into the pleural cavity; (3) reductions in plasma colloid osmotic pressure; and

(4) infection or any other inflammatory process of the pleural membranes that alters capillary membrane permeability.

Treatment modalities include tube thoracostomy, thoracentesis, and pleurodesis. Pleurodesis is a procedure used to prevent the reaccumulation of pleural fluid. Inflammation is produced with injection of a sclerosing agent, usually tetracycline, into the chest tube; adhesion formation and fusion of the pleural membranes result.

SKELETAL DISORDERS

The primary pathophysiology of skeletal disorders is an alteration in the structure of the thorax that diminishes chest-wall excursion. Disorders commonly producing this restriction of breathing include sternal deformities, kyphoscoliosis, and ankylosing spondylitis (AS).

Pectus Deformities

Pectus Excavatum

Pectus excavatum, also referred to as *funnel chest*, is the most common chest wall deformity, occurring in 1 in 400 children.[319] It is a congenital anomaly characterized by depression of the sternum (usually above the xiphoid-sternal junction) and symmetric or asymmetric prominence of the ribs on either side. Pectus excavatum has a genetic linkage, which is shared with that of adolescent scoliosis.[320] If uncorrected, the disease usually worsens at adolescence. A widely used surgical procedure, the Nuss procedure, inserts a metal rod behind the sternum to reverse the concavity.[321]

Clinically the majority of patients are asymptomatic unless pectus excavatum is extreme. Patients with pectus excavatum have reduced chest cavities and TLC compared with normal subjects; however, pulmonary function often is normal except in severe cases, in which VC, TLC, and maximum breathing capacity may be diminished. The indications for repair of pectus excavatum are the subject of controversy. Conflicting data have been presented regarding whether the repair of pectus excavatum is performed only for cosmetic purposes or whether it actually improves cardiorespiratory function and exercise tolerance.[321] Patients with Marfan syndrome have a high incidence of chest-wall deformities. They usually are seen in their most severe form and often are accompanied by scoliosis. Other musculoskeletal diseases may be present in patients with pectus excavatum. Congenital heart disease, mitral valve prolapse, and asthma also occur more frequently in patients with pectus excavatum. Electrocardiographic abnormalities are common and attributable to the abnormal chest-wall configuration and to the displacement and rotation of the heart into the left thoracic cavity. A systolic ejection murmur of grades II to III or IV often is identified.

Pectus Carinatum

Pectus carinatum is characterized by a longitudinal protrusion of the sternum. It is the second most common chest deformity, occurring in 1 or 2 persons per 1000. A familial tendency exists, and the disorder is more frequent in males than in females (4:1). The pathogenesis is unclear, and the disorder may be congenital or acquired. The development of pectus carinatum is thought to result from the overgrowth of the costal cartilages, which results in displacement of the sternum. The development of pectus carinatum also has been associated with severe childhood asthma and rickets.[322] The physiologic effects are probably related to the restriction of thoracic excursion. Patients with pectus carinatum have an increased incidence of congenital heart disease, including ventricular septal defect, patent ductus arteriosus, atrial-septal defects, and mitral valve abnormalities.[323] Surgery is the only effective treatment for pectus carinatum and is performed to alleviate possible cardiopulmonary dysfunction and to prevent progressive postural deformities, as well as for cosmetic reasons.

Kyphoscoliosis

Definition

Kyphosis is a deformity marked by an accentuated posterior curvature of the spine. Scoliosis is a lateral curvature. Kyphoscoliosis results when kyphosis and scoliosis occur concomitantly, causing a lateral bending and rotation of the vertebral column. Scoliosis alone, despite its severity, does not cause sensory or motor impairment. In contrast, kyphosis and kyphoscoliosis may induce cord damage because of the sharp angulation of the spine. Respiratory dysfunction is associated with scoliosis, significant kyphosis, and severe kyphoscoliosis.

Incidence and Outcome

Scoliosis is the most common spinal deformity, with an incidence of 4 persons per 1000.[324] The etiologic classification of scoliosis falls into five categories: idiopathic, congenital, neuropathic (e.g., poliomyelitis, cerebral palsy, syringomyelia, and Friedreich's ataxia), myopathic (e.g., muscular dystrophy and amyotonia congenita), and traumatic. Idiopathic scoliosis is the most common deformity, accounting for 80% of all cases. The presence of cervical scoliosis should alert anesthesia personnel to potential difficulties in airway management. Any significant curvature involving the thoracic spine may alter lung function. Unless deformity is severe, patients with kyphosis are able to maintain normal pulmonary function. In contrast, even mild forms of scoliosis can result in impaired ventilatory function.

Although not totally consistent, VC and FEV_1 less than 50% of that predicted during initial testing suggest an increased risk of pulmonary complications postoperatively.[325-327] The Cobb angle (being greater than 100-110 degrees) is also moderately predictive of complications.[325,326]

Severe thoracic deformity may result in respiratory alterations during sleep. Several types of breathing abnormalities have been documented, including obstructive apnea and hypopnea. The lowest $HgbO_2$ saturations occurred during REM sleep.[328,329] Because of chronic effects on the pulmonary system, surgical correction results in immediate and short-term deterioration of respiratory mechanics in anesthetized patients.[330]

Clinical Features and Diagnosis

Diminution of pulmonary function occurs with curvatures of greater than 60 degrees, and pulmonary symptoms develop with curvatures greater than 70 degrees (as measured by the Cobb technique; Figure 26-33). Curvatures greater than 100 degrees may be associated with significant gas exchange impairment.[331] In general, the greater the curvature, the greater the loss of pulmonary function. Because of this, mechanical ventilation becomes inefficient; this inefficiency is the major factor causing respiratory embarrassment.[329] At the time of diagnosis, it is often possible to document a reduction in lung capacity. The characteristic deformity seen in scoliosis causes one hemithorax to become relatively smaller than the other.

Skeletal chest wall deformity in kyphoscoliosis leads to a reduction in lung volumes and the pulmonary vascular bed.[332] Ventilatory failure associated with severe kyphoscoliosis produces a lung size that is 30% to 65% of normal. As the patient ages, the chest wall becomes less compliant; this increases the work of breathing and leads to hypoventilation and respiratory muscle weakness.

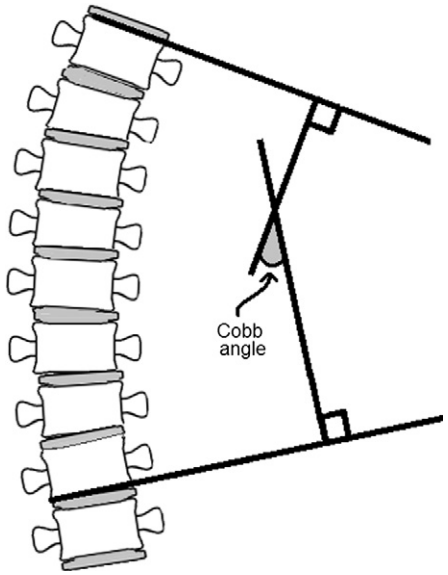

FIGURE **26-33** Cobb method of measuring scoliosis curves. The most tilted vertebrae above and below the curve are identified. Horizontal lines are drawn parallel with the plane of each vertebra. Perpendicular lines intersecting those horizontal lines intersect at the angle of curvature.

The main features of lung mechanics in the patient with early-stage scoliosis are reduced lung volumes (VC, TLC, FRC, and RV) and reduced chest wall compliance; in the late stages of disease, $\dot{V}/\dot{Q}$ mismatching with hypoxemia (attributed to alveolar hypoventilation because of a decrease in V_T), increased PAP, hypercapnia, abnormal response to CO_2 stimulation, increased work of breathing, and cor pulmonale occur and eventually lead to cardiorespiratory failure.[332] Reduction in VC to 60% to 80% of the predicted value is a typical finding.[331] FEV_1/FVC is normal unless other pulmonary diseases are present. Although normocarbia prevails for most of the clinical course, an elevated $Paco_2$ signifies the onset of respiratory failure. The severity of hypercapnia most closely correlates with the patient's age and inspiratory muscle strength.

Associated Conditions

Scoliosis may be associated with several cardiovascular abnormalities, of which mitral valve prolapse is the most common. If mitral regurgitation is present, antibiotic prophylaxis is indicated before surgical manipulation. Other common changes include an increase in PVR and ensuing PAH, which leads to the development of right ventricular hypertrophy. Several contributing factors are thought to be responsible for the development of increased PVR. First, arterial hypoxemia results in pulmonary vasoconstriction. Second, changes in the pulmonary arterioles as a consequence of the increased pulmonic pressure may cause narrowing and result in irreversible PAH. Third, a compressed chest wall may increase vascular resistance in affected areas. Fourth, development of scoliosis at an early age inhibits growth of the pulmonary vascular bed.

Treatment

The management of scoliosis may include: (1) observation of the problem without active medical treatment, (2) treatment by nonoperative methods that include the use of braces or electronic stimulators, and (3) operative methods such as anterior or posterior spinal fusion and instrumentation, such as Harrington rod insertion.[333] Discussion continues regarding the long-term effectiveness of various treatment modalities vis-à-vis short- and long-term complications that can also arise after surgery.[334]

Anesthetic Management

Preoperative Evaluation. Preoperatively a thorough review of systems is essential. The severity of scoliosis and any underlying conditions must be noted. Any reversible pulmonary involvement such as pneumonia should be corrected before elective surgery. ABG analysis may be indicated if there is suspicion of significant pulmonary impairment. Because these procedures can potentially involve large blood losses, young, healthy, asymptomatic patients may donate autologous blood. Blood typing and cross match also are required.

When sedatives are used in the preoperative area, care must be taken to ensure that respiratory status is not depressed. The need for intraoperative monitoring is dictated by the type of surgery and the physical status of the patient. No specific anesthetic techniques have been shown to be superior in patients with scoliosis, but N_2O may increase PVR by direct vasoconstrictive effects on the pulmonary vasculature. It has been suggested that scoliosis is associated with an increased incidence of malignant hyperthermia.[335]

With significant manual distraction of the spine during the procedure, assessment of neural integrity may be required. Although increasingly less common, a "wake-up" test may be requested after placement of surgical instrumentation. This should be communicated between surgeon and anesthetist before the procedure. At the designated time, the anesthetic is lightened and the patient is observed to follow commands and demonstrate motor function. The anesthetic must be planned to allow the patient to become able to hear and follow commands, while still tolerating the endotracheal tube in the prone position. After successful demonstration, anesthesia is quickly reinstituted to facilitate the conclusion of the procedure. The use of somatosensory evoked potentials and motor evoked potential monitoring has reduced the requirement for the wake-up test. Neural monitoring, however, also necessitates customization of the anesthetic plan to reduce interference with the signals. High-dose volatiles or any wide swings in anesthetic level can influence sensory evoked potential monitoring, and muscle relaxants can interfere with motor response monitoring. All anesthetic agents depress somatosensory evoked potentials to a varying degree. Administration of volatile anesthetics should not exceed a minimum alveolar concentration of 1. A technique using primarily N_2O or propofol for hypnosis and continuous infusion of opioid is a common approach. Communication between the monitoring technician and anesthetist is essential.

Intraoperative Management. Considerable fluid and blood loss may occur during surgery. The surgeon may request the institution of deliberate hypotension. Deliberate hypotension can be produced with the use of one or more of the following: potent inhalation anesthetics; vasodilators (e.g., sodium nitroprusside, or nitroglycerin) or β-adrenergic blocking agents (e.g., propranolol or esmolol). The risks and potential benefits should be weighed against the effects of deliberate hypotension. Traditional wisdom was that the mean arterial blood pressure can be safely maintained at a lower level of 60 mmHg. However, the lower limit of cerebral autoregulation is not dependably at this level, and discrepancies between blood pressure measurement devices and the actual perfusion pressure of the brain may be significant. The incidence of both blindness from retinal hypoperfusion in the prone position and cerebral injury from deliberate hypotension call for extreme caution in driving the blood pressure down during this procedure.[336-338] Interventions for prevention of hypothermia, such as use of a hot-air warming blanket, should be used. Careful positioning is essential.

Postoperative Care. The decision of whether to use mechanical ventilation postoperatively is based on the severity of scoliosis

and intraoperative events. Most patients with mild to moderate pulmonary dysfunction are able to undergo safe extubation in the operating room. Those with severe deformity should be weaned slowly.

Ankylosing Spondylitis

Definition

Ankylosing spondylitis (AS), also known as *rheumatoid spondylitis* and *Marie-Strumpell disease*, is a chronic inflammatory disorder that primarily affects the spine and sacroiliac joints and produces fusion of the spinal vertebrae and the costovertebral joints.

Etiology and Incidence

The cause of AS remains unclear. However, it is strongly associated with the histocompatibility antigen HLA-B27, the presence of which is detected in more than 90% of Caucasians with the disease.[339] It is a disease of adults younger than 40 years, and it demonstrates a predilection for males (male-to-female ratio, 9:1). The disease is rare in non-Caucasians.

Clinical Features and Diagnosis

AS is diagnosed on the basis of clinical criteria that include: (1) chronic low back pain with limitation of spinal motion (less than 4 cm as measured by the Schober test), (2) radiographic evidence of bilateral sacroiliitis, and (3) limitation of chest wall expansion (less than 2.5 cm increase in chest circumference measured at the fourth intercostal space). Extraskeletal manifestations of this disease include iritis, cardiovascular involvement (cardiac conduction defects, aortitis, and aortic insufficiency in 20% of individuals), peripheral arthritis, fever, anemia, fatigue, weight loss, and fibrocavitary (fibrobullous) disease of the apexes of the lungs. The most limiting factors associated with the disease are pain, stiffness, and fatigue.

Complications

Pulmonary complications are reported to occur in 2% to 70% of patients with AS. Apical fibrosis is the most commonly occurring abnormality, followed by interstitial lung disease, respiratory impairment due to chest wall restriction, sleep apnea, and spontaneous pneumothorax.[340] In apical fibrosis, the pulmonary lesion begins with apical pleural thickening and patchy consolidation of one or both apexes and often progresses to dense bilateral fibrosis and air space enlargement. Patients with apical fibrosis usually have advanced AS. Cardiac complications associated with AS include aortic valve diseases, conduction disturbances, cardiomyopathy, and ischemic heart disease.[340]

The most common thoracic complication is fixation of the thoracic cage as a result of costovertebral ankylosis, which can lead to pulmonary dysfunction.[341] In patients with this complication, motion of the thoracic cage is restricted due to fusion of the costovertebral joints; this restriction leads to a decrease in thoracic excursion. Respiratory function typically demonstrates a restrictive pattern with mild diminution of TLC, VC, and DLCO and normal or slightly increased RV and FRC. Pulmonary compliance, diffusion capacity, and ABG values usually are normal.[341] Despite having abnormal pulmonary function, the majority of patients with AS are able to perform normal physical activities without pulmonary symptoms.

Bone ankylosis may occur in the numerous joints around the thorax (i.e., the thoracic vertebrae and the costovertebral, costotransverse, sternoclavicular, and sternomanubrial joints), resulting in limitation of chest-wall movement. Patients with AS rarely complain of respiratory symptoms or functional impairment unless they have coexisting cardiovascular or respiratory disease. Progressive kyphosis is equivalent to progressive rigidity of the thorax. Increased diaphragmatic function compensates for decreased thoracic motion, allowing lung function to be well preserved. Regional lung ventilation in patients with AS is normal unless they have preexisting apical fibrosis.

Cervical spondylosis affects levels C5 to C6 and C6 to C7 most often, and less frequently, C4 to C5, C7 to T1, and C3 to C4. The degenerative changes may result in nerve root entrapment by foraminal encroachment. The phrenic nerve, which innervates the diaphragm, is supplied primarily by the C4 nerve root, and to a lesser extent, by the C3 and C5 nerve roots. A case of hemidiaphragmatic paralysis secondary to C4 nerve root compression has been reported.

Cricoarytenoid involvement may exist and can lead to respiratory dysfunction and upper airway obstruction. Cricoarytenoid dysfunction can manifest as a hoarse, weak voice. Respiratory failure from cricoarytenoid ankylosis has necessitated therapeutic tracheostomy. In all reported cases, laryngeal symptoms were present before cricoarytenoid arthritis caused airway compromise. A case of acute respiratory failure and cor pulmonale resulting from cricoarytenoid arthritis also has been reported in a patient with AS.

Treatment

Medical therapy for adult patients with AS is supportive and preventive. Most patients with AS are asymptomatic. Depending on the severity of disease involvement, management may consist of the use of corticosteroids and nonsteroidal antiinflammatory agents. Patients should refrain from smoking tobacco.

Anesthetic Management

Patients with AS have specific anesthetic requirements.[342] Management of the upper airway is the priority because of the potential for obstruction. Cervical spine involvement may result in limitation of movement. The ankylosed neck is more susceptible to hyperextension injury, and cervical fracture may occur. Intubation awake with or without the use of a fiberoptic bronchoscope is indicated. In rare situations, tracheostomy must be performed with the patient under local anesthesia before anesthesia can be induced. A regional anesthetic technique may not be feasible because of skeletal involvement that precludes access or because of neurologic complications such as spinal cord compression, cauda equina syndrome, focal epilepsy, vertebrobasilar insufficiency, and peripheral nerve lesions. Patients with cardiovascular system involvement may require antibiotic coverage, treatment of heart failure, or insertion of a temporary pacemaker before surgery. Restriction of chest expansion and rarely pulmonary fibrosis necessitate performance of a thorough preoperative assessment and immediate postoperative mechanical ventilation. Careful attention to positioning is essential.

SUMMARY

To conduct an accurate patient assessment and manage relevant pathophysiology, knowledge of the anatomy and physiology of the respiratory system is imperative for the anesthetist. Anatomic idiosyncrasies (such as the shorter, straighter, right mainstem bronchus), physiologic derangements from anesthesia (such as the atelectasis and ventilation-perfusion mismatch that occur), perianesthetic complications (such as aspiration pneumonitis), preexisting illness (such as COPD), and iatrogenic illness (such as pulmonary toxicity from chemotherapeutic agents) are all concerns for the anesthetist in caring for the pulmonary system.

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27 CHAPTER Anesthesia for Thoracic Surgery

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Thoracic surgery is greatly facilitated by the contribution of anesthesia care, which can isolate the lungs and create a quiet surgical field. Although this procedure is an advanced technique of airway management, it has been in existence almost as long as tracheal intubation itself. In 1928, Guedel, Magill, Waters, and other pioneers first achieved closed endotracheal anesthesia. The treatment of tuberculosis and empyema, however, required isolation of the infected lung, and in 1931 Joseph Gale and Ralph Waters first described "closed endobronchial anesthesia." Bronchial blockade for selective ventilation and lung isolation was reported by Magill in 1936. In 1950, Björk and Carlens are credited with the first use of a double lumen endotracheal tube for thoracic surgery, the bronchospirometric double-lumen tube, which Carlens described the year before.[1,2] Double-lumen tubes evolved in design, and the use of the Fogarty embolectomy catheter for bronchial blockade gave way in 1982 to the Univent tube invented by Inoue and colleagues.

Development of airway devices continues, and anesthetists caring for patients undergoing thoracic surgery must be skilled at insertion, maintenance, and monitoring of these devices for proper function. However, the process of lung isolation facilitates the surgical procedure but compounds a central concern in thoracic anesthesia: maintaining effective gas exchange in the face of ventilation and perfusion mismatch. General anesthesia creates atelectasis, which is compounded by muscle relaxants and lateral positioning, but ventilation and perfusion are further mismatched when the thorax is opened, and ceasing ventilation of one lung is the final insult. The cardiac output persists, but only one lung is ventilated. Fortunately, physiologic processes combat the inherent shunt, and anesthetic management is geared toward supporting those processes while fostering oxygenation through various ventilation modalities. The general incidence of hypoxemia is 5% to 10% during one lung ventilation (OLV).[3]

Besides managing a complex tracheal tube, the anesthetist must also be cognizant of the effects of underlying disease as it relates to management of ventilation (bullous disease contraindicating nitrous oxide [N_2O]), interactions with anesthetic drugs (small cell carcinoma being associated with myasthenic syndrome), and even concerns about oxygen toxicity (in patients treated with bleomycin and other chemotherapeutics).

PREOPERATIVE PREPARATION

Bronchogenic carcinoma is the leading cause of cancer deaths in the United States.[4] Because lung cancer is most often discovered only once symptomatic (i.e., advanced), even with aggressive multimodal treatment, prognosis is poor. A review of patients with non–small cell carcinoma found a 5-year survival rate of less than 7%.[5] However, resection of affected lung tissue offers a better prognosis than radiation and chemotherapy, and so cancer is a common indication for lung surgery. There is a strong association between lung cancer and chronic obstructive pulmonary disease (COPD), such that the incidence of lung cancer is four times higher among COPD sufferers than it is in the general population, and underlying COPD almost doubles the 3-year mortality of lung cancer.[6-8] Because many patients presenting for lung surgery will have complex underlying pathology, evaluating respiratory function and predicting postresection function are crucial to anticipating the patient's intraoperative and postoperative care.

The surgical risk assessment for patients in need of pulmonary resection surgery focuses on the risk of potential postoperative complications and whether postoperative pulmonary function will be sufficient to allow reasonable quality of life. Between 20% and 30% of patients with lung cancer are found to be surgical candidates,[9] and almost 40% of them are disqualified based on poor lung function alone.[10] The anesthetic risk assessment specific to pulmonary surgery focuses on how the underlying pathology will challenge the maintenance of adequate gas exchange and general homeostasis under OLV and the potential for postoperative respiratory failure to make weaning and extubation difficult. However, mortality from unresected carcinomas is sufficiently high that the risks of postoperative complications would need to be extraordinarily high before they would preclude surgery. COPD is a disease requiring years of development. Considering the aging nature of our population and the increase in the incidence of obesity, it is not surprising that lung resection surgeries are now being performed on more patients who have end-stage COPD, morbid obesity, or who are of advanced age.[11,12] Evidence shows that these patients can be treated safely. The American College of Chest Physicians does not set a maximal age cutoff for pulmonary surgical candidacy.[13] Changes in surgical techniques, especially the use of video-assisted thoracoscopic surgery, have markedly decreased the incidence of postoperative pulmonary complications and will necessitate a reevaluation of the testing required for preoperative assessment.[14] For smaller lung resections, minimal preoperative evaluations of cardiac disease, gas exchange, and oxygenation may suffice. Given the large physiologic changes that occur after pneumonectomy, complete pulmonary function testing, as well as cardiac testing, may still be reasonable in these patients.

Fear of creating pulmonary insufficiency by lung resection is an important concern, and numerous studies have attempted to determine the lowest limit of pulmonary function that will allow surgery to be safely performed. Research findings are limited in their ability to predict particular complications, though. Studies performed to predict postoperative pulmonary complications after lung resection demonstrate that patients develop both pulmonary and cardiac complications such as dysrhythmias, myocardial infarction, pulmonary embolism, pneumonia, and empyema. These complications influence the duration of mechanical ventilation and outcome; however, none of these complications can be predicted by preoperative studies of pulmonary function. Box 27-1 presents some commonly used preoperative assessment criteria for lung resection.

BOX 27-1

Summary of Preoperative Factors That Predict Postoperative Complications

Factors That Characterize Average Risk

- FEV_1 > 2 L or 80% of predicted
- PPO FEV_1 > 80% of predicted
- PPO FEV_1 + PPO DLCO both > 40%
- $\dot{V}O_2max$ > 15 mL/kg/min
- Ability to climb 3 flights of stairs

Factors That Characterize Elevated Risk

- FEV_1 <2 L or < 40% of predicted
- PPO FEV_1 < 40% of predicted
- PPO DLCO < 40% of predicted
- PPO product, (FEV_1 × DLCO) < 1650
- $\dot{V}O_2max$ < 10 mL/kg/min
- Inability to climb 1 flight of stairs
- Oxygen desaturation > 4% during exercise

DLCO, Carbon monoxide diffusion in the lung; *FEV_1*, forced expiratory volume in 1 second; *PPO*, predicted postoperative; *$\dot{V}O_2max$*, maximum volume of oxygen utilization.

TABLE 27-1 Anesthetic Considerations in Lung Cancer Patients: "The 4 Ms"

Preoperative Parameter	Clinical Assessment
Mass effects	Obstructive pneumonia, lung abscess, superior vena cava syndrome, tracheobronchial distortion, Pancoast syndrome, recurrent laryngeal nerve or phrenic nerve paresis, chest wall or mediastinal extension
Metabolic effects	Lambert-Eaton syndrome, hypercalcemia, hyponatremia, Cushing syndrome, syndrome of inappropriate antidiuretic hormone
Metastases	Particularly to brain, bone, liver, and adrenal glands
Medications	Chemotherapy-induced lung changes bleomycin = pulmonary toxicity, doxorubicin = cardiac toxicity, cisplatin = renal toxicity

Modified from Slinger PP, Johnston MR. Preoperative assessment and management. In: Kaplan JA, Slinger PD, eds. *Thoracic Anesthesia*. 3rd ed. Philadelphia: Churchill Livingstone; 2003.

History and Physical Examination

Cancer patients who undergo lung resection typically have a history of multiple risk factors and signs of respiratory disease. Risk factors include cigarette smoking, air pollution, and industrial chemical exposure. The smoking history that is so common to these patients should also lead to suspicion of ischemic heart disease or hypertension. Therefore, patients must be evaluated for exertional dyspnea, productive cough, hemoptysis, cyanosis, poor exercise tolerance, and chest pain.

The presence of ischemic cardiac disease that is severe, unstable, or associated with dysrhythmias should indicate consultation with a cardiologist to help mitigate risk of cardiac complications. Because severe COPD may significantly limit physical activity, a provocative dobutamine or other type of cardiac stress test may be helpful to identify coronary insufficiency.[15] The use of perioperative beta blockade is controversial, and nonselective agents may be particularly detrimental if they inhibit bronchodilation. However, cardioselective beta-blockers have been found beneficial in COPD patients undergoing vascular surgery.[16] Beta blockade may be considered to reduce cardiac risk,[17] or at the least, patients currently taking beta-blockers should continue their regimen throughout the surgical encounter. The surgical plan must be carefully considered for patients with coronary diffusion defects that show greater than 20% reversibility. In cases of high-risk cardiac disease, lung surgery may be delayed for 6 weeks to allow coronary artery bypass first.[15] With the popularity of off-bypass coronary revascularization, the two procedures can more easily be performed in a single surgical encounter.[18]

Lung cancer patients should be assessed for effects of the primary tumor, as well as effects of secondary pathologies and side-effects of therapy (Table 27-1). Supine dyspnea may result from COPD or compression of the airway by a mediastinal mass. A high index of suspicion should also be maintained for hormonal abnormalities, because many lung tumors cause paraneoplastic syndromes characterized by secretion of endocrine-like substances such as adrenocorticotropic hormone,[19] antidiuretic hormone,[20] serotonin, parathyroid-like hormone,[21] and insulin-like growth factor,[22] causing a variety of metabolic abnormalities.[23] Cushing disease may lead to metabolic alkalosis, hypokalemia, and hyperglycemia.[24,25] Hypercalcemia occurs in 10% to 25% of lung cancer patients and is related to parathyroid-like hormone, increased calcitriol, or overactivity of osteoclasts.[26] The finding of hypercalcemia carries a very poor prognosis. Clinical signs may include polyuria, polydipsia, confusion, vomiting, abdominal cramps, bradycardia, and mental status changes.

Neuroendocrine tumors comprise 20% of lung cancers, and 5% of them produce carcinoid syndrome.[26] In those patients, histamine-stimulating drugs and adrenergics may precipitate the flushing, hypotension, and tachyarrhythmias related to serotonin release. Paraneoplastic neurologic syndromes represent autoimmune dysfunctions associated with cancers; 1% to 2% of patients with small cell cancer develop Lambert-Eaton myasthenic syndrome (LEMS).[27] In this syndrome, antibodies are formed against the voltage-gated calcium channels,[28] causing weakness and sensitivity to nondepolarizing muscle relaxants. The usual presentation is first with autonomic dysfunction (80% of patients with LEMS) such as orthostatic hypotension, and then weakness that progresses upward from the legs.[29] In contrast to myasthenia gravis, because LEMS involves dysfunction of the calcium channels, repetitive stimulation or activity improves function (as more acetylcholine is mobilized), and anticholinesterase drugs are not an effective treatment. Treatment is with immunoglobulin, corticosteroids, or with 4-diaminophridine (DAP), which opens potassium channels and increases calcium in the nerve terminal. Other autoimmune channelopathies can affect voltage-gated potassium channels and prolong acetylcholine release, causing a myotonia, or they can affect autonomic ganglia, causing orthostatic hypotension and arrhythmias.[30]

Physical examination findings in COPD are commonly barrel chest deformity, accessory muscle use or paradoxical breathing movement, pursed-lip breathing, and tympanic percussion notes on the chest. Auscultation reveals rhonchi or wheezing. Signs of cor pulmonale include jugular vein distention or peripheral edema, split S_2 heart sound, pulmonary or tricuspid valve insufficiency murmurs, and rales auscultated over the lungs.[31] Nutritional status, commonly compromised in patients with cancer, is also important to note because hypoalbuminemia and malnutrition are associated with increased postoperative complications such as pneumonia.[32] Box 27-2 lists important elements of the preoperative evaluation.

BOX **27-2**

Preoperative Evaluation of Patients for Pulmonary Surgery

1. Evaluate comorbidities:
   - Smoking-related complications
   - Cor pulmonale
   - Effects of paraneoplasms
   - Cardiovascular disease (unstable angina, MI within 6 weeks, or significant dysrhythmias = high risk of cardiac complications)
   - Treatment side effects (particularly from cytotoxic drugs and radiation)
2. ECG and chest x-ray for signs of cardiovascular dysfunction and effects of lung pathology
3. Laboratory assessment of electrolytes, blood count, albumin, and renal function indicators
4. Lung function testing: 80-40-15 rule:
   - FEV_1 and DLCO > 80% predicted = no additional testing needed; if < 80 or dyspnea present, diffusing capacity and postoperative function should be predicted
   - PPO FEV_1 and DLCO < 40% predicted = increased risk; exercise testing should be evaluated
   - $\dot{V}O_2max$ < 15 mL/kg/min = increased risk
5. For COPD, consider blood gas and response to bronchodilators.

COPD, Chronic obstructive pulmonary disease; *DLCO,* carbon monoxide diffusion in the lung; *ECG,* electrocardiogram; *FEV_1,* forced expiratory volume in 1 second; *MI,* myocardial infarction; *PPO,* predicted postoperative; *$\dot{V}O_2max$,* maximum volume of oxygen utilization.

Diagnostic Data

Chest Radiograph

The chest radiograph should be obtained to assess for associated disease and complications of COPD (tumor infringement on airway or vascular structures, bullous disease, congestive heart failure, or pneumothorax). The radiograph does not provide abundant information regarding the degree of COPD, but findings characteristic of COPD include hyperinflation, increased anteroposterior diameter, and diaphragm flattening. Bullae of emphysema may be present, and infection or pleural effusions may be noted preoperatively and treated to improve the postoperative course. The locations of masses can be identified. In some patients, it can be ascertained whether lesions compress mediastinal structures, cause tracheal shift, or invade the airway. This information is important to predict whether intubation will be difficult, whether induction of anesthesia could cause collapse of the airway, or whether surgical dissection may be difficult and potentially involve excessive bleeding. Evidence of increased pulmonary vascular resistance (PVR) resulting from compression of the vascular bed increases the likelihood of right ventricular failure and worsens the prognosis after lung resection. Relevant signs include prominent pulmonary arteries with rapid tapering of the vasculature, and a widened right heart border.

Electrocardiogram

Assessment of the electrocardiogram (ECG) is useful to assess signs of right ventricular hypertrophy. In such a case, the ECG shows a tall R wave in V_1 (greater than 6 mm), R/S ratio greater than 1 in lead V_1 and a ratio less than 1 in V_6, along with a right-axis deviation and diminished amplitude limb leads.[33-35] Right atrial hypertrophy causes the initial component of a biphasic P wave in lead V_1 to be larger than the second component. Strain characteristics such as S-T segment depression and T-wave inversion, as well as incomplete or complete right bundle branch block, may be observed. The ECG has excellent specificity for identifying left ventricular hypertrophy (LVH), but less sensitivity for detecting it.[36,37] Therefore, if ECG criteria are inconclusive, echocardiography may be helpful to further elucidate the status of the right ventricle. Findings of pathologic Q waves and evidence of left ventricular hypertrophy preoperatively correlates with an increased incidence of postoperative ischemia and infarction.[38]

Echocardiogram

Expected echocardiographic findings are increased thickness of the right ventricular free wall, chamber enlargement, pulmonary artery systolic hypertension, septal shift, tricuspic regurgitation, and decreased right ventricular ejection fraction. Increased PVR and right ventricular strain cause concern in patients undergoing pneumonectomy or extensive partial resection because of the added resistance produced by clamping the vasculature of one lung in the surgical procedure. Echocardiography is the best initial tool for assessing pulmonary hypertension, but additional studies with pulmonary angiography, ventilation-perfusion scintigraphy, computed tomography, and magnetic resonance imaging also may be used for more in-depth evaluation.[39]

Laboratory Assessment

Measurement of preoperative room air arterial blood gases should be considered for patients with COPD, and is useful in guiding the weaning of O_2 and ventilation postoperatively. Carbon dioxide (CO_2) retention with an arterial partial pressure ($PaCO_2$) greater than 45 mmHg is an indicator of poor ventilatory function. However, hypercapnia is not a reliable predictor of increased risk of perioperative pulmonary complications.[40] Preoperative hypoxemia (SpO_2 less than 90%) and particularly desaturation during exercise may be predictive of increased complications after thoracic surgery;[41,42] however, in general, blood gas analysis is not a reliable tool in predicting postoperative pulmonary complications,[43] and the correlation between desaturation during exercise and postoperative complications is not a consistent finding.[44]

Hypoalbuminemia is the most common laboratory finding, which serves as an important predictor of pulmonary complications. Numerous studies have demonstrated increases in postoperative pulmonary complications among patients with low serum albumin levels (generally less than 3.6 g/dL).[45-48] This factor increases risk as much as 2.5 times,[47] and albumin level maintenance is a measured factor in the American College of Surgeons' National Surgical Quality Improvement Program (NSQIP).[49] The blood urea nitrogen is also a factor identified by NSQIP data as a predictive factor for pulmonary complications when the level is greater than 22 mg/dL.[47,48]

Other laboratory analysis of interest includes renal function indicators (particularly for patients treated with nephrotoxic drugs, such as methotrexate, gemcitabine, cisplatin),[50,51] sodium (related to syndrome of inappropriate antidiuretic hormone),[23] and calcium (due to parathyroid hormone-like protein).[21,52]

Pulmonary Function Tests

Patients presenting for lung resection should undergo pulmonary function testing to assess for airflow limitation, diffusion defect, and cardiopulmonary reserve.[53] Assessment should include the response to bronchodilators for patients who demonstrate obstructive disease (see Figure 26-19). In that case, assessment of spirometry should be based upon values obtained postbronchodilator

therapy, because these would represent the patient's potential lung function once optimized on medications. No single measurement provides the overall risk assessment. For example, although the forced expired volume in 1 second (FEV_1) is the most prevalent spirometric measurement, one case series of 100 thoracic surgery patients with very low FEV_1 values (less than 35%) demonstrated a low rate of mortality and ventilator dependence (but patients did show a prolonged duration of hospitalization and air leak).[54] In another series of 109 elderly patients, stair-climbing ability was better correlated (inverse relationship) to postoperative cardiopulmonary complications than was forced vital capacity (FVC) or predicted postoperative (PPO) FEV_1.[55] Therefore, a multimodal approach must be taken, considering airflow (PPO FEV_1), parenchymal function (carbon dioxide diffusion in the lung [DLCO]), and cardiopulmonary reserve ($\dot{V}O_2$max).The general cutoff points indicating increased risk among these parameters is below 40% for predicted postoperative FEV_1 and DLCO, and 15 mL/kg/min for $\dot{V}O_2$max.

It should be noted that guidelines to assess surgical candidacy are not intended to dictate candidacy for anesthesia. If indications are that the patient is a candidate for surgery, it is less likely that there will be anesthetic-specific concerns about pulmonary function that would override the surgical decision, particularly since many of these surgeries are performed to treat cancer. That notwithstanding, it is helpful for the anesthetist to understand the patient's risk stratification to plan for the level of ventilatory support required during and after surgery. Assessment must consider multiple variables of function. Similar to standards set by the American Thoracic Society and the European Respiratory Society, the American College of Chest Physicians (ACCP) proposes the following assessment of risk factors for patients with lung cancer undergoing lung surgery.[40] Preoperative FEV_1 greater than 80% of predicted value (or greater than 2 L for pneumonectomy or greater than 1.5 L for lobectomy) indicates average risk, and no further assessment of lung function is required. The diffusing capacity for carbon monoxide (DLCO) should be assessed if diffuse parenchymal disease or dyspnea on exertion is noted. If the FEV_1 or DLCO is less than 80% of predicted, then the predicted postoperative FEV_1 and DLCO are assessed.[40] This is accomplished either through radionucleotide scanning or mathematically, based on the proportion of total lung that will remain after the planned resection. The PPO FEV_1 can be calculated by multiplying the current FEV_1 by the fraction of functioning lung or the fraction of lung segments that will remain after surgery.[15] For high-risk patients, more detailed assessment via radionuclide scanning, computed tomography (CT) scanning, or magnetic resonance imaging (MRI) is advisable. Predicted postoperative values of PPO FEV_1 greater than 40% of predicted for the patient indicate average risk. Values less than 30% of predicted indicate increased risk, and values in between warrant exercise testing to assess oxygen consumption ($\dot{V}O_2$max). A $\dot{V}O_2$max less than 15 mL/kg/min indicates high risk, whereas a value greater than 15 indicates average risk.[40] The European Respiratory Society places cardiopulmonary reserve ($\dot{V}O_2$max) more prominently in the assessment and considers high-risk cutoffs as being less than 30% for PPO FEV_1 and DLCO, and less than 10 mL/kg/min for $\dot{V}O_2$max.[53] As related to anesthetic planning, average-risk patients (e.g., PPO FEV_1 greater than 40%) are likely to be extubated immediately after surgery. High-risk patients (e.g., PPO FEV_1 less than 30%) have a higher likelihood of requiring some degree of postoperative ventilation. Planning for intermediate-risk patients (e.g., PPO FEV_1, 30%-40%) is further individualized, based upon other assessment parameters.

Ventilation-Perfusion Assessment

When the preoperative lung function tests indicate that the patient is at increased risk for perioperative complications, split lung function tests of ventilation and perfusion are valuable in the prediction of postresection lung function.[53,56] Removal of a diseased portion of lung may not decrease overall lung function; in fact, it may improve it. The extent of pulmonary surgery has been found to correlate inversely with the intraoperative Pa_{O_2}, where patients undergoing pneumonectomy had higher Pa_{O_2} than those undergoing lobectomy, which in turn were higher than those undergoing segmentectomy.[3] This paradox is related to the corresponding amount of perfusion of the diseased lung. With larger, central tumors (such as would require a pneumonectomy), perfusion, and thus shunting under OLV, is diminished in comparison to a more peripheral lesion requiring a limited resection. Likewise, the results of perfusion scanning can provide a prediction of the degree of hypoxemia under OLV, because the degree of perfusion to the operative lung is proportional to the degree of potential shunt produced when ventilation to that lung ceases.[3]

Ventilation can be measured by having the patient inhale one vital capacity breath of a radioisotope and measuring isotope counts with multiple scanners placed over the chest wall. Radioisotope injected intravenously and imaged shows the distribution of perfusion to all areas of the lung. After determining function in various areas of the lung, calculations can then estimate postresection function by multiplying current function by the fraction of functioning lung that will remain postoperatively. Calculations based on segmental lung regions may help predict outcomes for patients undergoing lung volume reduction surgery. This procedure of removing emphysematous portions of lung to improve overall lung function has proved efficacious and particularly beneficial in allowing resection of cancerous lung tissue from patients in whom overall lung function studies would have contraindicated surgery.[40] Lung volume reduction surgery is most useful in patients with heterogeneous emphysema (particularly when the emphysematous lobe is also the one containing the tumor), where removal of a lung segment or lobe will result in better pulmonary function overall. Incidentally, this effect is appreciated more often with upper rather than lower lobectomy, in which patients with a low preoperative FEV_1 tend to demonstrate improvement in the FEV_1 after upper lobectomy.[57]

Dynamic MRI and quantitative CT are newer modalities used to determine postresection pulmonary function.[58,59] Dynamic MRI traces movement of oxygen or sulfur hexafluoride to reflect diffusing capacity.[60] Quantitative CT is intended to provide more specific data than global measurements such as FEV_1. CT can be used to quantify low attenuation (emphysematous) areas of lung to determine both overall proportion and regional distribution of disease. Results are comparable to FEV_1 in predicting obstruction.[61]

Diffusion Capacity

Diffusion capacity of the lung tests the lung's ability to allow transport of gas across the alveolar-capillary membrane. Because it is difficult to measure the diffusing capacity of oxygen, carbon monoxide is used, in which the patient inhales a small amount of carbon monoxide, holds the breath for 10 seconds, exhales, and the amount of carbon monoxide in the exhaled breath is measured. After subtracting the amount of carbon monoxide that should be expired with dead space air, the amount exhaled provides an indicator of the diffusion of gases in the lung. A carbon monoxide diffusing capacity of the lungs (DLCO) less than 40% of predicted has been associated with increased complications after pulmonary surgery. However, DLCO has been found to have good specificity

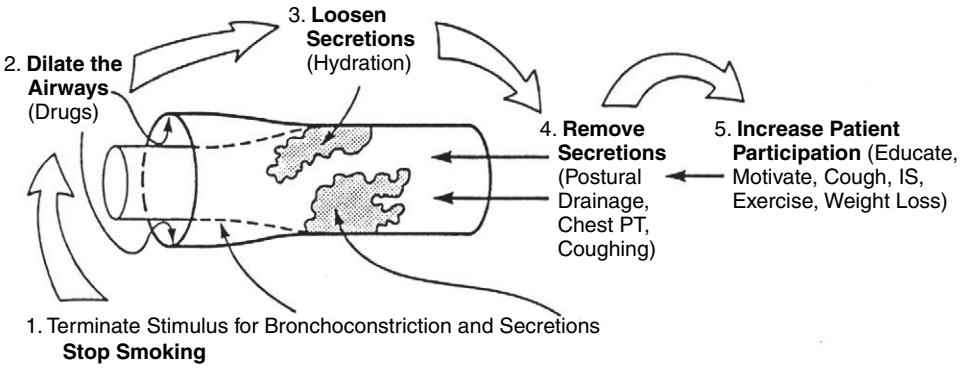


FIGURE **27-1** A full, aggressive preoperative respiratory preparation regimen entails a five-pronged attack. *(1)* Require the patient to stop smoking. *(2)* Dilate the airways. *(3)* Loosen secretions. *(4)* Remove secretions. *(5)* Increase patient participation. *IS*, Incentive spirometry; *PT*, chest physiotherapy. (From Wilson WC, Benumof JL. Anesthesia for thoracic surgery. In: Miller RD, et al, eds. *Miller's Anesthesia*. 6th ed. Philadelphia: Churchill Livingstone; 2005.)

but low sensitivity as an independent measurement. The product of the predicted values for DLCO and FEV_1 may provide better reliability than single measures. This measurement, called the *predicted postoperative product*, was found by Pierce to be less than 1650 in 75% of those who died.[62]

Cardiopulmonary Reserve

Maximal oxygen consumption ($\dot{V}O_2$max) during exercise testing is also assessed as a strong predictor of outcomes.[31,40,63] A $\dot{V}O_2$max less than 10 mL/kg/min (or 40% of predicted) is associated with increased mortality, whereas a $\dot{V}O_2$max greater than 20 mL/kg/min is a favorable finding.[64] These values may be roughly estimated by evaluating the patient's physical ability, in which the ability to climb five flights of stairs suggests $\dot{V}O_2$max greater than 20 mL/kg/min, and the inability to climb one flight of stairs suggests $\dot{V}O_2$max less than 10 mL/kg/min.[65]

Patient Optimization

Aggressive treatment of acute or reversible components of respiratory disease greatly decreases the risk of postoperative complications. Treatable preoperative conditions include infections, excess bronchial secretions, bronchospasm, dehydration, electrolyte imbalance, cigarette smoking, alcohol abuse, and malnutrition (Figure 27-1).

Smoking is not only a major risk factor for chronic lung disease, but it is a strong predictor of perioperative complications, as well. Among patients undergoing noncardiac surgery, pulmonary complications occurred in 22% of smokers, 13% of past smokers, and only 5% of nonsmokers.[66] In a study of lung cancer patients, 87% were smokers, and the smokers had 1.5% mortality, whereas nonsmokers had only 0.4% mortality. Smokers in that study demonstrated twice the rate of complications as did nonsmokers.[67] The correlation of complications with the duration of smoking history can be performed through the pack-year index (the product of the packs per day smoked times the years of smoking at that rate). Patients with greater than a 20 pack-year history have demonstrated increased incidence of complications compared with those who have a more modest smoking history.[68,69]

Smoking cessation may reduce postoperative complications; however, the timing of this intervention is important. Most recent research indicates that smoking cessation for less than 4 weeks prior to surgery does not alter risk of complications at all.[66,70,71] Some data suggests that short-term smoking cessation (less than 1 month) may cause increases in mucus production, which may *increase* complications;[66,72] however, research findings are equivocal on the concept of increasing complications.[71,72] Carboxyhemoglobin levels have shown a significant decrease that occurs rapidly after smoking cessation, and improvement of nasal mucociliary clearance occurs within 1 to 2 weeks; however, the implications of these findings on postoperative complications are unclear.[73,74] Reduction in complication rates occur in proportion to the amount of time after quitting, with a threshold of at least 4 weeks to observe improvement, with even more improvement noted after 8 weeks.[70,71] Only in one very large study was a trend toward *slight* reduction in complications noticed with less than 1 month of smoking cessation, and complications further decreased in proportion to the total duration of cessation.[67] Smoking cessation counseling and intervention is a widely recommended strategy for medical management of COPD patients; however, owing to the urgent nature of treating pulmonary carcinoma, delaying surgery to allow for an adequate period of smoking cessation is an impractical goal.

Monitoring Plan

The purpose of monitoring during thoracic surgery is the quick recognition of sudden and severe changes in ventilation and hemodynamics that can accompany positioning, one-lung ventilation (OLV), and surgical manipulation of the airway and thoracic structures. Standard monitors, according to American Association of Nurse Anesthetists (AANA) guidelines, should be used.[75] An airway pressure monitor helps detect changes in airway compliance and assists in identifying the proper placement of double-lumen tubes (DLTs). Capnography is useful for determining the adequacy of ventilation when one lung is deflated, and also useful for detecting abrupt changes in cardiac output, which may accompany positioning or surgical manipulation. Considering preexisting ventilation derangements and changes with lateral position, the gradient of end-tidal to arterial CO_2 may be wider than the typical 5 mmHg. There is evidence that even if the gradient is determined early, it may not remain the same throughout the case. One-lung ventilation is a good application for transcutaneous CO_2 monitoring where that modality is available.

Electrocardiogram

All patients require continuous monitoring of the ECG. Typically, anesthetists monitor a limb lead (II) for easy rhythm recognition, and a precordial lead to add sensitivity for detection of ischemia. A landmark article by London identified V_5 as the precordial lead

that would add the most sensitivity to ischemia detection.[76] That article noted that monitoring a combination of leads II and V_5 would help detect more than 85% of ischemia. A more recent study, which accounted for both the changing pattern of ischemia over time (onset vs. peak), as well as comparison to preoperative values, found lead V_4 to be the most sensitive for detecting ischemia, followed by V_5.[38] In practice, concerns for positioning, surgical site preparation, and access to the skin electrode may result in the precordial lead not being placed in the precise location needed. Various studies have found ischemic evidence to be frequent in leads V_3 through V_6.[38,77,78] A consistent finding is that monitoring a combination of leads is significantly more effective than monitoring a single lead.[38,76,79] A second intraoperative lead monitored in the V_4 to V_5 position or in whatever anterolateral position provides the most isoelectric S-T segment is desirable.[38]

Arterial Pressure Monitoring

Arterial blood pressure monitoring instantly identifies acute hypotension with surgical manipulation. It also facilitates sampling of arterial blood for gas analysis. For thoracotomies, the arterial cannula is generally placed in the dependent arm, where it is more easily stabilized. For mediastinoscopy, the arterial monitoring site is selected to provide indication of innominate artery occlusion (see Mediastinoscopy later in chapter).

Central Venous Pressure Monitoring

Central venous pressure (CVP) monitoring is not required for routine thoracotomies but may be indicated if the patient's volume status is unclear or if large fluid shifts are anticipated. In complex cases, a CVP line may help manage fluid status. Increased filling pressures (CVP or pulmonary capillary wedge) have been associated with greater lung injury and prolonged mechanical ventilation after complex pulmonary surgery.[80] In addition, a large-bored CVP line can provide access for rapid infusion and an access site if transvenous pacing or pulmonary artery pressure monitoring become necessary.

The CVP line can be inserted via the external or internal jugular veins or the subclavian veins. An external jugular line is more easily kinked in the lateral position. One should remain alert to the possibility of pneumothorax with the insertion of central lines. A pneumothorax on the ventilated (nonoperative) side can lead to severe hypoxemia during OLV. If a subclavian puncture is planned, the insertion site should be on the same side as the planned thoracotomy.

Cardiac Performance Monitoring

Pulmonary artery pressure monitoring is intended to provide estimation of left ventricular pressures and guide the support of cardiac performance with fluids and cardiovascular drugs. In spite of its past popularity, pulmonary artery catheterization has not been demonstrated to improve patient outcomes in either cardiac or noncardiac surgery,[81] nor is it helpful in predicting postoperative complications.[53,82] There have even been suggestions that right heart catheterization may *promote* cardiac complications.[83] If pulmonary artery monitoring is deemed useful, the anesthetist must be cautious in interpreting values in pulmonary disease because the normal correlation of right and left ventricular pressures may be disturbed. The use of pulmonary artery catheters has specific limitations during OLV. Lung pathology or hypoxic pulmonary vasoconstriction may alter the resistance in pulmonary vessels and reduce the correlation between pulmonary artery occlusion pressure and left ventricular pressure.[84] More than 90% of pulmonary artery catheters float into the right lung.[85] During right thoracotomy, then, the catheter will likely be in the nondependent, collapsed lung and give a false low reading for cardiac output. Finally, care must be taken to ensure that a pulmonary artery catheter is not situated in a vessel that will be clamped during the course of lung resection. A better evaluation of cardiac filling, contractility, and valvular performance would come by way of echocardiography. Preoperative echocardiography is indicated when suspicion exists of valvular disease, outflow tract obstruction, ventricular dysfunction, or pulmonary hypertension.[17,53]

LATERAL DECUBITUS POSITION

The position most commonly chosen for surgical exposure during thoracotomy is the lateral decubitus position. A roll is placed beneath the torso just caudal to the axilla to prevent compression of the neurovascular bundle and forward rotation of the humeral head. It is important to note that this commonly called "axillary roll" is better considered an "axillary *support* roll," because positioning it *in* the axilla may cause neurovascular compression. Hyperabduction of the arms is prevented to keep the brachial plexus from stretching against the humeral head. Arms can be separately padded and extended forward with armboards. Strategies for supporting the nondependent arm may include a pillow between the arms, a padded Mayo stand (which provides good access to intravenous or arterial lines in the dependent arm), or specially made double armboards. Pulse oximetry or frequent palpation of the radial pulse ensures the integrity of circulation to the hand.

The head is supported on pillows to maintain alignment of the head and neck with the spine. Lateral flexion of the neck can cause compression of the jugular veins or vertebral arteries, compromising cerebral circulation. The dependent ear can be compressed by the weight of the head. Careful padding or use of a foam doughnut relieves this pressure, but care must be taken to prevent corneal abrasion and retinal ischemia by avoiding pressure on the eyes.

Other pressure points of concern in the lateral position include the peroneal nerve in the area of the fibular head of the dependent leg and the femoral head of the nondependent leg if a stabilizing strap is placed over the patient.

Physiology of the Lateral Decubitus Position

Positional changes and changes in chest-wall integrity produce significant alterations in ventilation and perfusion of the lungs during thoracic surgery.

Upright Position

The distribution of perfusion in the lungs depends on gravity in relation to the level of the heart and on pressures transmitted through alveoli. In a spontaneously breathing, upright patient, perfusion increases from the apex to the base of the lung (Figure 27-2). Ventilation also increases from apex to base, based on the relative compliance of alveoli. Owing to downward traction from gravity, pleural pressure is most negative at the apex of the lung, and this keeps alveoli distended (Figure 27-3). Dependent alveoli are less distended and therefore more compliant (i.e., can expand by a greater volume for a given pressure change because they are starting at a lower resting volume). Therefore, most of a tidal breath is distributed to the dependent alveoli (Figure 27-4). The increase in both ventilation and perfusion from apex to base is not parallel, and is certainly more complexly arranged than in neatly divided zones. However, the general increase in both from top to bottom results in efficient gas exchange.

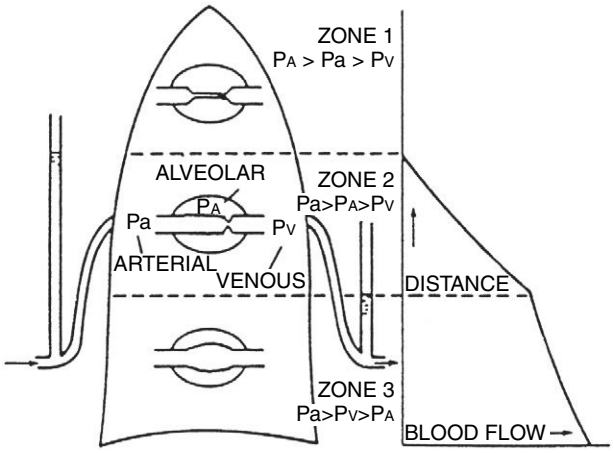


FIGURE **27-2** The lung is divided into three zones according to the relative magnitudes of the pulmonary arterial, venous, and alveolar pressures (*Pa*, *Pv*, and *PA*, respectively). In *zone 1*, alveolar exceeds arterial pressure, so the collapsible vessels are held closed and there is no flow. In *zone 2*, arterial exceeds alveolar pressure, but alveolar exceeds venous pressure. Under these conditions, a constriction occurs at the downstream end of each collapsible vessel, and the pressure inside the vessel at this point is equal to alveolar pressure, so the pressure gradient causing flow is arterial-alveolar. This gradient increases linearly with distance down the lung, and therefore so does blood flow. In *zone 3*, venous exceeds alveolar pressure, and the collapsible vessels are held open. Here, the pressure gradient causing flow is arteriovenous, and there is constant perfusion of alveoli. (From West JB. Explanation of the uneven distribution of blood flow in the lung, based on the pressures affecting capillaries. In: West JB. *Respiratory Physiology: The Essentials*. 8th ed. Philadelphia: Lippincott Williams & Wilkins; 2008.)

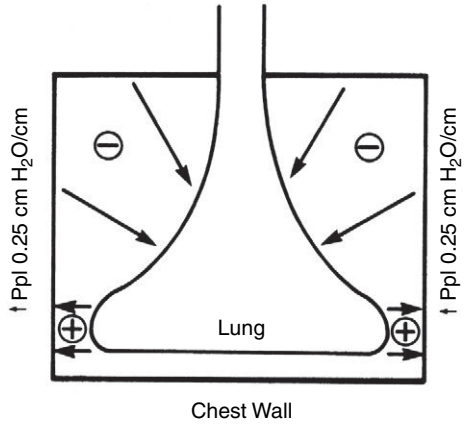


FIGURE **27-3** Schematic diagram of the lung within the chest wall, showing the tendency of the lung to assume a globular shape because of its viscoelastic nature. The tendency of the top of the lung to collapse inward creates a relatively negative pressure at the apex, and the tendency of the bottom of the lung to spread outward creates a relatively positive pressure at the base. Therefore pleural pressure *(Ppl)* increases by 0.25 cm H_2O per centimeter of lung dependency. (From Triantafillou AN, et al. Physiology of the lateral decubitus position, the open chest, and one-lung ventilation. In: Kaplan JA, Slinger PD, eds. *Thoracic Anesthesia*. 3rd ed. Philadelphia: Churchill Livingstone; 2003.)

Awake Lateral Position

Less vertical distance is present to cause differences in the intrapleural pressure and blood pressure gradients in the lateral position (Figure 27-5). Abdominal contents displace the diaphragm in a cephalad direction on the dependent side. Starting from a higher position in the thorax, the dependent hemidiaphragm can contract further. During inspiration, therefore, contraction of the diaphragm causes more of the tidal volume (V_T) to fill the dependent lung. Because perfusion is dependent upon gravity, perfusion in the lateral position is also greatest in the dependent lung (Figure 27-6). Overall, the relationship of greater ventilation and perfusion in the dependent lung is unchanged, and gas exchange remains efficient.

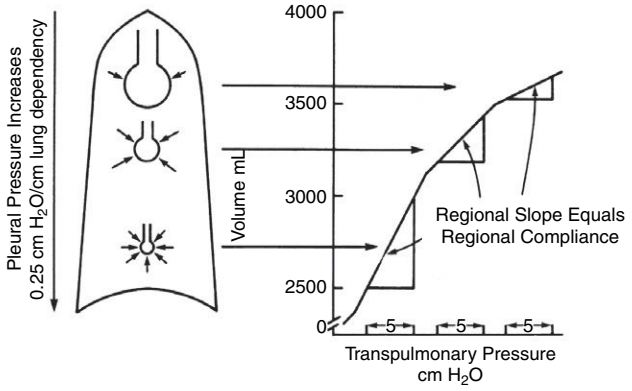


FIGURE **27-4** Due to gravity, alveoli in the most dependent portions of lung are compressed by the tissue above, while those in the most nondependent portions are suspended open. At end-inspiration and end-expiration, pressure inside all alveoli is equalized with atmospheric; however, an increasing gradient of pleural pressure toward dependent areas creates a gradient in transpulmonary pressure at rest. Although the *change* in transpulmonary pressure during inspiration is equal for all, alveoli in dependent regions are on the steep portion of the compliance curve and therefore receive the largest share of the tidal volume. (From Triantafillou AN, et al. Physiology of the lateral decubitus position, the open chest, and one-lung ventilation. In: Kaplan JA, Slinger PD, eds. *Thoracic Anesthesia*. 3rd ed. Philadelphia: Churchill Livingstone; 2003.)

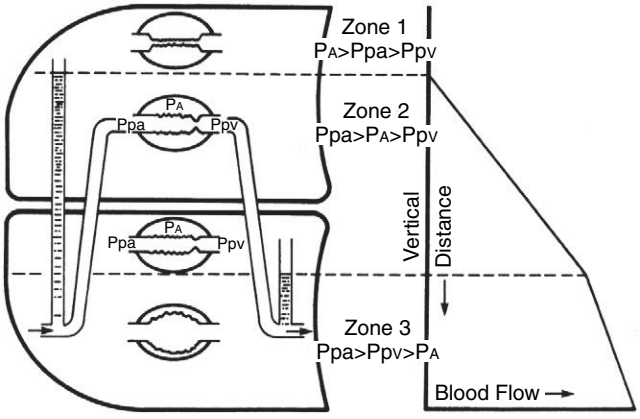


FIGURE **27-5** Schematic representation of the effects of gravity on the distribution of pulmonary ventilation and blood flow in the lateral decubitus position. The vertical gradient in the lateral decubitus position is less than in the upright position; consequently, blood flow in zones 2 and 3 is less. Nevertheless, pulmonary blood flow increases with lung dependency and is greater in the dependent lung than in the nondependent lung. *PA*, Alveolar pressure; *Ppa*, pulmonary arterial pressure; *Ppv*, pulmonary venous pressure. (From Triantafillou AN, et al. Physiology of the lateral decubitus position, the open chest, and one-lung ventilation. In: Kaplan JA, Slinger PD, eds. *Thoracic Anesthesia*. 3rd ed. Philadelphia: Churchill Livingstone; 2003.)

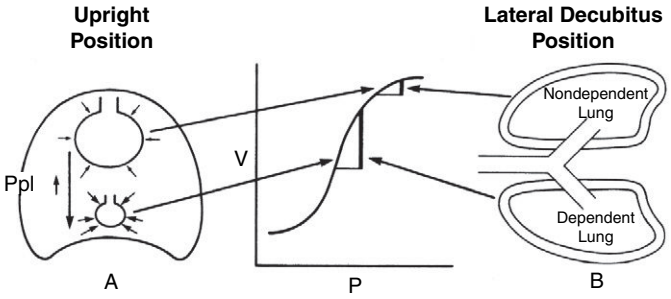


FIGURE **27-6** **A,** An increasing gradient of intrapleural pressure from top to bottom of lungs creates different resting volumes of alveoli and creates variation in regional compliance as described in Figure 27-4. **B,** In the lateral decubitus position, gravity-related effects translate to greater compliance of the dependent lung and less of the nondependent lung. Therefore, in the spontaneously breathing person, more ventilation is delivered to the dependent lung. *Ppl*, Intrapleural pressure; *P,* Transpulmonary pressure; *V*, alveolar volume. (From Triantafillou AN, et al. Physiology of the lateral decubitus position, the open chest, and one-lung ventilation. In: Kaplan JA, Slinger PD, eds. *Thoracic Anesthesia*. 3rd ed. Philadelphia: Churchill Livingstone; 2003.)

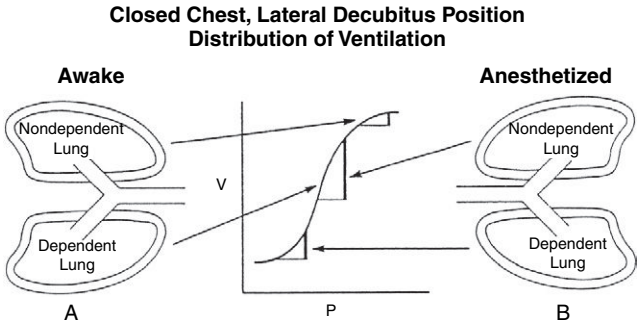


FIGURE **27-7** Diagram showing **A,** regional compliance of lungs in the awake patient in lateral decubitus position and **B,** regional compliance of lungs in the anesthetized patient in lateral decubitus position. Induction of anesthesia causes a loss of lung volume in both lungs, with the nondependent lung moving from a flat, noncompliant portion of the pressure-volume curve to a steep, compliant portion. The dependent lung moves from the highly compliant portion toward the lower flattening of the curve. In some areas of the dependent lung, resting alveolar volume is so low that atelectasis and airway closure impede inflation. Therefore, in the anesthetized patient in lateral decubitus position, more tidal ventilation shifts toward the nondependent lung (where there is the least perfusion), creating ventilation-perfusion mismatch. *P*, Transpulmonary pressure; *V*, alveolar volume. (From Triantafillou AN, et al. Physiology of the lateral decubitus position, the open chest, and one-lung ventilation. In: Kaplan JA, Slinger PD, eds. *Thoracic Anesthesia*. 3rd ed. Philadelphia: Churchill Livingstone; 2003.)

Anesthetized Lateral Position, Chest Closed, with Spontaneous Ventilation

A change in the distribution of ventilation is seen with the induction of anesthesia, even when spontaneous respiration is maintained. Functional residual capacity (FRC) decreases almost immediately with the induction of anesthesia. The weight of the mediastinum and the cephalad displacement of the diaphragm by abdominal contents further decrease FRC in the dependent lung and reduce the proportion of the favorable zone 3 area. Lower volumes in each lung shift their place on the compliance curve. The lungs are less compliant when they are either at a very high volume (distended alveoli) or a very low volume (atelectasis). In the anesthetized patient, the nondependent lung moves from a flat, noncompliant portion of the compliance curve to a more compliant position. Although anesthesia results in a net loss of FRC, the relative proportion of FRC in the nondependent lung increases in contrast to the dependent lung.[86] As the dependent lung loses FRC, its volume becomes so low as to decrease its compliance. It shifts to a less compliant, flatter portion of the curve (Figure 27-7). Ventilation is therefore preferentially distributed to the nondependent lung, whereas gravity-dependent blood flow preferentially goes to the dependent lung, resulting in a mismatch of ventilation and perfusion.

Anesthetized, Paralyzed, Mechanically Ventilated

Under mechanical ventilation, the diaphragm no longer contributes to ventilation of the lower lung, and FRC further declines because the compression from abdominal viscera is no longer counteracted by the force of the contracting diaphragm (Figure 27-8). With the initiation of mechanical ventilation and the deletion of effect of the contracting diaphragm, ventilation further shifts to follow the path of least resistance, favoring the nondependent lung. The ventilation-perfusion relationship further deteriorates. The addition of positive end-expiratory pressure (PEEP) to mechanical ventilation may help restore FRC and improve the ventilation-perfusion ratio.

Anesthetized, Open-Chest

The open chest greatly reduces resistance to gas flow in the nondependent lung by detaching the lung from its pleural connection with the chest wall. This causes further loss of ventilation to the dependent lung, in preference for the nondependent lung. The

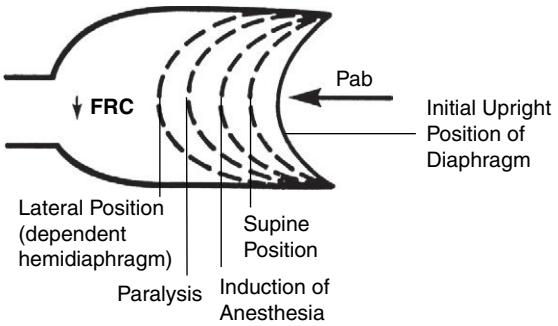


FIGURE **27-8** Anesthesia and surgery may cause a progressive cephalad displacement of the diaphragm. The sequence of events involves assumption of the supine position, induction of anesthesia, causation of paralysis, and lateral decubitus positioning (wherein abdominal contents mostly press upon the dependent hemidiaphragm). This movement of the diaphragm and downward displacement of the mediastinum result in decreased functional residual capacity (FRC) and contribute to pushing the dependent lung to the lower flattening of the compliance curve. *Pab*, Pressure of the abdominal contents. (Adapted from Benumof JL. *Anesthesia for Thoracic Surgery*. 2nd ed. Philadelphia: Saunders; 1995.)

mediastinum also further shifts downward because of loss of negative intrapleural pressure in the nondependent lung, which helped to distend it. Ventilation to the dependent lung is decreased in proportion to the displacement of the lung by the mediastinal structures. Compression of the great vessels may cause a decrease in cardiac output and circulatory compromise. Any spontaneous respiration becomes very inefficient because paradoxical movement of air occurs on inspiration from the open-chest lung into the dependent lung, which has the greater negative intrapleural pressure. On expiration, gas exits the dependent lung and enters both

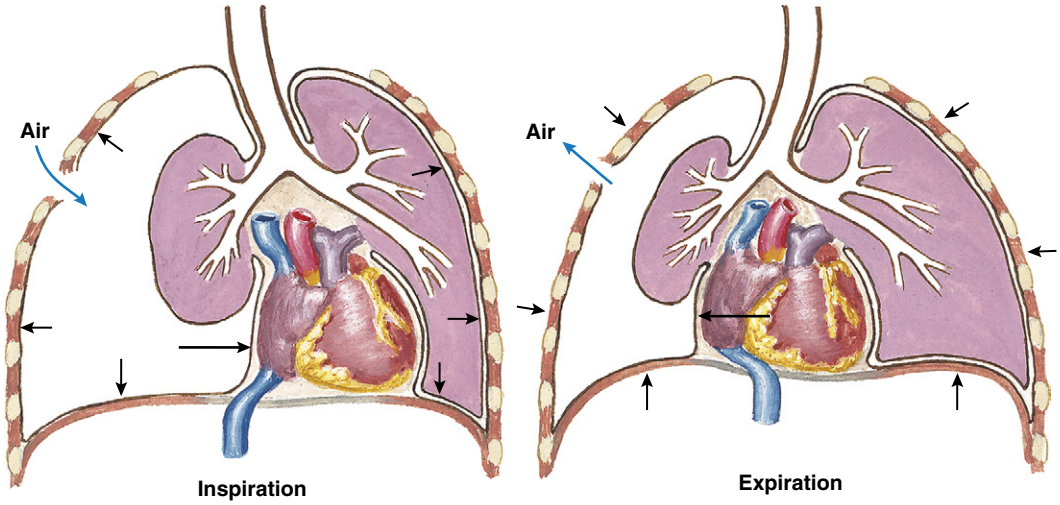


FIGURE **27-9** Paradoxical respiration in the spontaneously breathing patient with open chest. (Netter illustration from www.netterimages.com. ©Elsevier Inc. All rights reserved.)

the trachea and the open-chest lung, causing the lung to expand (Figure 27-9). Paradoxical respiration compromises fresh gas exchange in the dependent lung because part of the V_T moves to and fro between the lungs. Positive-pressure ventilation diminishes the effects of mediastinal shift and paradoxical respiration. However, during mechanical ventilation, the open chest provides no resistance, and the greatly increased compliance of that lung allows a higher proportion of ventilation to go to the nondependent lung, the least perfused area of the thorax. The less ventilated, better-perfused, dependent lung contributes to physiologic shunt, because blood flows through atelectatic areas without acquiring oxygen. Although the prevalence of different zones is not as evenly distributed as diagrams would suggest, the lateral, anesthetized, paralyzed, open-chest patient does exhibit the epitome of significant regional areas of disparity between ventilation and perfusion.

Anesthetized Open-Chest, with One-Lung Ventilation

The succeeding cascade of changes leading up to the anesthetized open-chest patient results in significant ventilation-perfusion mismatch. There is little resistance to ventilation of the nondependent lung, whereas the effects of gravity promote perfusion to the dependent lung. When ventilation to the nondependent lung is ceased, the whole ventilation is directed to the dependent lung. Remaining perfusion to the nondependent lung creates a shunt, but hypoxic pulmonary vasoconstriction reduces the shunt by 50% by diverting much of that blood toward the dependent lung. The Pa_{O_2} is higher during one-lung ventilation in the lateral position than it is in the supine position, because clamping the airway to the nondependent lung reverts some of the changes that caused $\dot{V}/\dot{Q}$ disparity in the anesthetized patient.

ONE-LUNG VENTILATION

Indications for Lung Separation

The ability to provide distinct ventilation to the separate lungs facilitates pulmonary surgery by providing a quiet surgical field. This is particularly helpful in the case of thoracoscopic surgery, in which visualization and the ability to manipulate the operative lung are limited. Thoracic surgeons will commonly consider lung separation an absolute requirement for pulmonary surgery. However, surgery can be performed on a lung that is being ventilated, and thoracic surgery alone is not an absolute indication for OLV. In fact, in the case of pediatric patients, gentle dual-lung ventilation is indicated and appropriate in either the presence of airway concerns that preclude use of a lung-separating device or the inability to maintain oxygenation with OLV. Certain situations, such as infectious contamination of one lung, are absolute indications for OLV, but most common thoracic surgeries create *relative* indications for lung separation in that they can safely be accomplished without it. Indications for lung separation are noted in Box 27-3.

BOX 27-3

Indications for Lung Separation

I. Absolute
- A. Isolation of one lung from the other to avoid spillage or contamination
  1. Infection
  2. Massive hemorrhage
- B. Control of the distribution of ventilation
  1. Bronchopleural fistula
  2. Bronchopleural cutaneous fistula
  3. Surgical opening of a major conducting airway
  4. Giant unilateral lung cyst or bulla
  5. Tracheobronchial tree disruption
  6. Life-threatening hypoxemia related to unilateral lung disease
- C. Unilateral bronchopulmonary lavage
  1. Pulmonary alveolar proteinosis

II. Relative
- A. Surgical exposure—high priority
  1. Thoracic aortic aneurysm
  2. Pneumonectomy
  3. Thoracoscopy
  4. Upper lobectomy
  5. Mediastinal exposure
- B. Surgical exposure—medium (lower) priority
  1. Middle and lower lobectomies and subsegmental resections
  2. Esophageal resection
  3. Procedures on the thoracic spine
- C. Postcardiopulmonary bypass pulmonary edema/hemorrhage after removal of totally occluding unilateral chronic pulmonary emboli
- D. Severe hypoxemia related to unilateral lung disease

Adapted from Hagberg CA, ed. *Benumof and Hagberg's Airway Management*. 3rd ed. Philadelphia: Saunders; 2013.

Methods of Lung Separation

Several devices have been developed to enable isolation of one lung and ventilation of the other. The single-lumen endobronchial tube was developed in 1931 to isolate an infected lung.[87] Mimicking this simple approach by advancing a 7.5-mm, 32-cm endotracheal tube (ETT) over a fiberoptic scope into one bronchus may still be used in some circumstances. A disadvantage to use of a single-lumen tube for OLV is that the ability to ventilate or suction the operative lung is lost. Another disadvantage is that use of a single-lumen tube in the right lung would probably occlude the right upper lobe orifice. However, in an emergent situation, use of a single-lumen tube advanced blindly down the right bronchus or placed into the left bronchus aided by a bronchoscope can be life saving. A summary of lung separation devices is presented in Table 27-2. Given that each approach (DLT vs. bronchial blocker) has relative merits, neither can be recommended as a clearly superior method of lung separation for thoracic surgery.

Double-Lumen Endobronchial Tubes

Double-lumen tubes (DLTs) consist of a single tube with two lumens. The bronchial lumen is designed to be inserted into either the left or right lung, and the corresponding port will ventilate that lung. The other lumen opens into the trachea, and the corresponding port will ventilate the opposite lung. The bronchial lumen does not necessarily have to be in the operative lung (Figure 27-10).

Features

Several types of DLTs are used in thoracic surgery. DLTs are designed for insertion either in the right or the left bronchus. Right-sided tubes include features to accommodate the proximity of the upper lobe bronchus. Disposable polyvinyl chloride tubes are available in French (Fr) sizes 26, 28, 35, 37, 39, and 41. The internal lumen diameters range from 3.4 mm to 6.6 mm,[88] although there is wide size variation between manufacturers.[89,90] It would be most important for the anesthetist to ascertain the appropriate size fiberscope

TABLE 27-2 Types of Lung Separation Devices

Type	Examples	Notes
Endobronchial tube	Bronchocath, Carlens, Robertshaw, White	Left bronchus intubation preferable; large size increases difficulty of transoral insertion, but facilitates emptying of surgical lung; right side more challenging to position, but may be preferable for descending aortic aneurism; Carlens and White: carinal hook aids placement when visualization is poor (hemorrhage/hemoptysis)
Bronchial blocker	Ardnt, Cohen, Coopdech, Univent	Easier basic tube insertion, but blocker requires fiberscope—longer time to situate; lung deflation may require suction; more often dislodged; preferable if postoperative intubation planned; Cohen: flexible tip can be manipulated; Arndt, Coopdech: blocker is adapted to a regular endotracheal tube

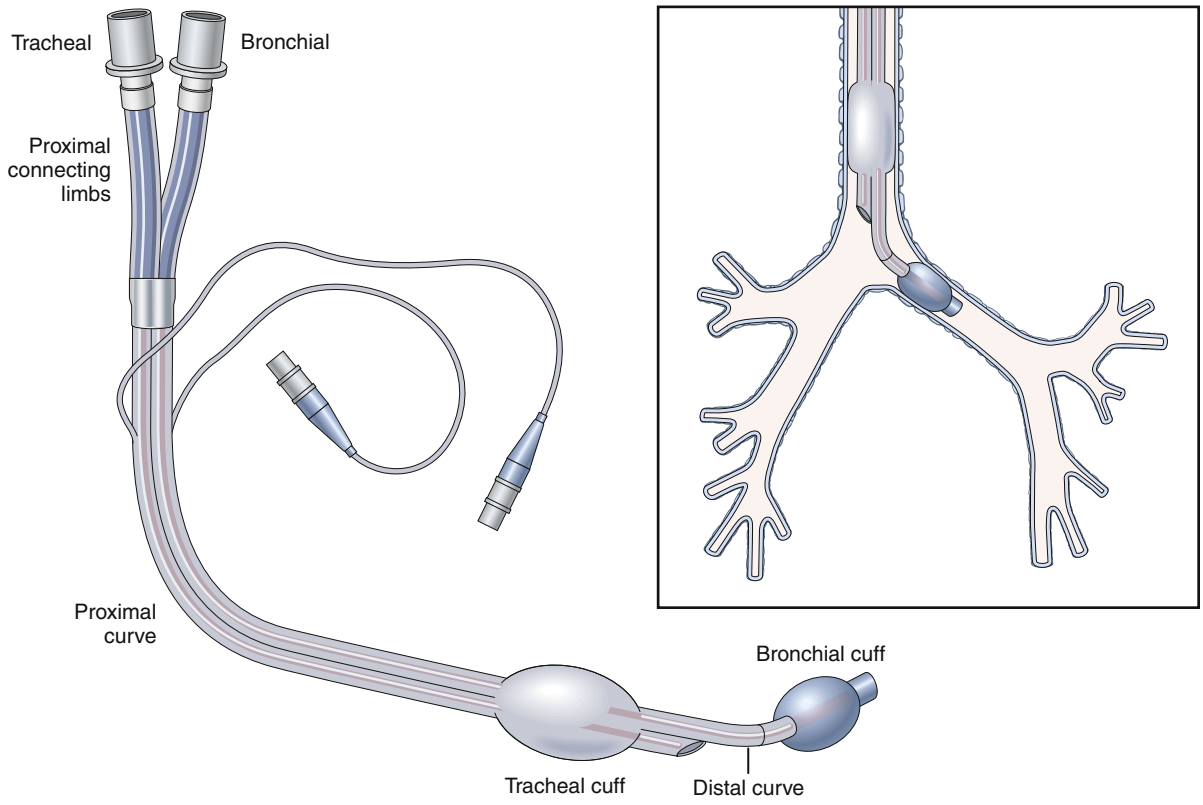


FIGURE 27-10 The double-lumen endobronchial tube. Inset shows a left-sided tube correctly positioned in the bronchus. (From Miller RD, Pardo MC, eds. *Basics of Anesthesia*. 6th ed. Philadelphia: Churchill Livingstone; 2011.)

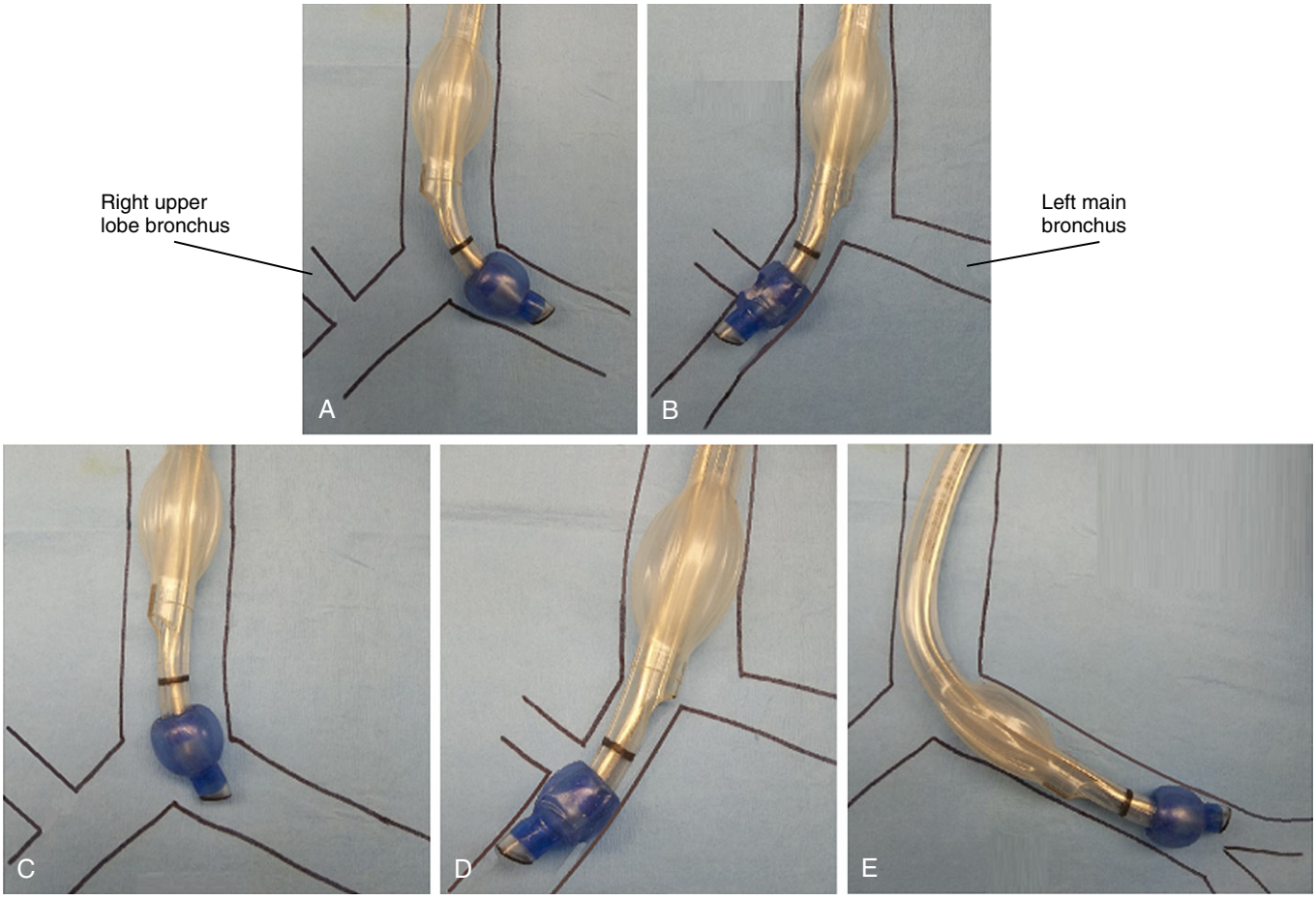


Figure	Description	Ventilating through the bronchial lumen produces breath sounds:	Ventilating through the tracheal lumen produces breath sounds:
A	Correct position of left DLT	Left lung	Right lung
B	Correct position of right DLT	Right lung	Left lung
C	DLT insertion too shallow	Both lungs	Diminished or absent if bronchial cuff obstructs trachea; otherwise, both lungs
D	DLT too deep in right bronchus	Right middle and lower lobes	Left lung or right upper lobe (depending on depth of tracheal cuff)
E	DLT too deep in left bronchus	Left lung	Left lung
Additional variations are possible, such as if a left-sided DLT is inadvertently positioned in the right bronchus, or vice versa. Auscultation provides a quick check, but fiberoptic confirmation is preferable for definitive confirmation.			

FIGURE **27-11** Positioning variations of the double-lumen endobronchial tube.

that will fit through the intended tube. In spite of the perceived smaller size of the lumens, DLTs do not increase breathing resistance significantly in comparison to single-lumen tubes.[88,91]

Advantages and Disadvantages

Although the presence of dual lumens limits the internal diameter of each, the external diameter of a DLT is very large. The 37-F DLT has an outer diameter equivalent to that of a standard 11-mm internal diameter (ID) ETT. For this reason, DLTs are not used for small children; the external diameter of the 26-F DLT is 7.5 mm.[92] Sizing of DLTs is determined by patient height, usually leading to use of 35-F to 37-F tubes in females, and 39-F to 41-F tubes in males.

The short distance from the carinal bifurcation to the right upper lobe is 2.5 cm or less, as compared with a 4- to 5-cm left mainstem bronchus. Modifications have been made in right-sided tubes to allow ventilation through a slot in the endobronchial cuff or to use two bronchial cuffs, but even slight movement of the right DLT can lead to malposition. Many practitioners have resolved to use left-sided DLTs for all right and left thoracotomies unless a left-sided tube is contraindicated by internal lesions of the airway, compression of the trachea or main bronchi by an external mass, or the presence of a descending thoracic aortic aneurysm, which can compress or erode the left main bronchus. Intubation with the large DLT can pose a challenge, even in patients with a normal airway; insertion in those with poor airway anatomy may be particularly challenging.

Complications of Double-Lumen Tubes

The most common complication of DLT use is malpositioning of the tube. Figure 27-11 demonstrates some variations of DLT positioning. Rupture of a thoracic aneurysm is possible with a left DLT

BOX **27-4**

Auscultation of Breath Sounds After Placement of a Double-Lumen Tube

1. Inflate the tracheal cuff.
2. Verify bilaterally equal breath sounds. If breath sounds are present on only one side, both lumens are in the same bronchus. Deflate the cuff and withdraw the tube 1 to 2 cm at a time until breath sounds are equal bilaterally.
3. Inflate the endobronchial cuff.
4. Clamp Y-piece to the endobronchial lumen and open the lumen to atmosphere.
5. Verify breath sounds in the correct lung (tracheal side) and the absence of breath sounds in the opposite lung (bronchial side).
6. Verify the absence of air leakage through the bronchial lumen.*
7. Unclamp and reconnect the endobronchial lumen and verify bilateral breath sounds.
8. Clamp Y-piece to the tracheal lumen and open the lumen to atmosphere.
9. Verify breath sounds in the correct lung (bronchial side) and the absence of breath sounds in the opposite lung (tracheal side).
10. Verify that breath sounds are equal at the apex of the lung and at the base. If the apex is diminished, withdraw the tube until upper lung sounds return.
11. Verify the absence of air leakage through the tracheal lumen.*

*When absolute lung separation is needed, as in bronchopulmonary lavage, connecting tubing from the open, nonventilated lumen to an underwater drainage system will show air bubbles if a leak is present (see Figure 27-13).

if the aneurysm compresses the left mainstem bronchus. Damage to the vocal cords or arytenoid cartilages is possible from a carinal hook. A carinal hook also can break off, requiring retrieval with a bronchoscope. Bronchial rupture, which was thought to be caused by overinflation of the bronchial cuff, has been reported.[93,94] Owing to the possibility of its being inserted too deeply, a DLT also can cause the entire tidal volume to be delivered to a single-lung lobe, creating the potential for barotrauma. The larger size of the DLT is probably also responsible for the slightly increased incidence of hoarseness and vocal cord lesions observed in patients after DLT, versus using a bronchial blocker for lung separation.[95]

Insertion of Double-Lumen Tubes

The DLT has two curves along its length to aid in its placement. A stylet aids placement through the larynx. Some practitioners prefer the Macintosh blade for intubation because it offers greater clearance for the tube and may decrease the chance of balloon rupture from the teeth.[96] For laryngoscopy, the lubricated DLT is advanced with the distal curve concave anteriorly until the vocal cords are passed. The stylet is usually removed at this point to reduce concern about the rigid tube causing mucosal damage. The tube is then rotated 90 degrees toward the bronchus to be intubated. The tube is advanced to around a 27-cm depth in females or 29 cm in males, or until resistance is met.[97]

The tracheal cuff requires 5 to 10 mL of air, and the bronchial cuff requires 1 to 2 mL of air. Overinflation of the bronchial cuff can cause its lumen to be narrowed or occluded and increases the risk of tearing the bronchus. Unlike most tracheal high-volume, low-pressure cuffs, the bronchial cuff holds a small volume and can produce high pressures on the endobronchial mucosa. For that reason, unless unilateral lung contamination exists, the bronchial cuff should be deflated during the procedure once OLV is no longer needed. After the tube is situated in the bronchus, adapters are attached to the two lumens for interface with the anesthesia circuit. Auscultation of breath sounds is a simple though not highly reliable method of determining the position of a double-lumen tube (Box 27-4). When properly positioned, breath sounds should be auscultated in all fields of the lung corresponding to the bronchial lumen (depending on left- or right-sided tube) when that lumen alone is ventilated. Breath sounds should be heard only in the opposite lung, then, when the tracheal lumen is ventilated. Figure 27-11 outlines some auscultation findings expected with various tube positions.

Flexible fiberoptic bronchoscopy is essential to verify placement of the DLT (Figure 27-12 and Box 27-5). Fiberoptic bronchoscopy has revealed a 38% to 83% incidence of malpositioning of DLTs that were judged by auscultation to be properly placed.[88,98] Some particular advantages of fiberoptic inspection of the DLT over auscultation are guidance during initial placement, ability to visualize correct depth of the bronchial cuff, and visualization of proper positioning of the right upper lobe port (if present). Placement of the tube should again be verified by bronchoscopy after the patient is positioned laterally because the DLT will commonly withdraw from the bronchus by 1 cm.[99] When absolute separation of the lungs is required to prevent cross-contamination, the integrity of the bronchial seal can be tested by connecting a tube from the bronchial port to a water seal and then providing ventilation through the tracheal lumen. Incompetence of the bronchial cuff will be evidenced by egress of bubbles in the water seal (Figure 27-13).

Bronchial Blockers

Bronchial blockers consist of catheters with an inflatable balloon that blocks the bronchus of the operative lung. Blockers can be incorporated into a side-channel of an endotracheal tube (e.g., Univent tube) or they can be separate devices and inserted either through the regular endotracheal tube lumen or outside of it (more common in pediatrics) (Figure 27-14). Common options for stand-alone bronchial blockers include the 8F-Fogarty embolectomy catheter, the Cohen Flextip blocker, the Coopdech blocker, the EZ blocker, and the Arndt Bronchial blocker (formerly called the Wire-Guided Endobronchial blocker).

Features

Bronchial blockers are guided into the appropriate bronchus with the aid of a bronchoscope (Figure 27-15). Wire-guided blockers have a loop on the end through which the fiberscope is passed, facilitating guidance of the blocker into the bronchus after the fiberscope. The Cohen blocker has a steerable tip to facilitate advancement into the appropriate bronchus. The Univent tube consists of an integrated ETT with a second lumen for a deployable bronchial blocker. The EZ blocker has a forked distal end that functions like the Carlens hook to rest on the carina. One arm of the fork has the inflatable balloon to occlude the bronchus it occupies.

Advantages and Disadvantages

Because insertion of the DLT is more complicated, bronchial blockers are more useful in patients with a difficult airway or a tracheostomy. These devices are beneficial for patients already intubated, when changing to another tube would be dangerous. They can also be used for pediatric lung separation, even in children less than 2 years of age, with a special small-sized blocker.[100,101]

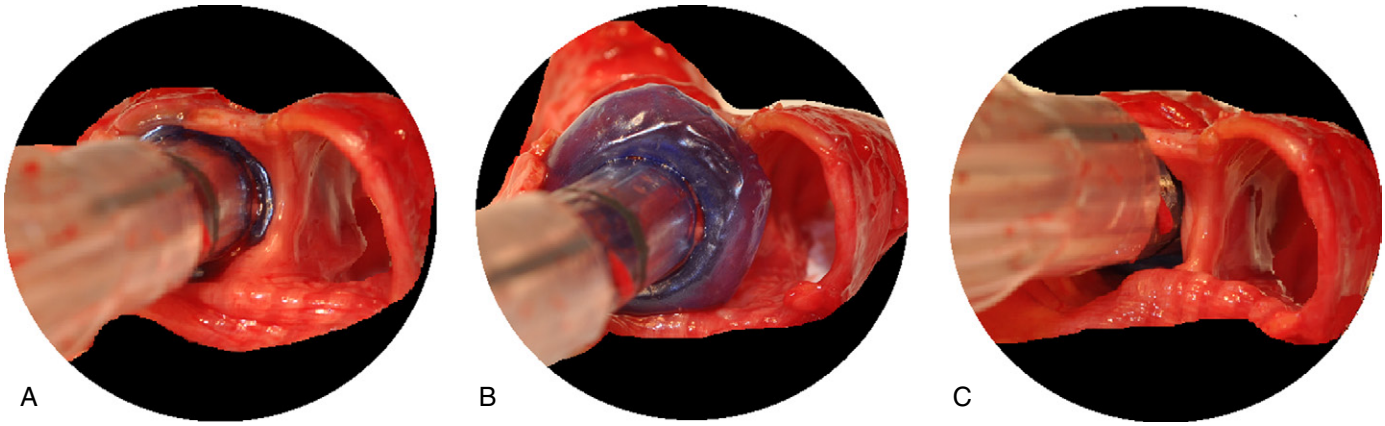


FIGURE **27-12** Verification of double-lumen tube position with fiberscope. **A,** Correct position; bronchial cuff visualized just beyond the carina. **B,** Tube too shallow; bronchial cuff herniating across the carina. **C,** Tube too deep. See additional description in Box 27-5.

BOX **27-5**

Fiberoptic Bronchoscopy to Verify Placement of a Double-Lumen Tube

1. Insert the scope through the tracheal lumen. Visualize the carina distally. (Confirm that the tracheal orifice is within the trachea and not a bronchus, or that the tube is not displaced proximally such that the bronchial cuff fills the trachea.)
2. Visualize the bronchial (blue) cuff 1 to 2 mm beyond the carina. Ensure that the cuff is not too proximal or overinflated such as to herniate across the carina and obstruct the contralateral bronchus.
3. Insert the scope through the bronchial lumen. Visualize that the tip of the bronchial lumen is unobstructed. For left-sided tubes, visualize the bronchial carina distal to the tube tip. For right-sided tubes with a right upper lobe (RUL) ventilation port, visualize that the RUL bronchus is aligned with the ventilation port.

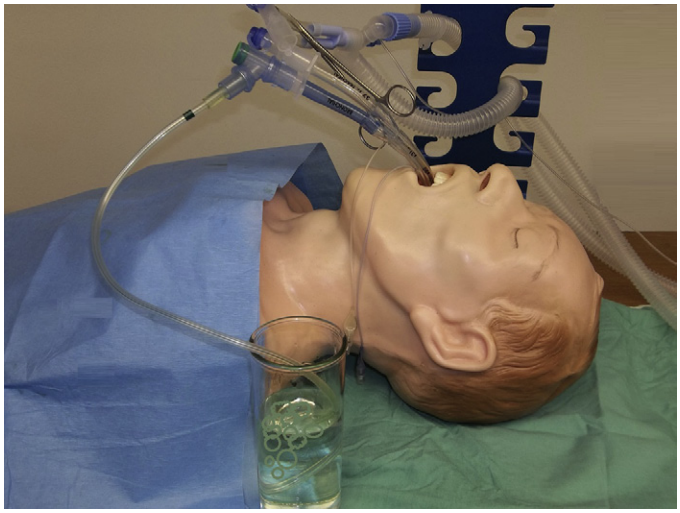


FIGURE **27-13** Water seal set-up to test for leaks around the bronchial cuff.

Although the regular tube is easy to insert, positioning the bronchial blocker requires more time than the DLT, and placement is dependent on use of a fiberscope. In comparison to DLT, blockers have a greater incidence of becoming malpositioned. Because a bronchial blocker affords little conduit for egress of gas, lung deflation is often less effective than with a double-lumen tube. This can be particularly troublesome in thoracoscopic surgery. Suction of the blocker port can be helpful, but excessive negative pressure or duration can cause damage. Blockers also do not allow suctioning for pulmonary toilet, particularly when separation is indicated by unilateral infection or bleeding. In that case, removal must follow special procedures to avoid contaminating the opposite lung.[102] The bronchial blocker is plagued with the same challenge as the DLT in blocking the right bronchus, but the DLT has the advantage of being able to exclude either lung with a left-sided device. Therefore, bronchial blockers are reserved by some exclusively for left-sided surgery.

Insertion of Bronchial Blockers

Insertion of the bronchial blocker depends on the device. Typically, it involves basic tracheal intubation followed by insertion of the blocker through the tube, followed by the fiberscope, which is used for final positioning. Variations include that wire-guided catheters are already mounted on the fiberscope when it is inserted, and pediatric extraluminal blockers are inserted in the trachea, followed by intubation, followed by fiberoptic inspection and positioning of the blocker.

Physiology of One-Lung Ventilation

During two-lung ventilation, blood flow to the dependent lung averages approximately 60% (Figure 27-16). When one lung is allowed to deflate and OLV is started, any blood flow to the deflated lung becomes shunt flow, causing the Pa_{O_2} to decrease. Without autoregulation of pulmonary blood flow, a 40% shunt would be anticipated. The lungs have a compensatory mechanism of increasing vascular resistance in hypoxic areas of the lungs, and this diverts some blood flow to areas of better ventilation and oxygenation. This mechanism, present in most mammals, is termed *hypoxic pulmonary vasoconstriction* (HPV). HPV is a reflex intrapulmonary feedback mechanism in inhomogeneous lungs to improve gas exchange and arterial oxygenation. Whereas hypoxemia causes vasodilation in the general circulation, alveolar hypoxia has the opposite effect on pulmonary arteries. HPV is a unique mechanism, suited specifically to match pulmonary blood flow with well-oxygenated areas of lung.

The cellular mechanism for HPV involves a redox-based oxygen sensor in smooth muscle cells of the pulmonary arteries (probably focused on the electron transport chain of the mitochondria

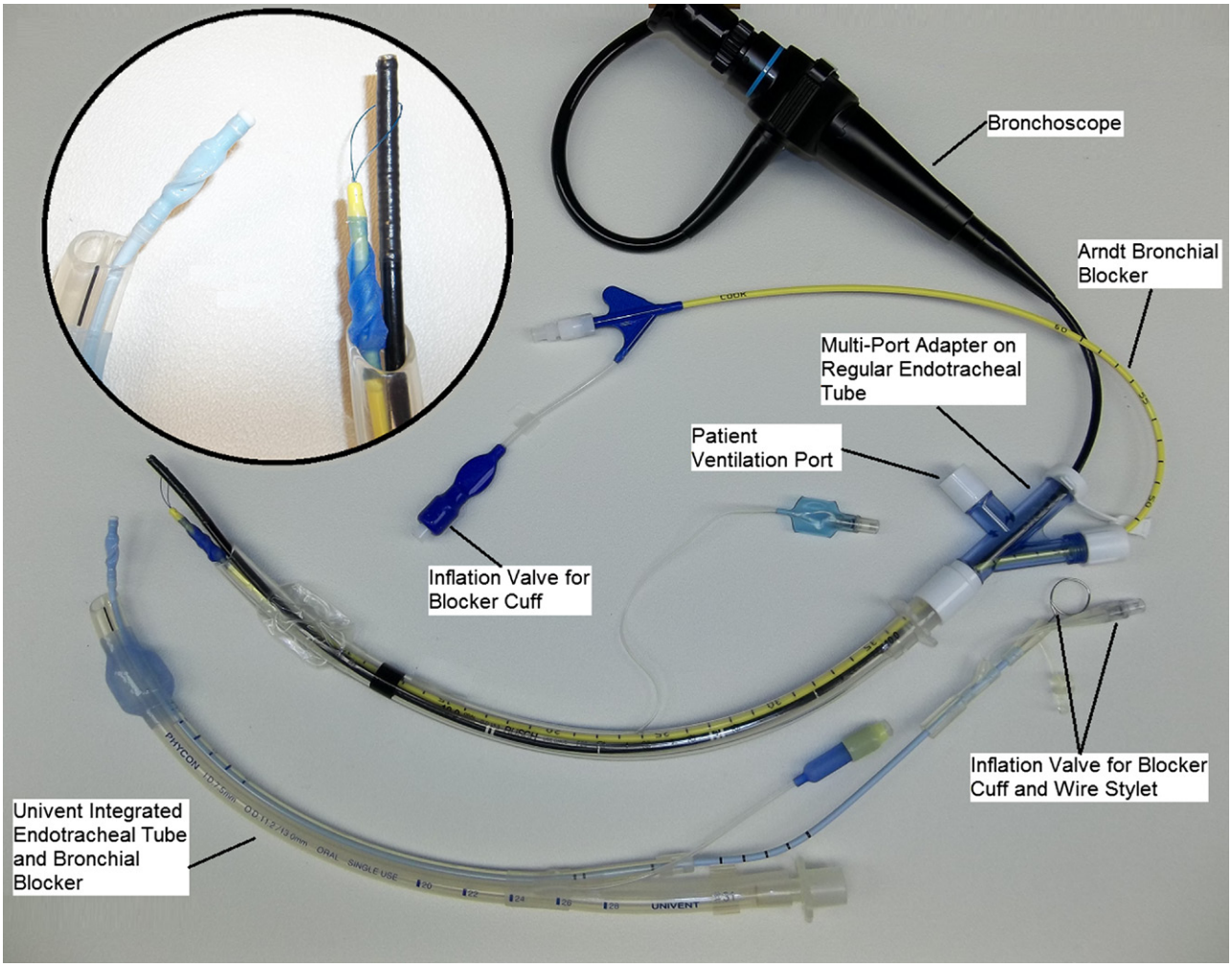
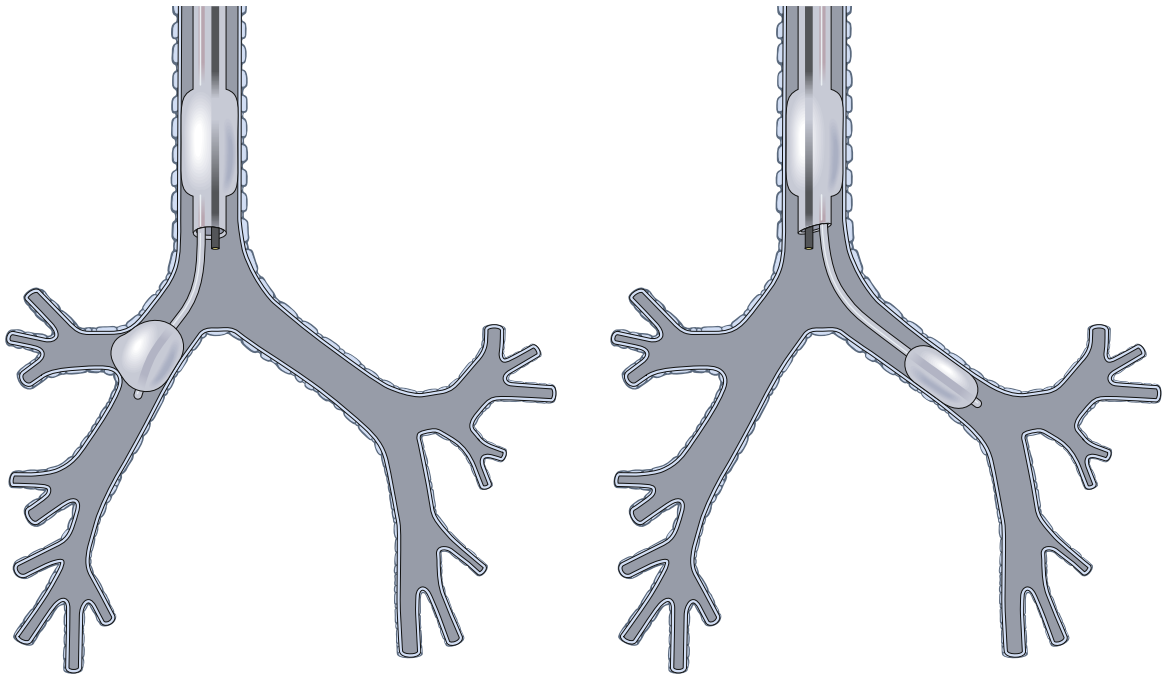


FIGURE **27-14** The Uninvent (bottom) and Arndt bronchial blocker. Inset shows detail of Uninvent dual-lumen tube design and Arndt wire guidance loop.



A B

FIGURE **27-15** Positioning of the bronchial blocker in the right **(A)** and left **(B)** lung. The fiberoptic bronchoscope is used to establish and verify correct position. (From Miller RD, Pardo MC, eds. *Basics of Anesthesia*. 6th ed. Philadelphia: Churchill Livingstone; 2011.)

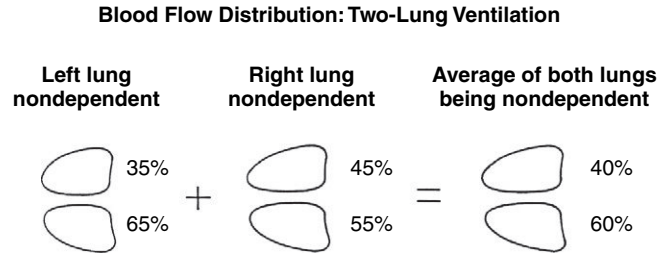


FIGURE **27-16** When the left lung is the nondependent lung, the distribution of blood flow between the nondependent and dependent lungs is 35%:65%. When the right lung is the nondependent lung, blood flow distribution between the nondependent and dependent lungs is 45%:55%. Average one-lung ventilation blood flow distribution is a nondependent-to-dependent ratio of 40%:60%. (From Benumof JL. *Anesthesia for Thoracic Surgery*. 2nd ed. Philadelphia: Saunders; 1995.)

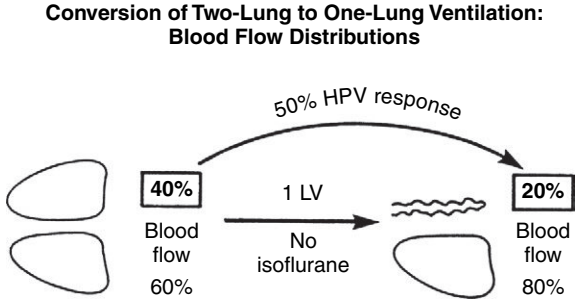


FIGURE **27-17** Two-lung ventilation nondependent/dependent lung blood flow ratio is 40%:60%. When two-lung ventilation is converted to one-lung ventilation *(1 LV)*, the hypoxic pulmonary vasoconstriction *(HPV)* response decreases the blood flow to the nondependent lung by 50%, and the nondependent/dependent lung blood flow ratio becomes 20%:80%. (From Benumof JL. *Anesthesia for Thoracic Surgery*. 2nd ed. Philadelphia: Saunders; 1995.)

BOX 27-6

Characteristics of Hypoxic Pulmonary Vasoconstriction

- A local reaction occurring in hypoxic areas of lung; may be very localized due to regional atelectasis (as in one-lung ventilation), or affect both lungs entirely in hypoxic situations (such as what leads to high-altitude pulmonary edema)
- Opposite to systemic reaction to hypoxia, causes vasoconstriction in all but very proximal pulmonary arteries
- Triggered by alveolar hypoxia, not arterial hypoxemia
- Onset and resolution are within seconds following changes in P_{O_2}
- Peak effect occurs within 15 minutes
- May be inhibited by vasodilators and augmented by chemoreceptor agonists (almitrine)

Data from Moudgil R, et al. Hypoxic pulmonary vasoconstriction. *J Appl Physiol*. 2005;98(1):390-403; Michelakis ED, et al. Hypoxic pulmonary vasoconstriction: redox regulation of O_2-sensitive K+ channels by a mitochondrial O_2-sensor in resistance artery smooth muscle cells. *J Mol Cell Cardiol*. 2004;37(6):1119-1136; Nagendran J, et al. An anesthesiologist's guide to hypoxic pulmonary vasoconstriction: implications for managing single-lung anesthesia and atelectasis. *Curr Opin Anaesthesiol*. 2006;19(1):34-43.

BOX 27-7

Factors That Reduce Effectiveness of Hypoxic Pulmonary Vasoconstriction

- Alkalosis
- Excessive tidal volume or PEEP
- Hemodilution
- Hypervolemia (LAP > 25 mmHg), atrial natriuretic peptide
- Hypocapnia
- Hypothermia
- Prostacyclin
- Shunt fraction < 20% or > 80%
- Vasodilators, phosphodiesterase inhibitors, and calcium channel blockers
- Volatile anesthetics > 1.5 MAC

LAP, Left atrial pressure; *MAC*, minimum alveolar concentration; *PEEP*, positive end-expiratory pressure.

of these cells). Hypoxia reduces production of activated oxygen species (AOS) such as H_2O_2. These AOS act as second messengers from the oxygen sensors, and reduction in their outflow leads to inhibition of voltage-dependent potassium channels. The result is influx of extracellular calcium, which causes vasoconstriction.[103,104] Box 27-6 lists the characteristics of HPV.

HPV during OLV is effective in decreasing the cardiac output to the nonventilated lung by approximately 50%[105] (Figure 27-17). HPV can increase the PVR by 50% to 300%, and the response can persist for long periods of time in the face of chronic hypoxia.[103] In fact, the chronic increase in PVR from COPD can be responsible for pulmonary vascular remodeling that leads to cor pulmonale.[106] HPV occurs whether the lung is rendered hypoxic by atelectasis or by ventilation with a hypoxic mixture. It is initiated within seconds of hypoxia and reaches its maximum effect in approximately 15 minutes. HPV improves arterial oxygenation when the amount of hypoxic lung is between 20% and 80%, which is the condition during OLV.[107] When less than 20% of the lung is hypoxic, the total amount of shunt is not significant. When more than 80% of the lung is hypoxic, HPV increases PVR, but the amount of well-perfused lung is not sufficient to accept enough diverted flow to maintain arterial oxygenation.

Because HPV is effective in decreasing shunt flow, avoidance of drugs or events that inhibit the mechanism is important (Box 27-7). Alveolar and intravascular volume derangements can inhibit the effect of HPV. Hypervolemia or high cardiac output may override HPV by recruiting constricted vessels.[108] Conversely, hypovolemia may trigger adrenergic vasoconstriction, reducing flow to well-ventilated portions of lung.[109] Overdistention of alveoli may also reduce perfusion to well-ventilated lung areas by creating the "zone 1" ventilation-perfusion scenario. For these reasons, normal fluid volume should be maintained during OLV; moderate tidal volumes (6 mL/kg) should be used, and excessive PEEP should be avoided.[86] Hypocapnia and alkalosis decrease HPV.

Many vasodilating drugs inhibit HPV, including nitroglycerin, nitroprusside, dobutamine, some calcium channel blockers (e.g., nifedipine nicardipine, and verapamil), and some β_2-agonists, such as isoproterenol.[86] Vasoconstrictive drugs, including dopamine, epinephrine, and phenylephrine, may preferentially constrict normally oxygenated pulmonary vessels and reestablish the shunt flow, in opposition to the effect of HPV.[107]

ANESTHETIC MANAGEMENT DURING ONE-LUNG VENTILATION

Choice of Anesthetic

Side effects of general anesthesia from a variety of mechanisms create concern for intraoperative and postoperative pulmonary function. They include impairment of hypoxic pulmonary vasoconstriction, disruption of ventilation-perfusion matching, neural and pain-induced hypoventilation, postoperative residual muscle relaxation, and atelectasis. Few studies have been able to demonstrate clear differences in patient outcomes based on anesthetic technique alone; however, some factors have emerged as being important in the pulmonary surgical patient.

On the basis of the discussion of HPV, clinical doses of potent inhalation agents do not significantly alter the mechanism of HPV. Volatile agents offer several benefits in thoracic surgery. They allow the use of a high F_{IO_2} to help prevent hypoxemia during OLV. They produce bronchodilatory effects and decrease airway irritability in patients to be subjected to direct manipulation of lung tissue. In some studies, volatile agents resulted in less inflammatory response than did IV agents.[110,111] In contrast, the dose of narcotics required to obtund airway reflexes could depress ventilation and necessitate postoperative ventilation. Volatile agents are rapidly eliminated at the end of surgery and allow for early extubation. For these reasons, volatile agents are usually chosen as the primary anesthetics during thoracic surgery.

No intravenous anesthetics inhibit HPV, and although all volatile agents theoretically do, the volatiles act as vasodilators in a dose-dependent manner.[112] HPV can be expected to remain intact if volatile agents are administered at less than 1.5 minimum alveolar concentration (MAC).[113-115] Most analyses fail to demonstrate a difference in gas exchange between intravenous and inhaled techniques.[116]

To prevent hypoxia and any significant increase in PVR, nitrous oxide is generally avoided in favor of an air-O_2 mixture. Nitrous oxide increases PVR in healthy patients as well as in those with preexisting pulmonary hypertension.[84] This is cause for even greater clinical concern with concurrent right ventricular dysfunction. Nitrous oxide should also be avoided in patients with bullous or emphysematous lungs, because it may increase the volume of trapped airspace. An air-oxygen mixture does prolong emptying of the operative lung, in contrast to pure oxygen or a nitrous oxide mixture.[117]

The choice of specific opioids or hypnotics will not influence pulmonary outcomes, but there is concern related to the choice of muscle relaxants used. Postoperative residual paralysis is a common occurrence with both intermediate and long-acting relaxants and is present regardless of the use of neuromuscular monitoring or reversal.[118] However, the incidence of residual relaxation associated with the use of long-acting relaxants (e.g., pancuronium) is significantly higher, and complications from it are more frequent compared with the use of intermediate-acting relaxants.[119] Muscle weakness may follow surgeries of long duration, even with adequate tests of neuromuscular recovery.[120] Therefore, the use of shorter-acting, fast-offset relaxants and conservative monitoring, dosing, and reversal practices are indicated in the pulmonary surgical patient.

The Role of Regional Anesthesia

When compared with general anesthesia, regional anesthesia may be beneficial in reducing atelectasis, pneumonia, respiratory failure, and other pulmonary complications.[121] Unfortunately, regional anesthesia without general is impractical for the open-lung case; however, regional anesthesia can offer postoperative analgesia without the respiratory depressant effects of systemic opioids, which confers great benefits. Epidural anesthesia was found to reduce complications both for patients with normal FEV_1, and those with airflow obstruction.[122] Because epidural sympathectomy causes vasodilation, some have questioned whether epidural anesthesia would inhibit HPV, but because HPV is a locally mediated event, epidural anesthesia is found to be similar to IV or balanced techniques with regard to gas exchange.[123]

Analgesia for Thoracic Surgery

Thoracotomy is known as one of the most painful operations, and postoperative pain can be very protracted (as in post-thoracotomy pain syndrome) and lead to complications such as pneumonia and atelectasis.[87] Pain immediately after thoracic surgery causes splinting, decreased respiratory effort, hypoxemia, and respiratory acidosis. Aggressive management of pain is aimed at seeking a balance between comfort and respiratory depression in patients with decreased lung function. Residual pain exists in half of thoracotomy patients after 1 year and in one third of patients after 4 years.[88]

Several options can be considered in the management of postoperative pain. Patients can titrate intravenous patient-controlled analgesia to obtain a more constant level of analgesia than that provided by intermittent intramuscular injections, but the benefits of avoiding systemic opioids have made regional anesthesia emerge as a superior method of pain control.

Thoracic epidural analgesia is considered one of the most effective methods for treating postoperative pain.[124] An epidural catheter is placed around T6 to T8 and infused with epidural opioids or dilute solutions of local anesthetics to provide analgesia. The efficacy of epidural analgesia may be improved with adjunctive interventions, such as IV administration of ketamine and nonsteroidal analgesics.[125]

As an alternative regional anesthesia technique, paravertebral nerve blocks can be placed at the level of the incision plus one or two intercostal interspaces above and below. This technique provides good short-term pain relief and reduces opioid requirements. Paravertebral block provides quality pain control to rival epidural analgesia.[126,127]

Management of One-Lung Ventilation

Ventilation Modes

The primary goal during OLV is maintaining adequate arterial oxygenation and protecting the lung, while providing a surgical field favorable for visualization and manipulation of the operative lung (Box 27-8). In the past, large tidal volumes (V_T) of 10 to 15 mL/kg were recommended to prevent atelectasis in the dependent lung and maintain an adequate FRC. Contemporary understanding is that high volumes predispose to volutrauma, which is associated with increases in cytokine inflammatory mediators and in alveolar fibrin deposition and other markers of procoagulant effect, which characterize acute lung injury.[128,129]

Many patients develop "auto-PEEP" during OLV and have an increased FRC, such that large tidal volumes are unnecessary in any case. Understanding the detrimental effects of high tidal volumes has led to the more contemporary approach of using more physiologic volumes (e.g., 6 mL/kg on the left and 8 mL/kg on the right), adding PEEP to those patients without auto-PEEP, and limiting plateau inspiratory pressures to less than 25 cm H_2O.[122,128-130] With this approach, patients will maintain adequate or even improved oxygenation (as compared with using higher) and minimal elevations in Pa_{CO_2}.[86,131] It is preferable to allow permissive hypercapnia, rather than too-aggressively attempting to maintain a normal

Pa_{CO_2} because hypercapnia supports HPV and also directly reduces cytokine response.[132,133] The Pa_{CO_2} should be maintained below 60 to 70 mmHg, to reduce the incidence of dysrhythmias, hypotension, and pulmonary hypertension. Although a high Fi_{O_2} should induce vasodilation in the dependent lung and improve blood flow, hypocapnia would cause vasoconstriction and should be avoided. PEEP must be employed when using low V_T; otherwise, alveolar derecruitment will occur and reduce the Pa_{O_2}.[134] Implementation of an alveolar recruitment maneuver prior to initiating OLV can help to support better Pa_{O_2} throughout the OLV period.[135] Recruitment maneuvers are not universally accepted. Besides opening airways, they may also translocate cytokines into the circulation,[136] impede hemodynamics, and provide only a transient effect.[137]

An appropriate air-O_2 mixture, at times as high as Fi_{O_2} of 1, is necessary to maximize the Pa_{O_2}. However, considering the potential for oxygen toxicity (particularly absorptive atelectasis or history of chemotherapeutic administration[138]), Fi_{O_2} should be maintained at the lowest level that will support adequate Sp_{O_2}.[112] This approach also leaves a "reserve" intervention in the case of hypoxemia. Increasing the Fi_{O_2} in the face of declining oxygenation allows time to plan other interventions (such as checking tube placement). On 100% oxygen, by the time the Sp_{O_2} falls, the insult will be more advanced and the saturation will continue to decline during diagnosis and management of the issue.

Recent research validates the "protective ventilation" strategy, including end-expiratory pressures above the lower inflection point on the pressure-volume curve, a tidal volume of less than 6 mL per kilogram, inspiratory pressures of less than 20 cm H_2O above the PEEP value, permissive hypercapnia, and preferential use of pressure-limited ventilatory modes.[139-141] The choice of pressure or volume modes of ventilation is not clear-cut. It is compelling to consider that pressure-controlled ventilation limits maximal airway pressure and that the square pressure waveform provides more widespread alveolar recruitment, but research has been equivocal about demonstrating consistently better outcomes based on the ventilation mode.[142-145]

Hypoxemia During One-Lung Ventilation

Hypoxemia occurs in 5% to 10% of patients under OLV.[3] Although hypoxic pulmonary vasoconstriction attempts to normalize the relationship of ventilation and perfusion, it is not 100% effective at doing so. Certain characteristics predict the degree of hypoxemia that will be exhibited by a patient under OLV. The simple fact that the anatomy of the right lung is larger than the left accurately predicts that hypoxemia is worse in right-sided surgery, because there is a greater baseline amount of perfusion to the right lung[146] (see Figure 27-16).The usual detrimental effect of lateral positioning on oxygenation paradoxically benefits the patient during OLV. Lateral positioning with mechanical ventilation normally imbalances $\dot{V}/\dot{Q}$ matching by distributing more ventilation to the nondependent lung, whereas gravity encourages more perfusion to the dependent lung. During lateral-positioned OLV, direction of all ventilation to the dependent lung creates a more beneficial match of ventilation and perfusion. In fact, Pa_{O_2} is found to be significantly worse in procedures (such as lung transplant) where OLV is performed in supine patients.[112] Some patient data also provide prediction of the degree of hypoxemia that will be encountered during OLV. The reduction in FEV_1, paradoxically, is sometimes inverse to the degree of hypoxemia experienced. As a measure of disease progress, a lower FEV_1 indicates worse disease; but as a measure of air-trapping, patients with a lower FEV_1 sometimes create intrinsic PEEP, which helps keep their airways patent and beneficially reduces hypoxemia during OLV.[146] Ventilation-perfusion scanning, if complete preoperatively, also can provide a suggestion of the potential for intraoperative shunt under OLV, because perfusion to the operative lung is inverse to the potential shunt.[147] A last-minute predictor is the end-tidal CO_2. Being dependent on blood flow to the lung, end-tidal carbon dioxide concentration (ET_{CO_2}) is a surrogate measure of perfusion.[148] The degree of decline in $ET_{CO_2}$when switching from two-lung to OLV indicates the degree of blood perfusing the nondependent lung, and therefore a greater initial decline predicts worse oxygenation during OLV.

If hypoxemia occurs during OLV, the anesthetist should assess for physiologic causes or tube malpositioning. Physiologic causes may include bronchospasm, decreased cardiac output, hypoventilation, low Fi_{O_2}, or pneumothorax of the dependent lung. Tube malpositioning implies that movement of the DLT may have excluded a portion of dependent lung, usually the upper lobe. Positioning should be checked first, because a large proportion of hypoxemic episodes are remedied by tube repositioning.[3] If physiologic causes have been ruled out and adequate lung separation and ventilation have been determined, one or more of the following interventions will help improve Pa_{O_2}. First, continuous positive airway pressure (CPAP) to the nondependent, nonventilated lung is almost 100% efficacious in increasing Pa_{O_2}. This can be accomplished with a compact breathing system, such as a Mapleson C with a manometer for pressure determination, attached to the lumen of the deflated lung (Figure 27-18) or with a calibrated, adjustable device made specifically for this purpose. Application of CPAP should help to oxygenate the persistent blood flow through the nondependent lung, but too much pressure will cause the lung to inflate, reducing surgical exposure. The lowest level of effective CPAP (start at 2 cm H_2O) should be sought. The reservoir bag on the CPAP device also can be used to provide intermittent ventilation to the operative lung, if that intervention becomes necessary. Providing gentle ventilation with a separate system will minimize the diminution of surgical exposure, as opposed to ventilating the lung with the same vigor as that required for the dependent lung. As an alternative to CPAP, a small catheter can be used to deliver low-flow oxygen insufflation to the nondependent lung without generating pressure. This approach may be adequate to reduce the shunt and reverse hypoxemia in mild cases.[149]

Besides shunt flow through the operative lung, atelectasis and reduced FRC in the dependent lung also may degrade the Pa_{O_2}. If CPAP to the nondependent lung does not improve oxygenation, PEEP applied (or titrated upward) in the dependent, ventilated lung acts to recruit collapsed airways, increasing compliance of the lung, and increasing FRC. Excessive PEEP

BOX 27-8

Overarching Goals of Ventilation

- Keep the dependent lung open (nonatelectatic) to avoid hypoxemia
- Prevent repetitive closure and opening of airways to avoid damaging shearing forces
- Prevent overdistention and overventilation to avoid inflammatory injury and auto-PEEP
- Promote perfusion to the dependent lung (permit mild hypercapnia; avoid hypoxia, "Zone 1" alveolar pressure, and vasodilators)

PEEP, Positive end-expiratory pressure.

may detrimentally reduce cardiac output. Combined with a fast respiratory rate and/or high inspiratory/expiratory (I:E) ratio, PEEP may impair adequate exhalation, leading to a net volume increase through auto-PEEP and the potential for volutrauma to the dependent lung. The actual end-expiratory pressure should be monitored during OLV to ensure that it does not significantly exceed the intended level of PEEP. Other methods of improving oxygenation during OLV include combining PEEP and CPAP to the respective lungs, and intermittent reinflation of the nondependent lung. Innovative ventilatory approaches such as high-frequency jet ventilation to the operative lung and selective oxygenation to nonoperative *lobes* of the operative lung via a bronchial blocker or bronchoscope also are used.[149-152] Jet ventilation is effective at reducing the shunt, but lung movement can be deleterious, and monitoring and effecting CO_2 removal becomes challenging.[153]

In the failure of CPAP and PEEP, early ligation of the pulmonary artery in pneumonectomy patients may be used to improve oxygenation. If the pulmonary artery is planned to be ligated during the procedure, clamping it will immediately stop all significant flow through the lung contributing to the shunt. For the same reason, manual compression of the lung also will improve the Pa_{O_2}, but the expense of cardiac output and tissue trauma advises against this as a regular strategy.[154] If it becomes impossible to maintain adequate oxygenation with OLV in spite of CPAP and PEEP, manual two-lung ventilation can be used, with pauses in ventilation coordinated with the surgeon's activities to facilitate exposure, suturing of the lung, or other needs. Communication with the surgical team is vital throughout the procedure, especially during the evaluation and correction of hypoxia.

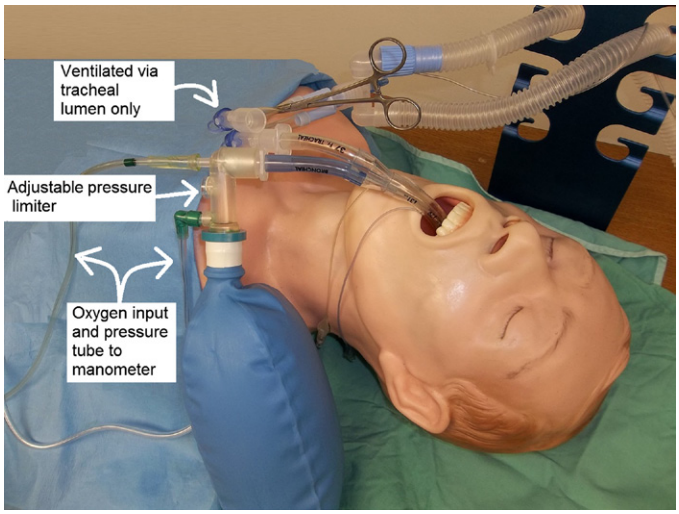


FIGURE **27-18** Continuous positive airway pressure apparatus for improving oxygenation of the nonventilated lung.

At the conclusion of the resection, the surgeon commonly will ask that the operative lung be reinflated using large tidal volumes so that air leaks may be detected. At this time, the lung separator (e.g., DLT clamp, bronchial blocker) should be discontinued and the lung inflated with slow breaths, achieving a peak inspiratory pressure of 30 to 40 cm H_2O.[86] Reexpansion of the lung can be observed while performing this maneuver, which also helps to reverse atelectasis in the lungs. After lung reexpansion, the bronchial cuff should be deflated on the DLT to both reduce pressure on the bronchial mucosa and obviate any detrimental effects of slight tube malpositioning. Deflated, the cuff does not pose the threat of herniating over the carina or obstructing the lobar bronchi. Box 27-9 outlines management of one-lung anesthesia.

Emerging techniques in management of OVL focus attention away from manipulating ventilation of the operative lung to manipulation of perfusion of the nonoperative lung. Ventilation-perfusion matching can be supported by encouraging more perfusion to the ventilated lung or selectively diminishing perfusion to the nonventilated one. Inhaled epoprostenol (prostacyclin) and nitric oxide are beneficial for increasing the perfusion of the dependent lung. The combination of inhaled epoprostenol and IV phenylephrine (for vasoconstriction of the operative lung) is found to be an effective strategy.[155] Another experimental approach is the use of almitrine, which enhances HPV of the nonventilated lung. Studies have shown more than 100% increase in Pa_{O_2} when almitrine and nitric oxide are used on their respective lungs;[156,157] however, toxicity, cost, and challenges to set-up and administer

BOX **27-9**

Management of One-Lung Anesthesia

- Ventilate:
  - Tidal volume: 6-8 mL/kg
  - Rate: 12-15 (permissive hypercapnia okay)
  - Fio_2: 0.4-0.8; maintain Spo_2 > 90%
  - PEEP: 5-10 cm H_2O (2.5-5 if COPD)
  - I:E ratio: 1:2 (1:3 if COPD or PEEPi)
- Consider alveolar recruitment maneuver prior to OLV
- Assess ABG 15 minutes after OLV initiated
- Volatile anesthetics < 1-1.5 MAC or IV agents
- Respond to hypoxemia:
  - Confirm tube position with fiberscope
  - Remedy detrimental effects of anemia or vasodilators
- Perform alveolar recruitment maneuver to DL
- Titrate PEEP in NDL
- Perform gentle recruitment, then CPAP 5-10 cm H_2O to NDL
- Increase Fio_2
- Intermittent or continuous two-lung ventilation
- Low-or no-pressure oxygen insufflation to NDL or selected lobe of NDL
- Reposition to lateral decubitus position if supine
- Alter perfusion with almitrine to NDL; nitric oxide to DL

Adapted from Dalibon N, et al. Treatment of hypoxemia during one-lung ventilation using intravenous almitrine. *Anesth Analg.* 2004;98(3): 590-594; Miller RD, Pardo MC, eds. *Basics of Anesthesia*. 6th ed. Philadelphia: Churchill Livingstone; 2011; Slinger P, ed. *Principles and Practice of Anesthesia for Thoracic Surgery*. New York: Springer; 2011.

ABG, Arterial blood gas; *COPD*, chronic obstructive pulmonary disease; *CPAP*, continuous positive airway pressure; *DL*, dependent lung; *NDL*, nondependent lung; *MAC*, minimum alveolar concentration; *OLV*, one-lung ventilation; *PEEP*, positive end-expiratory pressure; *PEEPi*, intrinsic (auto) PEEP. *FiO_2*, fraction of oxygen inspired; *SpO_2*, oxygen saturation; *I:E*, inspiratory:expiratory.

nitric oxide argue against this as part of a routine plan, except for last-resort cases.

THORACIC SURGICAL CONCERNS

Mediastinal Masses

Masses in the mediastinum can compress vital structures and cause changes in cardiac output, obstruction to airflow, atelectasis, or central nervous system changes. Masses can include benign or cancerous tumors, thymomas, substernal thyroid masses, vascular aneurysms, lymphomas, teratomas, and neuromas (Box 27-10). Surgical procedures for diagnosis or treatment of these masses may include thoracotomy, thoracoscopy, and mediastinoscopy.

Tumors within the anterior mediastinum can cause compression of the trachea or bronchi, increasing resistance to airflow. Changes in airway dynamics with supine positioning, induction of anesthesia, and positive-pressure ventilation can cause collapse of the airway with total obstruction to flow. General anesthesia can therefore be very dangerous in these patients. Total airway obstruction can occur at any phase of anesthesia and through the recovery phase. Positive-pressure ventilation may be impossible, even with a properly placed ETT, if the mass encroaches on the airway distal to the ETT. The airway can collapse, even when spontaneous respiration is maintained.[158] To anticipate this potential, anesthetic preparation should include availability of a rigid bronchoscope, and readiness to turn the patient lateral or prone in case of airway collapse. Cannulation for potential emergency femoral-femoral bypass should be considered if the tumor is large or symptomatic.[159,160] Localization of the mass by computed tomography or bronchoscopy may facilitate placement of the ETT distal to the mass. A major anesthetic goal is to maintain spontaneous ventilation, which retains normal airway-distending pressure gradients and can maintain airway patency when positive pressure ventilation will not.[161]

Signs and symptoms of respiratory tract compression should be sought preoperatively. Many mediastinal masses are asymptomatic, or characterized by vague signs such as dyspnea, cough, hoarseness, or chest pain. Wheezing may represent airflow past a mechanical obstruction rather than bronchospasm. Symptoms may be positional, worsening in the supine or other position. A chest radiograph may show airway compression or deviation. Computed tomography, transesophageal echocardiography, and magnetic resonance imaging may further delineate the size and effects of masses. Subclinical airway obstruction may be revealed by flow-volume loops, which demonstrate changes in flow rates at different lung volumes. Decreased maximal inspiratory or expiratory flow rate alerts the anesthetist to increased risk of obstruction perioperatively. Comparison of flow rates obtained with the patient in the upright and supine positions can reveal whether the supine position will exacerbate the obstruction intraoperatively (Figure 27-19 and Box 27-11).[162]

Biopsy of masses should be performed with the patient under local anesthesia whenever possible. Biphasic positive airway pressure (BiPAP) has been used in this situation to support the airway and maintain spontaneous ventilation while still providing sedation.[163,164] Radiation therapy may be helpful to decrease the mass of the tumor before major surgery is attempted. For airway management, awake fiberoptic bronchoscopy and intubation enables the anesthetist to evaluate the large airways for obstruction and place the ETT beyond the obstruction while maintaining spontaneous ventilation. The effect of positional changes can be assessed with the bronchoscope. Spontaneous ventilation should be maintained as long as possible or throughout the procedure if feasible. The ability to effectively provide positive-pressure ventilation should be guaranteed prior to administering muscle relaxants. The use of a helium-O_2 mixture can improve airflow during partial obstruction by decreasing turbulence past the stenotic area.[165]

Mediastinal masses can cause compression of great vessels or cardiac chambers. Patients with any cardiac or great vessel involvement should receive only local anesthesia whenever possible, remain in the sitting position, and maintain spontaneous respirations. Cardiopulmonary bypass must be able to be implemented within minutes in case of sudden cardiopulmonary collapse.

Patients with mediastinal masses may develop superior vena cava syndrome, venous engorgement of the upper body caused by compression of the superior vena cava. The following signs and symptoms

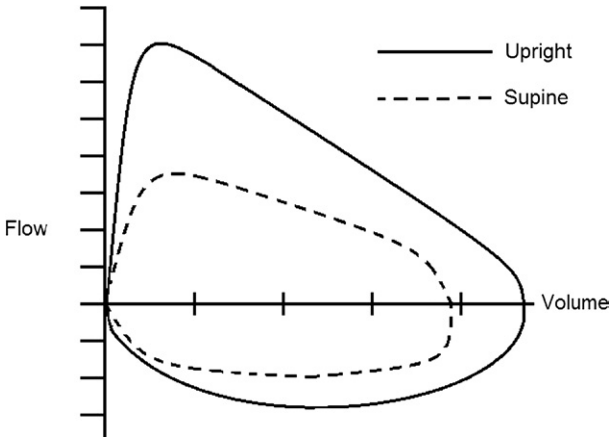


FIGURE **27-19** Upright and supine flow-volume curves representative of anterior mediastinal mass. Note abnormality appears in the supine position, when gravity causes the mass to impinge on the lower airway. The greatest decrement affects the expiratory limb of the loop, which is generally indicative of variable *intra*thoracic obstructions. Thoracic excursion during spontaneous inspiration relieves the pressure. This effect is lost when ventilation is changed to exclusively positive pressure input from above.

BOX 27-10

Common Tumors of the Anterior Mediastinum: "The 4 Ts"

- Thymoma
- Thyroid
- Teratoma
- "Terrible" lymphoma

BOX 27-11

Symptoms of Mediastinal Mass

- Sweats
- Stridor
- Syncope
- Cyanosis
- Orthopnea
- Hoarseness
- Inability to lie flat
- Chest pain or fullness
- Jugular vein distention
- Superior vena cava syndrome
- Cough (especially when supine)

Data from Slinger P, Karsli C. Management of the patient with a large anterior mediastinal mass: recurring myths. *Curr Opin Anaesthesiol.* 2007;20(1):1-3; Blank RS, de Souza DG. Anesthetic management of patients with an anterior mediastinal mass: continuing professional development. *Can J Anaesth.* 2011;58(9):853-859, 860-867.

may be noted: dilation of collateral veins of the upper part of the thorax and neck; edema and rubor of the face, neck, and upper torso and airway; edema of the conjunctiva with or without proptosis; shortness of breath, headache, visual distortion, or altered mentation.[166] Placement of intravenous lines in the lower extremities is preferred; insertion in sites above the superior vena cava could delay the drug effect as a result of slow distribution. Fluids should be administered with caution because large volumes can worsen symptoms.

Mediastinoscopy

Mediastinoscopy involves passing a scope into the mediastinum via an incision above the sternal notch. The scope is passed anterior to the trachea in close proximity to the left common carotid artery, the left subclavian artery, the innominate artery, the innominate veins, the vagus nerve, the left recurrent laryngeal nerve, the thoracic duct, the superior vena cava, and the aortic arch.

Complications of mediastinoscopy include hemorrhage resulting from disruption of major vessels, pneumothorax, dysrhythmias, bronchospasm, recurrent nerve palsy, laceration of the trachea or esophagus, and chylothorax secondary to laceration of the thoracic duct.[167] Large-bore intravenous access should be in place, and banked blood should be immediately available in the event of a tear in a major blood vessel. Air embolism is also a risk if a venous tear occurs. Dysrhythmias such as bradycardia are possible with manipulation of the aorta or trachea during blunt dissection.

The mediastinoscope can place pressure on the innominate artery as it passes through the upper thorax, causing a decrease in blood flow to the right common carotid artery and the right vertebral artery and a decrease in subclavian flow to the right arm (Figure 27-20).[116] The decrease in cerebral flow could be deleterious, especially if the patient has a history of cerebrovascular disease. Monitoring perfusion to the right arm with a pulse oximeter or radial artery catheter can detect decreased flow to the right arm and signal concurrent loss of flow to the brain via the innominate artery. Repositioning of the mediastinoscope is required to reestablish flow to the brain. A noninvasive blood pressure cuff placed on the left arm enables continued monitoring of systemic blood pressure during periods of innominate artery compression.

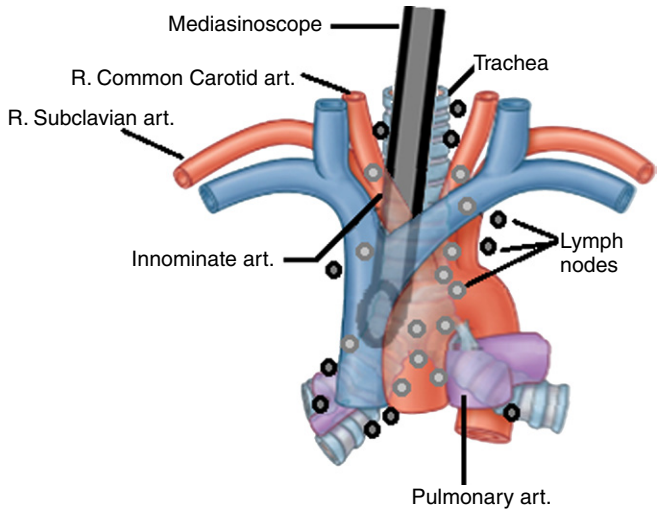


FIGURE **27-20** Placement of a mediastinoscope into the superior mediastinum. The mediastinoscope passes in front of the trachea but behind the thoracic aorta. The mediastinoscope can potentially compress or damage the aorta, innominate artery, trachea, and superior vena cava. (Adapted from Drake RL, Vogl AW, Mitchell WM. *Gray's Anatomy for Students*. 2nd ed. Philadelphia: Churchill Livingstone; 2010.)

Thoracoscopy

Advances in videoscopic technology have led to the increased use of thoracoscopy to replace open thoracotomy for a variety of intrathoracic procedures. *Video-assisted thoracoscopic surgery* (VATS) usually involves general anesthesia with a double-lumen endobronchial tube. Because of limited visualization and limited ability for the surgeon to manually compress the lung, a double-lumen tube may be preferable to a bronchial blocker to facilitate lung emptying. An arterial line is generally placed for thoracoscopy, except in selected healthy patients. However, the anesthetic plan should account for the potential need for rapidly obtaining arterial blood gas samples or for possible hemorrhage, which may be difficult to control in the endoscopic procedure. In cases of severe pulmonary compromise, VATS can be performed using epidural anesthesia in the spontaneously breathing patient who is sedated with a variety of techniques.[168]

Thoracoscopic sympathectomy for hyperhydrosis is an outpatient procedure. A DLT is preferred over a bronchial blocker, because the procedure is bilateral, and the DLT can more easily switch from ventilation of one lung to the other. The procedure is performed in the supine position, and no chest tubes are inserted.

Bullectomy

Patients with bullous COPD are often treated with VATS to prevent pneumothorax or tension pneumothorax, which may result from ruptured bullae. To reduce the risk of rupture of bullae, spontaneous ventilation is desirable under anesthesia until the chest is opened. Patients with severe cardiopulmonary disease may not be able to ventilate adequately under general anesthesia, however, and positive-pressure ventilation may be required. Small V_T s, high respiratory rates, and high Fio_2 can be delivered by gentle manual ventilation to keep airway pressures below 10 to 20 cm H_2O.[169] An alternative to positive-pressure ventilation is high-frequency jet ventilation, used to decrease the chance of barotrauma.[170]

Nitrous oxide should be avoided in bullous disease because it rapidly enlarges the air-filled spaces. The anesthetic plan can involve general or epidural anesthesia, and is based on the patient's cardiopulmonary status and the anesthetist's desire to maintain spontaneous ventilation. The risk of bulla rupture persists even after surgery, so the same concerns for avoiding high airway pressure must be observed.

COMPLICATIONS AFTER THORACOTOMY

A number of complications may occur after thoracic surgery. Various factors have been correlated to an increased risk of complications that suggest consideration of intensive care unit admission or heightened surveillance for postoperative patients: pulmonary fibrosis, age greater than 80 years, PPO FEV_1 or DLCO less than 40%, American Society of Anesthesiologists (ASA) status greater than 3, surgical time longer than 80 minutes, intraoperative hemorrhage, among others.[171-174] The following frequent predictors of pulmonary complications are quantified in the *FLAM score*, which shows good predictive capacity for impending respiratory complications: dyspnea, chest x-ray changes, required oxygen administration, auscultated changes, cough, and bronchial secretions.[175] Among the most common postoperative complications are respiratory failure, cardiac dysrhythmia or failure, and acute lung injury.

Significant factors associated with acute lung injury (ALI) after pulmonary resections include right pneumonectomy, intraoperative overhydration with high vascular volume, high intraoperative airway pressure during OLV, and preoperative alcohol abuse. Other factors that have been suggested are female gender, poor postoperative predicted lung function, trauma, infection, chemotherapy,

mediastinal lymphatic damage, transfusion and administration of fresh frozen plasma, O_2 toxicity, prolonged OLV greater than 100 minutes, and an increased postoperative urine output.[123,161,138]

OLV also leads to inflammatory changes in the ventilated and nonventilated lung, and some of the damage appears to occur upon reexpansion of the deflated lung.[176-180] Protective ventilation strategies should always be employed to reduce the generation of inflammatory processes.[131,181] There appears to be a lasting effect of OLV that is not reversed when reverting to two-lung ventilation. A small animal study demonstrated that after OLV has been discontinued, very low $\dot{V}/\dot{Q}$ ratios in the range of 0.3 to 0.5 persist in the dependent lung.[182] This, coupled with diffuse alveolar damage in comparison to controls, suggests that anesthetists should expect hypoxemia from the resultant $\dot{V}/\dot{Q}$ mismatch that may persist for some unknown period of time after OLV. Even in the absence of inflammatory response, there is evidence of vascular injury to lung tissue that is collapsed during OLV, which suggests that CPAP may have both short- and longer-term benefits.[183]

Minimizing pulmonary intravascular pressures by intraoperative fluid restriction is advocated to decrease postoperative complications.[184] Surgical requirements for proper hydration and tissue perfusion must be balanced with the desire to prevent high postoperative intravascular pressures and possible pulmonary edema.

Low cardiac output in the early postoperative period can be caused by several factors, including blood loss, herniation of the heart through a pericardial defect, right-sided heart failure, and dysrhythmias. Generally, blood entering the pleural space drains into chest tubes at a rate of less than 500 mL per day. Chest tube drainage greater than 200 mL per hour necessitates surgical exploration. An obstructed chest tube can conceal bleeding in a hemothorax. Hypotension, unexplained tachycardia, and decreasing hematocrit are other signs of bleeding.

Loss of pulmonary vasculature with lung resection can result in increased PVR and right-sided heart failure. Reduction in cardiac ejection fraction is greater after pneumonectomy than after lobectomy. Conditions that increase the likelihood of right-sided heart failure include postoperative pneumonia, hypercarbia, and acidosis. Vasodilators are useful to decrease the PVR. Amrinone or dobutamine can be administered if an inotrope is also needed.

Supraventricular dysrhythmias are relatively common after thoracotomy and may herald other serious complications.[185] Morbidity and mortality rates in patients with supraventricular tachydysrhythmias are high, with 25% associated with death within 30 days postoperatively, despite institution of aggressive treatment. Administration of a β-blocking agent can help prevent atrial dysrhythmias. Metoprolol or esmolol provide rate control whereas their cardioselectivity limits adverse effects on bronchial tone. Digitalis, adenosine, calcium channel blockers, and β-blockers are useful to treat supraventricular tachydysrhythmias.

Respiratory complications in the early postoperative period include atelectasis, pneumonia, respiratory failure, bronchopleural or bronchocutaneous fistula, pneumothorax, and pulmonary edema. Aggressive respiratory care to prevent deterioration and allow weaning from ventilation is vital.

Nerve injuries that may be evident after thoracic surgery include damage to the phrenic nerve as it passes through the mediastinum and damage to the left recurrent laryngeal nerve, which is vulnerable during dissection of aortopulmonary lymph nodes and mediastinal procedures.[186] Spinal cord injury is a possibility if an intercostal artery supplying a major radicular artery is injured or if an epidural hematoma is created by surgical dissection between the pleura and the epidural space. Nerve injuries related to surgical positioning are also possible complications.

SUMMARY

Anesthetizing a patient for thoracic surgery requires intricate consideration of multiple factors. The patient may have cardiac or respiratory diseases, masses, bullae, and other problems that complicate anesthetic management. Knowledge of respiratory physiology, pathophysiology, and the physiology of OLV is vital to safe and effective practice. Special equipment such as double-lumen endobronchial tubes, bronchial blockers, and fiberoptic bronchoscopes must be understood. A thorough understanding of the properties of anesthetic drugs is necessary so that the most beneficial combination of agents can be selected to manage the patient's anesthesia. Traditional ventilation concepts favoring high Fi_{O_2} and large tidal volumes have given way to protective ventilation strategies, considering the metabolic implications of oxygen toxicity and acute lung injury. Protective lung strategies use lower tidal volumes, PEEP, and modest Fi_{O_2} levels. For pulmonary surgery, lung separation may be achieved by double-lumen tubes or bronchial blockers. Each has its own advantages, but neither is clearly preferable over the other in every case. Fiberoptic bronchoscopy should be used to ensure proper placement of airway devices for lung separation. For hypoxemia caused by shunting during OLV, intermittent expansion of one or both lungs, CPAP applied to the operative lung, or PEEP applied to the nondependent lung should be used. Judicious fluid management is an important component of reducing postoperative lung injury. Regional anesthesia is a useful adjunct for postoperative pain control. Future research and directions will include more practical methods of reducing the shunt during OLV, and a better understanding of the implications of hypoxemia. More critical monitoring (such as effect-site monitoring) of oxygenation will improve the management of thoracic anesthesia.

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CHAPTER 28

Neuroanatomy, Neurophysiology, and Neuroanesthesia

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This chapter reviews the organization of the central nervous system (CNS). Specific neurophysiologic concepts that are essential for the anesthesia provider also are presented. These concepts include electrophysiology, cerebral blood supply, role of neurotransmitters, and the effects of selected anesthetic agents on cerebral physiology. This chapter also provides recommendations for the management of specific neurosurgical procedures.

ORGANIZATION OF THE CENTRAL NERVOUS SYSTEM

Cells of the Central and Peripheral Nervous Systems

The central nervous system (CNS) includes the brain and spinal cord. The peripheral nervous system includes the cranial and spinal nerves and their receptors and is divided into the somatic and autonomic nervous systems. The somatic nervous system contains sensory neurons for the control of skin, muscles, and joints. The autonomic nervous system, which consists of the sympathetic, parasympathetic, and enteric subdivisions, is responsible for involuntary innervation of various organ systems.

The CNS is derived from two primary cell types: neurons and neuroglial (or glial) cells. The neuron is the basic functional cell of the CNS and consists of a cell body (perikaryon) and specialized cytoplasmic processes, dendrites, and a single axon (Figure 28-1). A single axon emerges from the cell body at the axon hillock. The axon may branch to form collateral nerves at a point distal to the neuron cell body. Axon diameters range from 0.2 to 20 μm. Most of the axons in the brain are only a few millimeters long, although the axons that run from the spinal cord may be as long as 1 meter. Stimulation of the dendrites produces antegrade impulse conduction (toward the neuron cell body) with subsequent conduction away from the neuron cell body by way of the axon.

Neuron cell bodies vary in size and shape and are classified as unipolar, bipolar, pseudounipolar, or multipolar. Unipolar neurons are found only in lower invertebrates. Bipolar neurons are found in the retina, ear, and olfactory mucosa. Pseudounipolar neurons have one cytoplasmic process that exits the cell and divides into two branches, one serving as the dendrite, the other as the axon. Pseudounipolar neurons are present in the dorsal root ganglia and cranial ganglion cells, enabling sensory impulses to travel from the dendrite directly to the axon without passing through the cell body. Multipolar neurons have multiple dendritic processes but only one axon and constitute the majority of the CNS neurons.

The gray matter of the CNS is composed of neuron cell bodies in the CNS, and the white matter is composed of myelinated axons. Regions of concentrated cell bodies within the peripheral nervous system form the cranial, spinal, and autonomic ganglia.

Neurons may be classified according to their specific function: motor neurons, sensory neurons, or interneurons. Motor neurons are multipolar and innervate and control effector tissues such as muscles and glands. Sensory neurons are pseudounipolar and receive exteroceptive, interoceptive, or proprioceptive input. Interneurons are pseudounipolar and connect adjacent neurons.

The neuron is bound by a bilaminar lipoprotein membrane derived from phospholipid molecules arranged with their fatty acid chains facing one another, producing an inner hydrophobic membrane. The membrane surface in contact with the extracellular fluid contains polar hydrophilic groups of phospholipid molecules. The neuronal membrane contains integral membrane proteins, which form ionic pumps, ion channels, enzymes (e.g., adenylate cyclase), receptor proteins, and structural proteins.

The neuron contains a number of common cellular organelles including a well-developed nucleus, mitochondria (distributed throughout the cell body), and cytoplasmic processes. Ribosomes, endoplasmic reticulum, lysosomes, and Golgi complexes are also found. Neurotubules and neurofilaments extend through the cytoplasm from the dendrites to the axon terminal; they provide structural support and a pathway for intracellular transport of neurotransmitters.

The second major cell type found within the CNS is the neuroglial, or glial cell (Table 28-1). Four types of glial cells are found within the CNS: astrocytes, oligodendrocytes, microglial cells, and ependymal cells. Most neoplasms of the CNS arise from glial cells (astrocytes). Glial cells are smaller, outnumber neuronal cells, and lack dendritic and axonal processes. Although they do not participate in neuronal signaling, glial cells are essential for neuronal function. The role of neuroglia includes the maintenance of a proper ionic environment, the modulation of nerve cell electrical conduction, control of reuptake of neurotransmitters, and repair after neuronal injury.

The astrocyte is the predominant glial cell. Astrocytes provide structural neuronal support, group and pair neurons and nerve terminals, regulate the metabolic environment, and are active in repair after neuronal injury.

Two distinct types of astrocytes exist: fibrous astrocytes, found in the white matter, and protoplasmic astrocytes, concentrated in the gray matter. Astrocytes have multiple processes that radiate from the cell, producing a star-shaped appearance. Some of these processes (astrocytic feet) terminate on the surfaces of blood vessels within the CNS (perivascular feet). The contact of the cerebral endothelium by astrocytes has been proposed to be essential in the development of the blood-brain barrier.[1]

Oligodendrocytes have fewer branches than astrocytes (*oligo*, "few"; *dendro*, "branches"). Oligodendrocytes form the myelin sheath of axons in the brain and spinal cord and are capable of myelinating more than one axon. However, oligodendrocytes are incapable of division and fail to regenerate after injury.

The velocity of nerve impulse conduction in an unmyelinated axon increases with the square root of the diameter of the axon. Accordingly, a doubling of impulse conduction requires that the axon be doubled in size. One could only imagine the size of the peripheral nervous system without the presence of myelin. Myelin is essential to increase the velocity of impulse conduction and minimize the size of the axon.

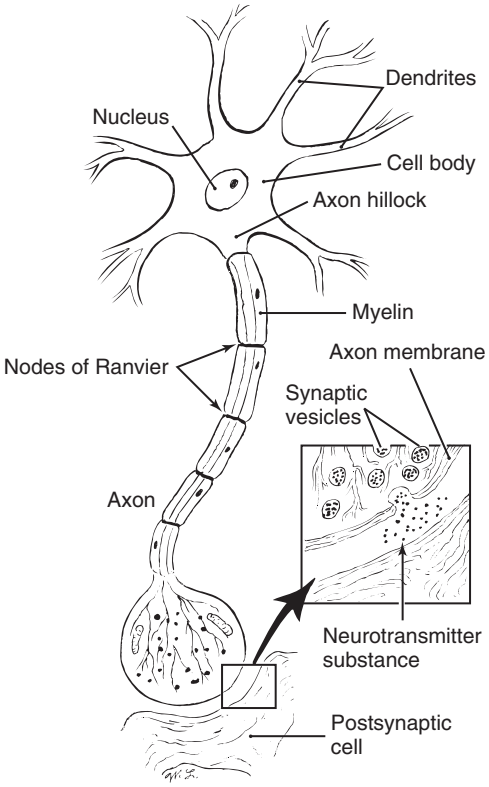

FIGURE **28-1** Neuron and chemical synapse.

TABLE **28-1** Glial Cells

Type	Major Functions
Astrocytes	Support (for neurons) Metabolic and nutritive functions
Ependymal cells	Probable role in cerebrospinal fluid production
Microglia	Phagocytosis
Oligodendrocytes	Insulation (form myelin sheath in the brain and spinal cord)
Schwann cells	Insulation (form myelin sheath in the peripheral nerves)

Myelin is formed in the vertebral peripheral nervous system by modified glial cells termed *Schwann cells*.[2] Unlike the oligodendrocyte, the Schwann cell myelinates only one axon, surrounding the axon and forming successive layers of plasma membrane. The resultant thickness is variable in different axons. The junction between adjacent Schwann cells is devoid of myelin at 1-mm intervals along the length of the axon. This nonmyelinated portion of the axon, the node of Ranvier, is the site of electrical impulse propagation. Impulses in myelinated axons travel from one node of Ranvier to another (saltatory conduction), bypassing the area between the nodes and increasing the velocity of conduction (see Figure 28-1). Wallerian degeneration results in the distal degeneration of the axon after peripheral nerve injury. Proximal axon degeneration also may occur. Within 1 week of the initial injury, Schwann cells proliferate to form a tube into the area of degeneration, forming a scaffold to direct axon regeneration. Myelin regeneration precedes axon regeneration, with the myelin eventually reaching its previous thickness.

Microglial cells are the smallest neuroglial cells and are scattered throughout the CNS. They are transported throughout the CNS to sites of neuronal injury or degeneration, where they proliferate and develop into large macrophages that phagocytize neuronal debris.

Ependymal cells line the roof of the third and fourth ventricles of the brain and the central spinal canal. Ependymal cells form the cuboidal epithelium (choroid plexus), which secretes cerebrospinal fluid (CSF).

Blood-Brain Barrier

The injection of an intravenous dye causes most of the body tissues and internal organs to be stained; yet the brain and spinal cord remain unblemished. This finding led to the discovery of the blood-brain barrier, which effectively isolates the brain and spinal cord extracellular compartment from the intravascular compartment.[3]

The endothelial cells of the CNS form tight junctions between adjacent cells, preventing the transport of polar substances from the intravascular to the cerebral extracellular fluid compartment. CNS endothelial cells lack transport mechanisms, so little intracellular transport takes place. A number of midline brain structures receive neurosecretory products from the blood and therefore lack a blood-brain barrier. These structures, the circumventricular organs, include the area postrema, pituitary gland, pineal gland, choroid plexus, and portions of the hypothalamus.[4]

The blood-brain barrier is incompletely developed in the newborn. The high vascular content of bile pigments in jaundiced newborns may enter the basal ganglia, producing kernicterus. Blood-brain barrier disruption can be caused by traumatic head injury, subarachnoid or intracerebral hemorrhage, or cerebral ischemia. The development of mass lesions also may produce blood-brain barrier disruption. Osmotically active substances may penetrate the brain or spinal cord after blood-brain barrier disruption. Intentional intracarotid injection of a hyperosmolar solution shrinks the endothelial cells, opens tight junctions, and disrupts the blood-brain barrier. This technique allows the delivery of chemotherapeutic drugs through the blood-brain barrier for the treatment of neural malignancy.[5,6]

ANATOMY OF THE CENTRAL NERVOUS SYSTEM

Cerebral Structures

The cerebral hemispheres are the most intricately developed and largest regions of the brain (Figure 28-2). They contain the cerebral cortex, hippocampal formation, amygdala, and basal ganglia. The cerebral cortex consists of the outer 3-mm layer of the cerebral hemispheres. The surface of the cerebral cortex is convoluted, increasing the surface area of the cerebral hemispheres. Elevated convolutions called *gyri* are separated by shallow grooves called *sulci* and by deeper grooves called *fissures*.

The medial longitudinal fissure divides the cerebral hemispheres into right and left halves. The lateral fissure of Sylvius and the central sulcus of Rolando divide each hemisphere into four lobes, which are named for the cranial bones that overlie each area. The frontal lobe, essential for motor control, and the parietal lobe, essential for the senses of pain and touch, are separated by the central sulcus. The cerebral cortex is divided into nearly 50 structurally distinct areas called Brodmann's areas (Figure 28-3). Voluntary muscle activity is controlled by the motor cortex located in the precentral gyrus, or Brodmann area 4. Brodmann's areas 1, 2, and 3 make up primary somtosensory area 1, also referred to as the somatosensory cortex. This area contains a high

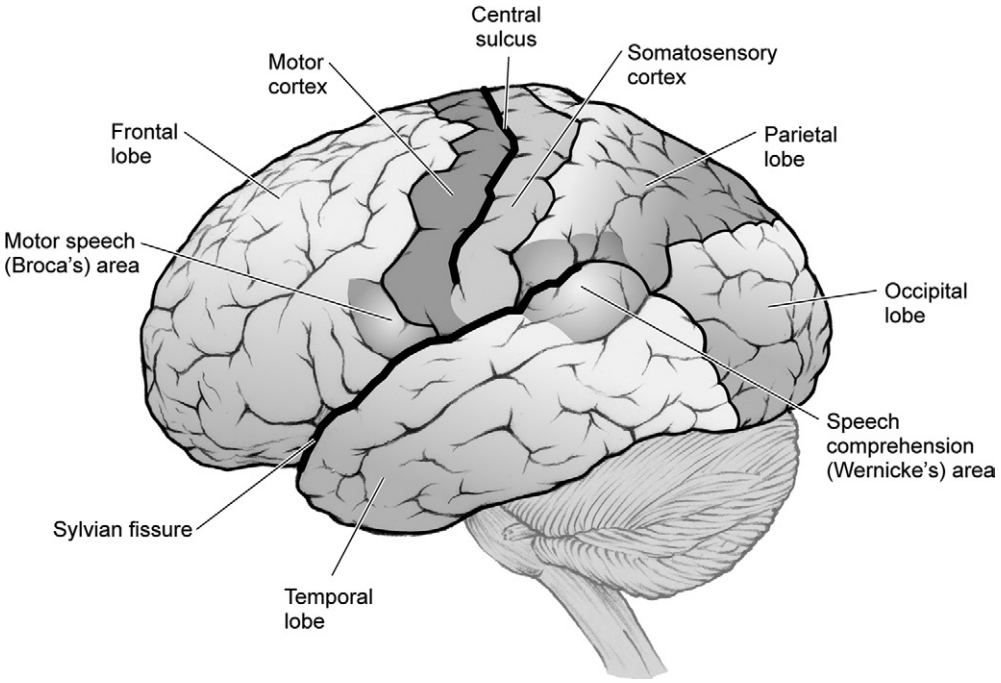

FIGURE **28-2** The cortex is highly convoluted with infoldings called *sulci* and bumps or ridges called *gyri*. Each hemisphere is divided into four major lobes: frontal, parietal, temporal, and occipital. Motor (Broca's) and receptive (Wernicke's) language areas are shown in the frontal and temporal-parietal lobes, respectively. (From Gupta AK, Gelb AW, eds. *Essentials of Neuroanesthesia and Neurointensive Care*. Philadelphia: Saunders; 2008:7.)

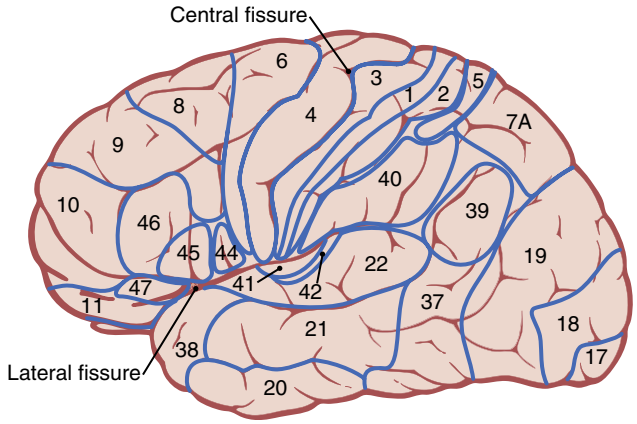

FIGURE **28-3** Structurally distinct areas, called Brodmann's areas, of the human cerebral cortex. Note specifically areas 1, 2, and 3, which constitute primary somatosensory area 1, and areas 5 and 7, which constitute the somatosensory association area. (From Hall JE. *Guyton and Hall Textbook of Medical Physiology*. 12th ed. Philadelphia: Saunders; 2011:575.)

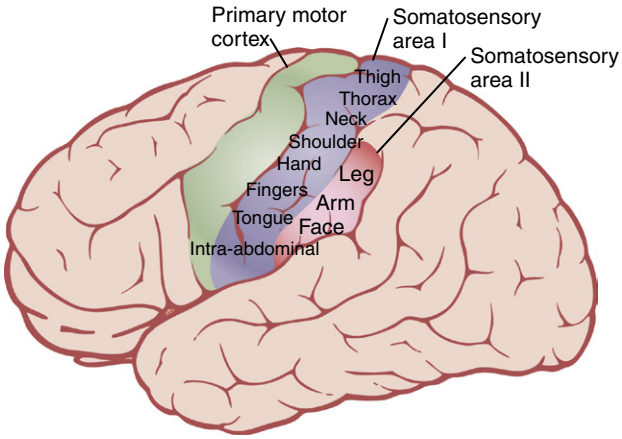

FIGURE **28-4** Two somatosensory cortical areas, somatosensory areas I and II. (From Hall JE. *Guyton and Hall Textbook of Medical Physiology*. 12th ed. Philadelphia: Saunders; 2011:575.)

degree of localization for various body parts, whereas areas 5 and 7 function as the somatosensory association area (Figure 28-4). The sensations of touch, pain, and limb position, as well as the sensory perception of grasped objects, are controlled by the somatic sensory cortex located in the postcentral gyrus of the parietal lobe. The temporal lobe, which contains the auditory cortex, is separated from the frontal and parietal lobes by the sylvian fissure. The occipital lobe lies posterior to the parietooccipital sulcus. Here the visual cortex lies within the walls of the calcarine fissure on the medial brain surface.

The corpus callosum lies deep in the longitudinal fissure and contains commissural fibers that interconnect the cerebral hemispheres. These fibers arise from neurons in one hemisphere and synapse with neurons in the corresponding area of the adjacent hemisphere. The remaining major structures of the cerebral hemispheres include the basal ganglia, the amygdala, and the hippocampal formation. The basal ganglia are involved in the control of movement. The amygdala functions in the regulation of emotional behavior, response to pain, and appetite and is essential in forming the response to stressors. The hippocampal formation is essential for memory formation and learning.

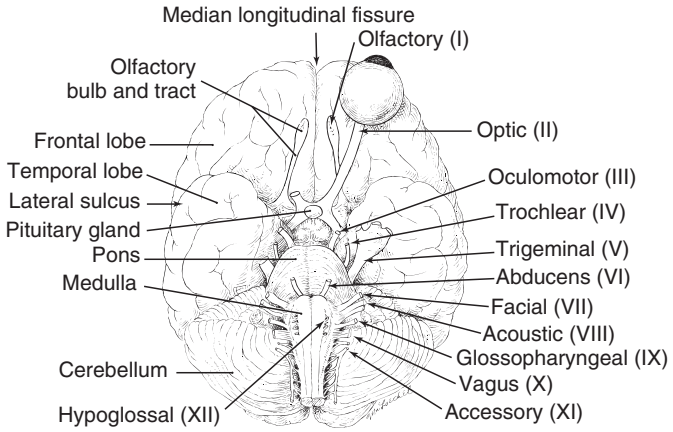

FIGURE **28-5** The pons and medulla and the origin of the cranial nerves.

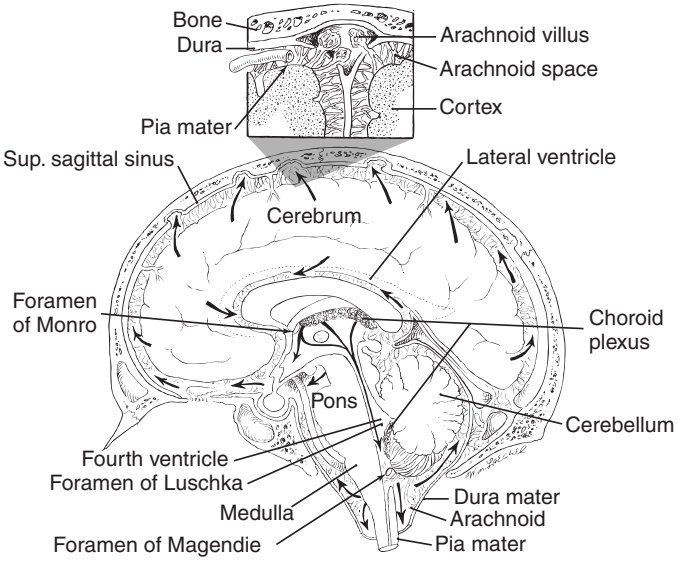

FIGURE **28-6** Meninges and the flow of cerebrospinal fluid through the ventricular system.

The diencephalon is located in the midline between the two cerebral hemispheres and contains two important structures—the thalamus and the hypothalamus. The oval-shaped thalamus integrates and transmits sensory information to various cortical areas of the cerebral hemispheres via separate thalamic nuclei. The hypothalamus is composed of several nuclei, including the mammillary bodies. The hypothalamus is the master neurohumoral organ.

The midbrain, pons, and medulla form the brainstem. The brainstem contains the reticular activating system, which functions to maintain consciousness, arousal, and alertness. The pons is anterior to the cerebellum, separated by the fourth ventricle, connecting the medulla oblongata and the midbrain (Figure 28-5). The pons contains ascending and descending fiber tracts and the nuclei of the trigeminal nerve (cranial nerve V) and the facial nerve (cranial nerve VII). The medulla extends from the pons to the foramen magnum, where it becomes continuous with the spinal cord (see Figure 28-5). In addition to ascending and descending fiber tracts, the medulla contains respiratory and cardiovascular control centers and the vestibulocochlear nerve (cranial nerve VIII), the glossopharyngeal nerve (cranial nerve IX), the vagus nerve (cranial nerve X), the spinal accessory nerve (cranial nerve XI), and the hypoglossal nerve (cranial nerve XII) nuclei.[7]

The cerebellum is convoluted in appearance and lies below the occipital lobe of the cerebral cortex and posterior to the pons and medulla. Structurally it resembles the cerebral cortex, containing an outer layer of gray matter and an inner core of white matter with several nuclei embedded within. The cerebellum can be divided into three functional areas. The flocculonodular lobe (archeocerebellum) is active in the maintenance of equilibrium, and the paleocerebellum (anterior lobe and part of vermis) regulates muscle tone. The neocerebellum (posterior lobe plus most of the vermis) is the largest subdivision of the cerebellum and is essential in coordinating voluntary muscle activity. The cerebellum integrates information received from other areas of the CNS and the peripheral nervous system. Information from the cerebellum is transmitted to the cerebral cortex and to lower motor neurons involved in the maintenance of muscle tone, equilibrium, and voluntary muscle activity.[7]

Meninges

The brain and spinal cord are enveloped by three meningeal layers: the dura mater, the arachnoid mater, and the pia mater (Figure 28-6). The dura mater, the thickest of the meningeal layers, overlies the cerebral hemispheres and brainstem and is functionally separated into an outer periosteal layer (adherent to the inner cranium) and an inner meningeal layer. The dura mater forms a fold, the falx cerebri, that functionally separates the cerebral hemispheres. A similar fold, the tentorium cerebelli, separates the occipital lobe and the cerebellum. The dura mater of the spinal cord is continuous with the meningeal layer of the cranial dura mater and the perineurium of the peripheral nerves. Innervation of the dura mater is provided by the first three cervical roots and the trigeminal nerve. During awake craniotomy, the patient may complain of pain "behind the eye" when traction is applied to the dura.

The arachnoid mater is a thin, avascular membrane joining the dura mater. The subdural space, a potential space between the dura mater and the arachnoid mater, is of clinical importance. The unintentional injection of local anesthetic during spinal anesthesia into the subdural space produces patchy, asymmetric block. In addition, injury to a blood vessel in the subdural space can create bleeding (subdural hematoma), requiring surgical intervention.

The pia mater is a thin avascular membrane adherent to the brain and spinal cord. The subarachnoid space lies between the arachnoid mater and the pia mater. In the spinal cord, the subarachnoid space extends to the S2 to S3 level and is filled with CSF. In addition, the vasculature that overlies the CNS is located within the subarachnoid space. Injury to the vascular structures may produce subarachnoid hemorrhage and hematoma.

The epidural space is located outside the dura but inside the spinal canal. The epidural space contains a venous plexus and epidural fat that provides protection of the neural structures. The distance from the skin to the epidural space may be as little as 3 cm or as large as 8 cm.

Cerebrospinal Fluid

CSF is contained within the ventricles of the brain, the cisterns surrounding the brain, and the subarachnoid space of the brain and spinal cord (see Figure 28-6). The total volume of cranial and spinal CSF in the adult is approximately 150 mL. The specific gravity is 1.002 to 1.009, and the pH is 7.32. CSF bathes the brain and spinal cord, cushioning these delicate structures, and controls and maintains the extracellular milieu for neurons and glial cells.

CSF is secreted by the ependymal cells of the choroid plexus within the ventricular system at a rate of approximately 30 mL/hr. Although CSF is isotonic with plasma, it is not a plasma filtrate. CSF concentrations of potassium, calcium, bicarbonate, and glucose are lower than their respective plasma concentrations, and concentrations of sodium, chloride, and magnesium are higher. The entire CSF volume is replaced every 3 to 4 hours. Normal CSF pressure is between 5 and 15 mmHg. CSF flows from the lateral ventricles of the cerebral hemispheres through the foramen of Monro into the third ventricle, through the aqueduct of Sylvius in the midbrain, into the fourth ventricle. CSF enters the subarachnoid space through the medial foramen of Magendie and the paired lateral foramina of Luschka, openings in the roof of the fourth ventricle.

The cisterna magna, located between the medulla and the cerebellum, is formed from the separation of the arachnoid mater from the pia mater and is filled with CSF. Two additional cisterns exist, the cisterna pontis and the cisterna basalis. CSF drains into the venous blood via the superior sagittal sinus and is absorbed by arachnoid granulations.

Spinal Cord

The spinal cord extends from the medulla at the foramen magnum to the filum terminale, a threadlike connective tissue structure that attaches to the first segment of the coccyx. Thirty-one pairs of spinal nerves carry motor and sensory information: 8 cervical, 12 thoracic, 5 lumbar, 5 sacral, and 1 coccygeal. The first pair of cervical nerves exits the spinal cord between the base of the skull and the first cervical vertebra (atlas), and the remaining 30 pairs exit between adjacent vertebrae. All of the exiting spinal nerves are covered with pia mater. Because the spinal cord is approximately 25 cm shorter than the vertebral canal in adults, the lumbar and sacral nerves have relatively long roots (the cauda equina). The spinal cord fills the canal in utero, but the canal elongates at a greater rate than does the neural tissue as the child ages, forming the cauda equina.

The spinal cord is divided into dorsal, lateral, and ventral regions by the entering dorsal sensory root fibers and the outgoing ventral motor root fibers. Neuron cell bodies and unmyelinated fibers lie in the H-shaped central gray region of the cord, surrounded by fiber tracts that form the white matter. Although it does not have a uniform appearance, this general arrangement continues throughout the entire spinal cord.

The spinal gray matter is divided into the ventral and dorsal gray commissures. The ventral projections of gray matter are called the *gray horns* or *columns;* the posterior projections are called the *posterior gray horns* or *columns*. Intermediolateral gray horns or columns are found between T1 and L2. The gray matter has been subdivided into 10 (I through X) laminae of Rexed. Rexed laminae I through VI are located in the dorsal (posterior) horn and contain cell bodies that receive sensory information from the periphery. Projections from the laminae form afferent tracts. A large number of interneurons are found in laminae V, VI, and X. Laminae VII, VIII, and IX make up the ventral (anterior) horn and contain motor neurons and interneurons involved in motor functions. The gray matter is enlarged in two areas of the spinal cord, C5 to C7 and L3 to S2. The cervical enlargement contains neuron cell bodies that innervate the upper extremities; the lumbosacral enlargement contains neuron cell bodies that innervate the lower extremities.

The tracts or fascicles that make up the white matter are highly organized, similar to the organization of the cerebral cortex and other areas of the brain. The dorsal white matter is composed almost exclusively of ascending sensory fiber tracts. The lateral and ventral white matter contain descending motor tracts. Commonly, fiber tracts at some level in the spinal cord or brain decussate, or cross over to the other side. As in the brain, spinal cord fiber tracts can be projection tracts connecting the spinal cord and brain, or they can be association (intersegmental, fasciculi proprii) tracts that originate and terminate entirely within the spinal cord. The association tracts play an important role in spinal reflexes.[7-10]

Shortly after leaving the spinal cord, the meningeal coverings of the peripheral nerves merge with the connective tissue layers that cover the peripheral nerve. The outermost covering of the peripheral nerve is called the *epineurium*. The bundles or fascicles of axons in each nerve are covered by the perineurium, and each axon in a fascicle is surrounded by the endoneurium.

Peripheral nerves may be classified according to their diameter. Generally, the larger the diameter, the faster the conduction velocity; therefore A alpha fibers, the fibers with the largest diameters, have the fastest conduction velocity, and C fibers, which have the smallest diameter, have the slowest conduction velocity. Between the two extremes lie A beta, A gamma, A delta, and B fibers, in decreasing order of size and conduction velocity. The degree of myelination affects the conduction velocity of the nerves.

PERIPHERAL NERVOUS SYSTEM

The peripheral nervous system is divided into the somatic and autonomic nervous systems (Figure 28-7). The somatic system contains sensory neurons for the control of skin, muscles, and joints. Somatic motor fibers arise from motor neurons in the ventral horn, their axons exiting the spinal cord via the ventral root. A few centimeters after leaving the spinal cord, the somatic motor fibers join with incoming sensory fibers carrying information from afferent receptors (muscles, skin, tendons, and joints) to form a mixed nerve. As a mixed nerve approaches its site of innervation, the motor and sensory fibers separate.

Cranial nerves emerge from the cranium. Cranial nerves provide sensory and motor innervation for the head and neck. The sensory cranial nerves include the olfactory nerve (cranial nerve I), optic nerve (cranial nerve II), and vestibulocochlear nerve (cranial nerve VIII); the motor cranial nerves include the oculomotor, trochlear, abducens, spinal accessory, and hypoglossal nerves; and the four mixed cranial nerves with both sensory and motor function are the trigeminal nerve (cranial nerve V), facial nerve (cranial nerve VII), glossopharyngeal nerve (cranial nerve IX), and vagus nerve (cranial nerve X). Table 28-2 lists cranial and peripheral nerve fiber types, locations, and functions.

The autonomic nervous system controls involuntary visceral functions and is composed of three subdivisions: the sympathetic, parasympathetic, and enteric nervous systems. The sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS) are functionally antagonistic.[8,11] The SNS and PNS originate within the CNS and require two efferent neurons—a preganglionic neuron originating within the CNS and a postganglionic neuron terminating within the effector organ (smooth muscle, cardiac muscle, or sweat gland). Autonomic fibers originating in the brain arise from cell bodies located in the brainstem. PNS fibers supplying the lower gastrointestinal tract and genitourinary systems arise from the sacral portion of the spinal cord.

Sympathetic Nervous System

Preganglionic neurons of the SNS originate in the intermediolateral gray horn of the spinal cord between the first thoracic (T1) and second or third lumbar vertebra (L2 or L3). The myelinated preganglionic axons (i.e., preganglionic fibers of the preganglionic

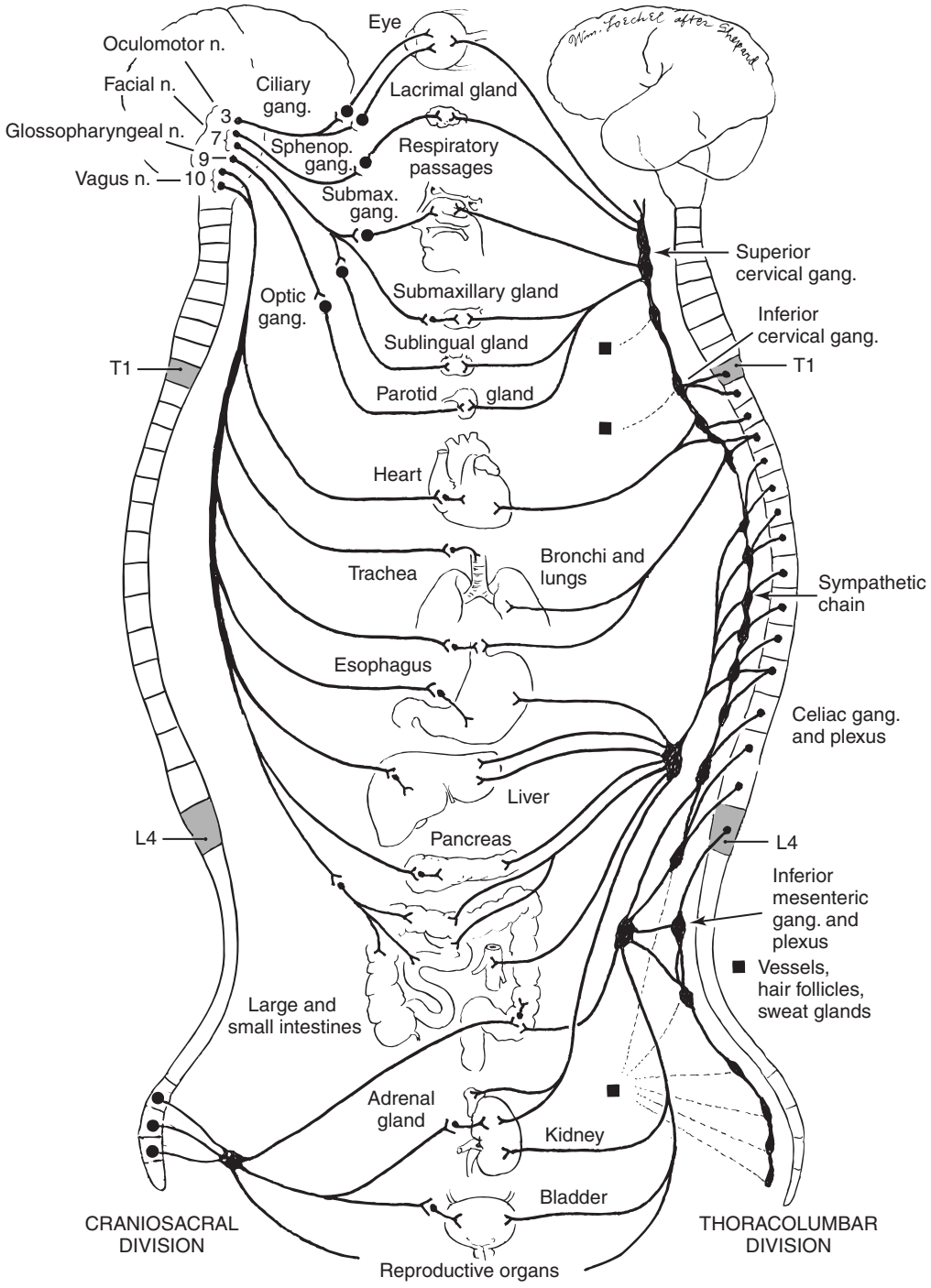

FIGURE **28-7** Both divisions of the autonomic nervous system. *gang.*, Ganglion; *n.*, nerve.

TABLE **28-2** Cranial and Peripheral Nerves

Fiber Type	Location	Information Conveyed
General somatic afferent	CN V, CN VII, CN IX, CN X, all spinal nerves	Pain, touch, temperature, pressure, and proprioception from muscles, tendons, and joint capsules
General visceral afferent	CN V, CN VII, CN IX, CN X, all spinal nerves	Conscious pain sensations
Special somatic afferent	CN II, CN VIII	Sight, hearing
Special visceral afferent	CN I, CN IX, CN X, CN VII (intermediate branch)	Olfaction, taste
Special visceral efferent	CN V, CN VII, CN IX, CN X, CN XI	Mastication, facial expressions
General somatic efferent	CN III, CN IV, CN VI, CN VII, all spinal nerves	Voluntary muscles (trunk and extremities), extrinsic muscles of eye, muscles of the tongue
General visceral efferent	CN III, CN VII, CN IX, CN X, spinal nerves T1 through L2 or L3, S2, S3, S4	Smooth muscle, cardiac muscle, some glands

CN, Cranial nerve.

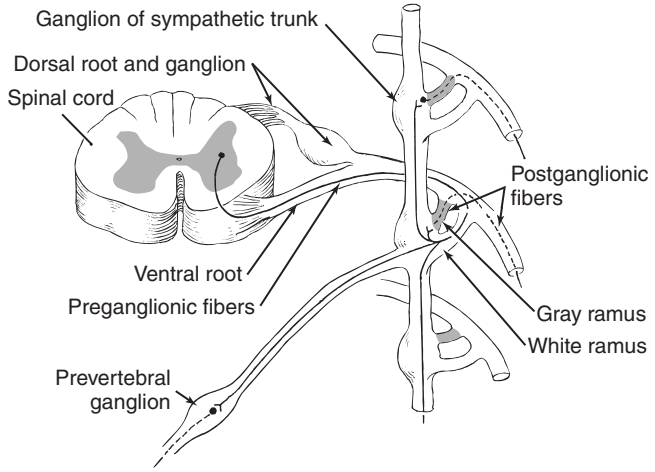

FIGURE **28-8** Sympathetic ganglia.

neurons) exit the spinal cord via the anterior (ventral) nerve root. These processes leave the spinal cord by way of a small trunk, the white rami communicans. A series of paired paravertebral ganglia is ranged bilaterally along the spinal cord (Figure 28-8). All of the paired segmental paravertebral ganglia are connected, forming the sympathetic trunks. These ganglia may contain the cell body of the second efferent neuron (postganglionic neuron). The preganglionic fibers of the preganglionic neuron enter the white rami communicans and may synapse with the second efferent neuron located within the ganglion. The postganglionic fiber of the postganglionic neuron may either exit the gray ramus to enter a spinal nerve or may extend through a connection between the paravertebral ganglion and one of the three (celiac, superior, or inferior) mesenteric ganglia. The postganglionic fibers then synapse with the smooth muscle of the digestive tract and other abdominal organs. SNS preganglionic axons secrete acetylcholine at their ganglionic synapses, and postganglionic fibers secrete norepinephrine.

Usually one paravertebral ganglion is present for each spinal nerve, except in the cervical area, where they fuse to form two or three ganglia. On entering the sympathetic chain, the preganglionic fiber may synapse at the entry level or travel up or down the ganglionic chain before forming a synapse. Some preganglionic axons pass through the sympathetic chain without synapsing and after leaving the chain form a distinct nerve (e.g., splanchnic nerve) before synapsing in prevertebral ganglia, such as the superior or inferior mesenteric ganglia. Some preganglionic axons in the sympathetic trunk synapse with several postganglionic neurons located in several chain ganglia. This arrangement explains the manner in which a central SNS discharge spreads over several segments. After synapsing in the sympathetic chain, the postganglionic axons, which are unmyelinated, enter the spinal nerve through the gray ramus communicans and travel to the periphery.

The cervical ganglia are divided into superior, medial, and inferior cervical ganglia. The inferior cervical ganglion fuses with the first thoracic ganglion to form the stellate ganglion. Stimulation of SNS fibers from the superior cervical ganglion produces contraction of the radial muscle of the iris (mydriasis), relaxation of the ciliary muscle of the eye, and constriction of the blood vessels of the head. Destruction of the superior cervical ganglion, central SNS damage, or injury to other cervical paravertebral ganglia produces Horner syndrome, clinically distinguished by miosis, anhydrosis (absence of sweating), and ptosis on the affected side. Ptosis is incomplete because the primary innervation to the levator palpebrae superioris muscle of the eyelid is through the oculomotor nerve, and only a few SNS fibers innervate this muscle.

Postganglionic fibers from the upper thoracic chain ganglia (stellate to T4 to T5) innervate the heart and lungs. β-Receptor stimulation produces an increased heart rate (positive chronotropic effect), an increase in conduction (positive dromotropic effect), and an increase in myocardial contractility (positive inotropic effect). Myocardial α-receptor stimulation produces coronary vasoconstriction. The resultant pulmonary effects also depend on the receptor type that is stimulated; bronchial dilation follows β_2-receptor stimulation, and mild bronchoconstriction follows α-receptor stimulation.

The SNS fibers supplying abdominal and pelvic viscera (T5 through L3) pass through the chain ganglia forming the greater and lesser splanchnic nerves, which subsequently terminate in preterminal ganglia. Postganglionic fibers from the prevertebral ganglia, such as the superior and inferior mesenteric ganglia, travel to the abdominal and pelvic viscera. Stimulation of these SNS fibers activates liver glycogenolysis and gluconeogenesis, decreases secretions from pancreatic acinar cells and β-cells, initiates lipolysis, decreases the tone and motility of the gastrointestinal tract, contracts gastrointestinal sphincters, relaxes urinary smooth muscle, and increases renin secretion from the kidney.

Parasympathetic Nervous System

The efferent neurons of the parasympathetic subdivision are located in the gray matter of the midbrain and medulla. The preganglionic fibers exit the brain via cranial nerves II, VII, IX, and X. The remainder of the cell bodies of the first efferent neurons arise from the lateral horn of the sacral portion of the spinal cord (S2 through S5). Acetylcholine is secreted by both parasympathetic preganglionic and postganglionic fibers (see Figure 28-8).

The second efferent neuron (postganglionic neuron) of the parasympathetic subdivision may be located in a small ganglion adjacent to the innervated organ or within the organ itself. Preganglionic axons travel with the vagus to ganglia located near the organ they innervate. The postganglionic axons innervate the bronchioles, heart, coronary arteries, stomach, and large intestine up to the left colic flexure. PNS postganglionic fibers to the descending colon and the genitourinary systems are supplied by parasympathetic fibers from sacral segments of the spinal cord. Most of the parasympathetic preganglionic fibers originate at the S3 and S4 segments. Shortly after exiting the spinal cord with the spinal nerves, the preganglionic fibers form the pelvic nerves (nervi erigentes), which synapse in ganglia in close proximity to the innervated organ.

VASCULATURE OF THE CENTRAL NERVOUS SYSTEM

The brain and spinal cord are dependent on an uninterrupted blood supply to deliver the essential fuels, oxygen, and glucose (Figure 28-9). The brain receives 15% of the cardiac output, or approximately 50 mL/100 g/min. The brain's blood supply originates from two arterial circulations that receive blood from two distinct systemic arteries: the anterior circulation receives blood from the carotid arteries, and the posterior circulation receives blood from the vertebral arteries. These arterial systems communicate through arterial anastomoses that form the circle of Willis. The paired anterior, middle, and posterior cerebral arteries originate from the circle of Willis. Although these arterial communications exist, under normal conditions, little mixing of blood flow occurs. Intraarterial contrast studies demonstrate that the carotid

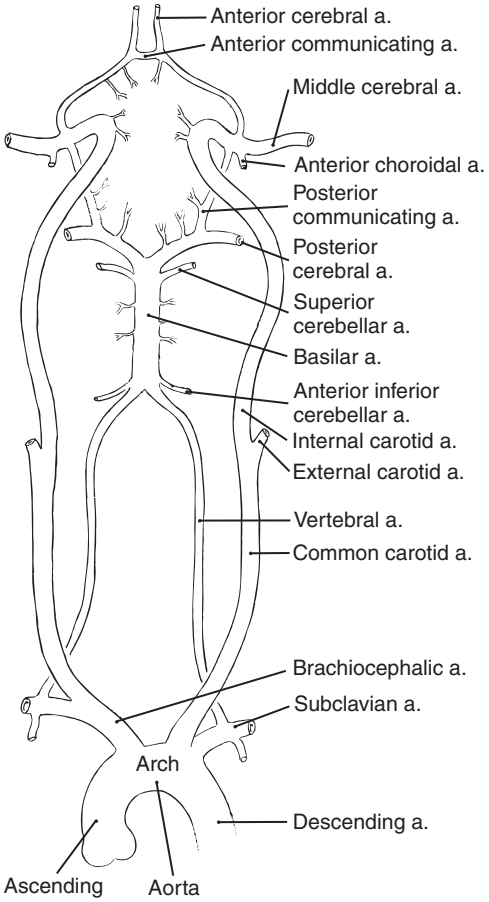

FIGURE **28-9** Cerebral vasculature. *a.*, Artery.

artery supplies the ipsilateral cerebral hemisphere, and the vertebrobasilar system supplies the structures of the posterior fossa.

The internal carotid arteries enter the skull through the foramen lacerum and bifurcate near the lateral border of the optic chiasm, forming the anterior and middle cerebral arteries. The anterior cerebral arteries supply the medial surface of the cerebral hemispheres, and the middle cerebral arteries supply the lateral surface of the hemispheres. The striate arteries, which are branches of the middle cerebral arteries, supply the internal capsule and its motor tracts. Cerebrovascular accidents commonly involve the striate arteries. Communicating arteries provide connections between the two anterior cerebral arteries of each hemisphere (anterior communicating arteries) and between the middle and posterior cerebral arteries (posterior communicating arteries).

The vertebral arteries, branches of the subclavian artery, enter the cranium through the foramen magnum and join to form the basilar artery in the vicinity of the pons. Branches of the vertebral and basilar arteries supply a wide area, including the cervical region of the spinal cord, the brainstem, the cerebellum, the vestibular apparatus and cochlea of the inner ear, parts of the diencephalon, and the occipital and temporal lobes of the cerebral hemispheres.

Venous blood exits the brain via two separate systems. The blood from the cerebral and cerebellar cortex flows through veins on the surface and empties into overlying dural venous sinuses. Venous blood from the basal portions of the brain empties into the great vein of Galen and the straight sinus. These sinuses empty into the internal jugular veins. The superficial veins of the scalp are linked to the dural sinuses by the emissary veins.[7,8]

Like the brain, the spinal cord receives blood from two arterial sources: the anterior and posterior spinal arteries, which are branches of the vertebral artery, and the radicular arteries, which are branches of segmental vessels (cervical, intercostal, and lumbar). The spinal cord blood supply is not continuous along its length, and although each spinal cord segment is perfused, blood is delivered preferentially by one of the supply sources. The cervical cord is supplied by the vertebral and radicular arteries, and the thoracic and lumbar cord is supplied by the radicular arteries arising from this respective region (intercostal and lumbar). Of particular importance is the radicular artery, the artery of Adamkiewicz, which enters the cord at approximately T7 and supplies the lumbosacral segment. Spinal cord segments that receive blood from one source are particularly prone to ischemic injury if this blood supply is interrupted. Interruption of the blood flow from the artery of Adamkiewicz results in paraplegia.

ELECTROPHYSIOLOGY

The physiologic basis for the propagation of a nerve impulse lies in the structural nature of the axolemma, the differential concentration of electrolytes within the axolemma and extracellular space, and the semipermeability of the axolemma to these specific ions. The resting nerve cell has a potential difference, or voltage, created by the asymmetric distribution of sodium and potassium ions. Sodium ions are 10-fold richer in the extracellular medium, and potassium ions are 10-fold richer in the intracellular medium. The resting membrane potential is created through the excess positive charges on the extracellular surface and excess negative charges on the interior of the cell membrane. The nerve cell is said to be *polarized* in the resting state.

In the resting state, the cell membrane permeability to sodium ions is low, so little movement of extracellular sodium ions to the cell interior occurs. Although larger than sodium ions, potassium ions are freely permeable through the axolemma, and their movement creates a net deficit of positive ions within the interior of the axolemma. This ionic asymmetry is maintained by the sodium-potassium adenosine triphosphate (ATP) pump. The distribution of ions outside the cell produces a negative resting membrane potential of approximately −60 to −90 mV.

Nerve impulses are transmitted through action potentials that are generated with membrane alterations in permeability of the axolemma to sodium and potassium ions. Depolarization occurs when a stimulus of sufficient intensity (threshold potential) increases membrane permeability to sodium ions, facilitating the passage of a greater number of sodium ions into the cell interior than potassium ions to the cell exterior. The lowering of the voltage difference of the axolemma occurs as a result of "gating," or the opening or closing of integral membrane proteins. Gating occurs in response to voltage differences across the axolemma (voltage-gated channel) or after the binding of a specific molecule to a receptor or channel protein (chemically gated channel, e.g., the binding of acetylcholine to the neuromuscular junction).

Sodium channels open when the threshold potential is reached, facilitating a rapid influx of sodium into the axolemma interior and producing depolarization (Figure 28-10). The initial flow of sodium ions results in the opening of additional sodium channels. The action potential develops as the cell interior undergoes a transition from negative to positive. At the peak of depolarization, the electrical potential is 30 to 40 mV higher than the cell exterior, and sodium channels close. The action potential develops as a result of the change from the resting potential of −60 to −90 mV to a peak of 30 to 50 mV at the completion of depolarization. The

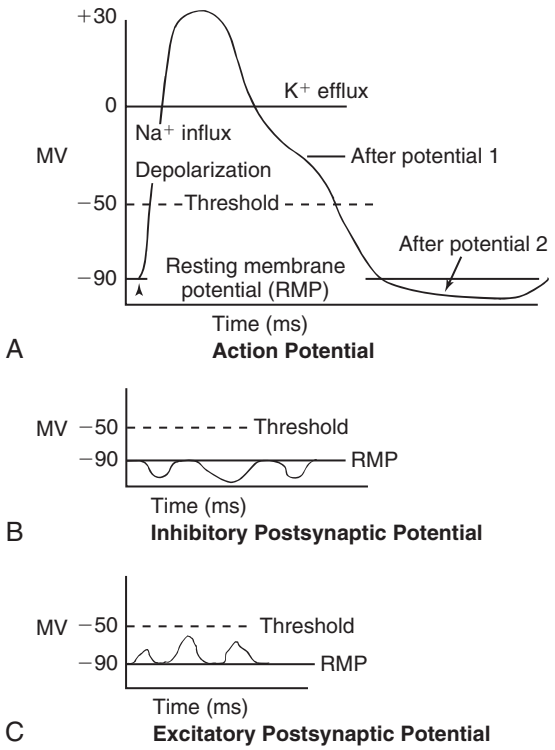

FIGURE **28-10** **A,** Phases of the action potential (AP) and major ionic movements during the AP. **B** and **C,** Subthreshold changes in the resting membrane potential.

action potential cannot occur without the delivery of a stimulus, or critical threshold potential.

For myelinated mammalian nerves, the threshold potential is 20 to 30 mV less than the resting potential. This threshold potential can be modified by a variety of factors, including pH, partial pressure of oxygen (P_{O_2}), and partial pressure of carbon dioxide (P_{CO_2}). Alkalosis increases neuronal excitability, and hypoxemia and acidosis depress neuronal excitability.

After depolarization, cell repolarization is initiated with the closing of sodium channels and the opening of potassium channels, allowing the flow of potassium ions to the exterior of the axolemma to return the axon to the resting potential of −60 to −90 mV. The sodium pump is active in reestablishing this ionic asymmetry. During repolarization, the axon is refractory, or unable to respond to an additional stimulus, no matter how strong (it will not respond to an action potential). In the later phases of repolarization, the axolemma is in a state of ready refractoriness, that is, depolarization can be initiated only by a stimulus with an intensity greater than that which produced the original depolarization.

Chemical, mechanical, and electrical stimulation may elicit an action potential. Mechanical stimulation via pinching or crushing increases the membrane's permeability to sodium ions. The resulting change in ion permeability determines whether the postsynaptic neuron is either excited or inhibited.

Tissues whose sodium channels are not completely closed at rest (cardiac and smooth muscle) have a constant leak of sodium inside the cell, and excitation occurs by electrical stimulation to produce an action potential. Because these tissues repetitively discharge, they are described as having *rhythmicity*. The usual resting membrane potential of cells displaying rhythmicity is −60 to −70 mV. After stimulation, a wave of depolarization is transmitted to the axon terminal. At electrical synapses, the wave of depolarization crosses the 2-nm synaptic space and spreads to the postsynaptic cell (neuron or muscle cell).

Synaptic Transmission

After depolarization, the flow of information is transmitted to adjacent neurons at specialized membrane sites called *synapses* (see Figure 28-1). Synapses are present on dendrites and axons. Synapses may be present on axon terminals of specific neurons in contact with endocrine glands (e.g., salivary glands) or skeletal muscle. The neuron sending the information is the presynaptic neuron, and the receiving neuron is the postsynaptic neuron. Separating the presynaptic and postsynaptic neurons is a small intracellular space (the synaptic cleft). The majority of synaptic transmission occurs in the direction from the presynaptic to the postsynaptic neuron, but retrograde nerve impulse conduction is known to occur and modulates the strength of synaptic connections.

Synaptic transmission may be electrically or chemically mediated. Electrically mediated synapses are large compared with chemically mediated synapses. Electrical synapses have direct cytoplasmic continuity and no synaptic delay. Electrical synapses are excitatory in nature and are located in the CNS, peripherally in smooth muscle, and in cardiac muscle. Synaptic delays (delayed synaptic transmission) occur in chemically mediated transmission because of the transit time of the chemical mediator (specific neurotransmitter) from the presynaptic terminal to the postsynaptic membrane.

The majority of CNS neurons have chemically mediated synapses. The presynaptic neuron releases a neurotransmitter, a low-molecular-weight compound that diffuses across the synaptic cleft and binds to specific receptors on the postsynaptic membrane. Depolarization stimulates the uptake of calcium by the nerve terminal, fusing intracellular vesicles that contain the neurotransmitter to the presynaptic membrane. The neurotransmitters are subsequently released into the synaptic cleft. The neurotransmitter diffuses across the synaptic cleft, interacting with a specific postsynaptic receptor. Neurotransmitters that increase the permeability of the axolemma to sodium ions are excitatory (e.g., acetylcholine, glutamate); neuroinhibitory neurotransmitters (e.g., γ-aminobutyric acid [GABA], glycine) hyperpolarize the membrane by increasing the permeability to chloride ions. The neurotransmitter serotonin excites some neurons and inhibits others. The attachment of the neurotransmitter to the postsynaptic receptor can produce either an immediate (fraction of millisecond) or a delayed (from a few milliseconds up to seconds) effect on the postsynaptic membrane. The delayed transmission involves second messengers, such as cyclic adenosine monophosphate and cyclic guanosine monophosphate, which are activated when the neurotransmitter attaches to the postsynaptic membrane.

NEUROTRANSMITTERS

Neurotransmitters are molecules contained within the presynaptic neuron that are discharged in a calcium-dependent manner after presynaptic depolarization and interact with specific receptors on the postsynaptic membrane. More than 100 molecules meet these criteria. Acetylcholine is an excitatory neurotransmitter that interacts with both nicotinic and muscarinic receptors. Additional neurotransmitters include biogenic amines (e.g., epinephrine, norepinephrine, dopamine, serotonin, histamine), amino acids (e.g., aspartate, glycine, GABA, glutamate), neuropeptides (e.g., substance P, the opioids, several hormones), and the second messenger nitric oxide (Table 28-3).

The synthesis of neurotransmitters occurs within the presynaptic neuron terminal. The neuron regulates the synthesis,

TABLE 28-3 Common Neurotransmitters

Class	Neurotransmitter
Monoamines	Epinephrine Norepinephrine Dopamine 5-Hydroxytryptamine (serotonin) Histamine
Amino acids	γ-Aminobutyric acid Glycine Glutamate
Neuropeptides	Calcitonin family Calcitonin Calcitonin gene-related peptide Hypothalamic hormones Oxytocin Vasopressin Hypothalamic releasing and inhibitory hormones Corcicotropin-releasing factor (CRF or CRH) Gonadotropin-releasing hormone (GnRH) Growth hormone-releasing hormone (GHRH) Somatostatin Thyrotropin-releasing hormone (TRH) Neuropeptide Y family Neuropeptide Y (NPY) Neuropeptide YY (PYY) Pancreatic polupeptide (PP) Opioid peptides β-Endorphin (also a pituitary hormone) Dynorphin peptides Leu-enkephalin Met-enkephalin Pituitary hormones Adrenocorticotropic hormone (ACTH) α-Melanocyte-stimulating hormone (α-MSH) Growth hormone (GH) Follicle-stimulating hormone (FSH) Luteinizing hormone (LH) Tachykinins Neurokinin A (substance K) Neurokin B Neuropeptide K Substance P VIP-Glucagon family Glucagon Glucagon-like peptide (ARP) Bradyknin Cholecystokinin (CKK; multiple forms) Cocaine- and amphetamine-regulated transcript (CART) Galanin Chrelin Melanin-concentrating hormone (MCH) Neurotensin Orexins (or Hypocretins) Orphanin FQ (or Nociceptin) (also grouped with opioids)
Other	Acetylcholine Nitric oxide

packaging, release, and degradation of the synthesized neurotransmitter. The enzymes essential for neuron transmitter synthesis are obtained by axonal transport and taken into the nerve terminal by transport proteins. The synthesized neurotransmitter is then packaged into synaptic vesicles by membrane transport proteins.

Acetylcholine

Acetylcholine is an excitatory neurotransmitter with a widespread distribution. It is the predominant neurotransmitter within the CNS, at the neuromuscular junction, within all autonomic nervous system preganglionic fibers and postganglionic parasympathetic fibers, and within postganglionic sympathetic fibers innervating sweat glands. Acetylcholine is synthesized in the presynaptic nerve terminal from acetic acid, coenzyme A, and choline in the presence of the enzymes acetyl kinase and choline acetylase. This enzyme is also referred to as *choline acetyl transferase*. Acetylcholine is packaged in vesicles and stored in the presynaptic terminal. Calcium uptake into the presynaptic terminal is required for acetylcholine release, and magnesium (Mg^{2+}) and manganese (Mn^{2+}) block the uptake of Ca^{2+} and the subsequent release of acetylcholine. Acetylcholine interacts with the postsynaptic receptor for a few milliseconds before being hydrolyzed by acetylcholinesterase to acetic acid and choline. Both the acetic acid and the choline are taken up by the presynaptic nerve terminal and recycled.

Cholinergic receptors are classified as either nicotinic or muscarinic. Nicotinic receptors are found in autonomic ganglia and at the neuromuscular junction. Muscarinic receptors are found on smooth muscle, cardiac muscle, and sweat glands. Acetylcholine is the neurotransmitter at cranial nerve nuclei and ventral horn motor neurons of the spinal cord, including various collateral nerves to Renshaw cells (interneurons). Acetylcholine may be interactive in neuronal circuits involved with pain reception. Acetylcholine also may act as a sensory transmitter in thermal receptors and taste bud endings.

Biogenic Amines

The biogenic amines include epinephrine, norepinephrine, dopamine, serotonin, and histamine. The catecholamines epinephrine, norepinephrine, and dopamine are synthesized in a series of hydroxylation, decarboxylation, and methylation reactions from the amino acids phenylalanine and tyrosine. The adrenal medulla secretes both epinephrine (75%) and norepinephrine (25%). Postganglionic adrenergic neurons secrete norepinephrine; norepinephrine and dopamine are probably neurotransmitters within the CNS. Amacrine cells of the retina and some neurons of the intrinsic nervous system of the intestine secrete dopamine. As with acetylcholine, the release of norepinephrine, epinephrine, and dopamine is calcium dependent. One notable difference from acetylcholine is that norepinephrine and dopamine act by means of second messengers (slow synaptic transmission), whereas most of the actions of acetylcholine are directly on ion channels (fast synaptic transmission). The duration of effect of catecholamines is regulated by presynaptic reuptake. Enzymatic breakdown of catecholamines by monoamine oxidase and catechol-*O*-methyltransferase within the liver is primarily responsible for terminating their effects.

Dopamine is an inhibitory neurotransmitter and the predominant biogenic amine within the CNS. Dopamine is concentrated within the basal ganglia. Dopamine's inhibitory effects occur through action on adenylate cyclase, which is dopamine sensitive.

Norepinephrine is concentrated in the reticular activating system and the hypothalamus. Norepinephrine acts as an inhibitory neurotransmitter, inhibiting impulses to the cerebral cortex.

Serotonin is an inhibitory neurotransmitter that influences behavior and mood. Histamine is also an inhibitory neurotransmitter concentrated within the hypothalamus and the reticular activating system. Histamine requires the second messenger cyclic adenosine monophosphate to mediate its inhibitory effects.

Amino Acids

Glutamate is the primary excitatory transmitter found within the cerebral cortex, the hippocampus, and the substantia gelatinosa of the spinal cord.[12] Glutamate plays a formidable role in learning and memory (perhaps interactive in memory formation during awareness during anesthesia) and the appreciation of pain. Glutamate also has been implicated in excitotoxic neuronal injury after ischemic or traumatic brain injury.

Glutamate is formed from the deamination of glutamine supplied by the Krebs cycle. Glutamate may activate either an inotropic or a metabotropic amino acid receptor. *N*-methyl-D-aspartate (NMDA) receptors are ligand-gated inotropic receptors that produce a conformational change in the receptor, opening a sodium channel, which results in the depolarization of the postsynaptic membrane. The metabotropic receptor is an integral transmembrane receptor that regulates intracellular second messenger systems.[13]

GABA is the major inhibitory neurotransmitter found in the CNS. It is concentrated in the basal ganglia, cerebral cortex, cerebellum, and spinal cord. Activation of the GABA receptor opens neuronal membrane chloride channels, producing hyperpolarization (the hyperpolarized neuron is resistant to excitation). GABA is important in antagonizing the excitatory effects of amino acid neurotransmitters.[14]

Glycine is the primary inhibitory neurotransmitter in the spinal cord. In the past, glycine irrigation was employed during transurethral resection of the prostate. Postoperative visual impairment after the intravascular absorption of glycine suggests that glycine may act as an inhibitory neurotransmitter within the retina.

Neuropeptides

Neuropeptides are either excitatory or inhibitory. Common neuropeptides include the opioids, substance P, and many pituitary and pancreatic islet hormones.

Substance P is an excitatory neurotransmitter found in the striatum and substantia nigra of the basal ganglia, hypothalamus, brainstem (raphe nuclei), and dorsal root ganglia of the spinal cord. Substance P is released by pain-fiber terminals that synapse with the substantia gelatinosa of the spinal cord.

The opioid neuropeptides include β-endorphin, enkephalins, dynorphins, and endomorphins. They act at opiate receptors distributed throughout the brain and spinal cord. Three classes of opiate receptors have been identified—delta, kappa, and mu. Dynorphin is a potent agonist at kappa receptors, and the enkephalins are agonists at delta and mu receptors. Opiate alkaloids like morphine interact with mu receptors. Morphine-like agents block slow pain pathways, raise the pain threshold, and modify the response to pain. Other effects, such as miosis and respiratory depression, result from the actions of these agents on opiate receptors located in the parts of the brain that control these functions.[2,10,15]

SENSORY PATHWAYS

Sensory or afferent pathways transmit pain, temperature, pressure, touch, vibratory sense, and proprioceptive information to the CNS. Sensory pathways also include the special senses of vision, taste, hearing, smell, and equilibrium.

Receptors for pain and temperature are located in the epidermis and the dermis; those for pressure, touch, vibratory sense, and proprioception are located in the dermis. Receptors can be classified as (1) exteroceptors, which are located near the surface of skin and oral mucosa, and (2) proprioceptors, which are located in deeper skin layers, joint capsules, ligaments, tendons, muscles, and periosteum. Several types of receptors exist. Pacinian corpuscles are

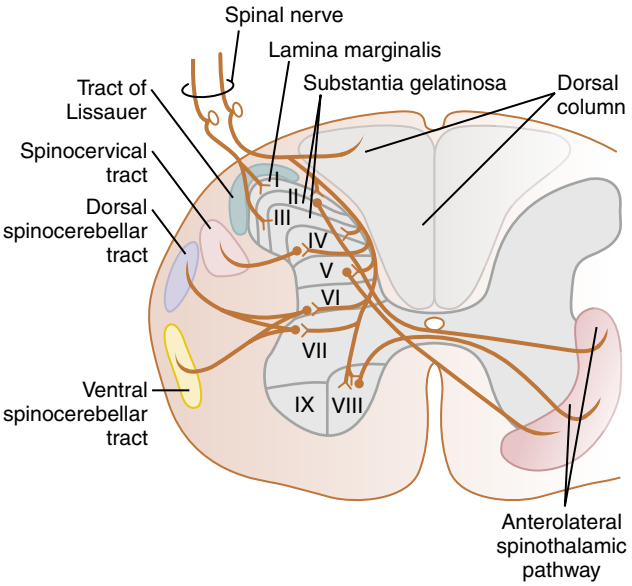

FIGURE **28-11** Cross section of spinal cord, showing the anatomy of the cord gray matter and of ascending sensory tracts in the white columns of the spinal cord. (From Hall JE. *Guyton and Hall Textbook of Medical Physiology*. 12th ed. Philadelphia: Saunders; 2011:573.)

receptors for vibration and pressure. Free nerve endings, Ruffini corpuscles, muscle spindles, and Golgi tendon organs are involved in movement sense. The receptors for light (or crude) touch sensations include Merkel disks, Meissner corpuscles, and the nerve plexuses surrounding some hair roots. Fibers travel from these receptors to a ganglion, where they synapse with first-order neurons, the fibers of which continue to the CNS. Fibers from receptors in the trunk and extremities travel to the dorsal root ganglion, where they synapse with first-order neurons. Most of the sensory fibers from the head, excluding those from the special sense organs (hearing, equilibrium, vision, taste, and smell), synapse in first-order neurons located in the semilunar or trigeminal ganglion.[10,11]

Pain and Temperature Pathways

Pain and temperature fibers from the head synapse in the trigeminal ganglion and enter the pons, forming the trigeminal nerve (cranial nerve V). These fibers subsequently synapse with second-order neurons in the nucleus of the descending tract of cranial nerve V. The second-order axons cross to the ventrolateral side and ascend as the ventral trigeminal tract to the ventral posteromedial nucleus of the thalamus, where they synapse with third-order neurons. From the ventral posteromedial thalamic nucleus, third-order axons ascend in the internal capsule and end in the postcentral gyrus of the cerebral cortex, which is the primary somatic sensory area of the brain.

Pain and temperature receptors in the skin of the trunk and extremities send signals to the spinal cord via the dorsal roots of the spinal nerves. The majority of these dorsal root sensory nerve fibers terminate in the dorsal horn on laminae I, IV, V, and VI (Figure 28-11). This is the origination site of the anterolateral pathway for signal transmission up the spinal cord to the brain.[16] From this point in the dorsal horn, the anterolateral fibers decussate (cross) in the ventral commisure to the opposite anterior and lateral white columns (Figure 28-12). The fibers then ascend cephalad via the anterior spinothalamic and lateral spinothalamic tracts to the ventral posterolateral thalamic nucleus, where they synapse with third-order neurons. Axons from the third-order neurons

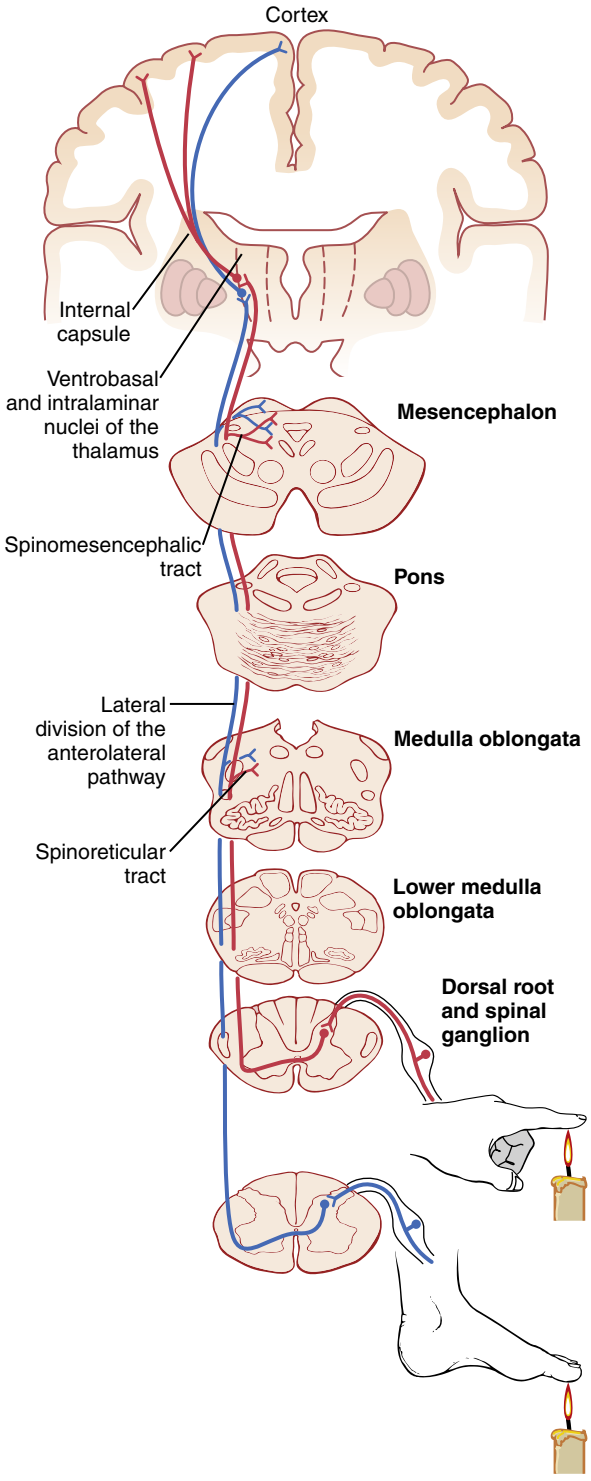

FIGURE **28-12** Pain, temperature, and crude sensations travel via the anterior spinothalamic and lateral spinothalamic tracts. (From Hall JE. *Guyton and Hall Textbook of Medical Physiology.* 12th ed. Philadelphia: Saunders; 2011:581.)

travel in the posterior limb of the internal capsule and ultimately synapse in the postcentral gyrus, where sensations of pain, temperature, touch, and pressure are interpreted, and responses to the sensations are initiated.

Some pain and temperature fibers in the dorsal horn give off branches that synapse with internuncial (messenger) neurons. The internuncial neurons have axons that synapse with motor neurons in the ventral horn, which are not necessarily at the same level of the spinal cord. The axons can cross over and travel up or down the spinal cord before synapsing. These circuits are part of the reflex response to pain, which results in a rapid, automatic response to nociceptive stimuli.

The afferent fibers from each dorsal root ganglion come from a relatively limited area of the skin termed a *cutaneous dermatome*. Some overlap exists, so if a spinal nerve that supplies a certain dermatome is severed, pain and temperature sensations from that dermatome are supplied by adjacent dermatome fibers. For example, if T6 is severed, T5 and T7 sensory neurons carry pain and temperature sensations from the skin area supplied by T6. Axons entering the dorsal horn from the dorsal root ganglion send branches to one spinal segment above and one segment below in the dorsolateral column of Lissauer.[2,9,11,17]

Pressure and Crude Touch

Pressure and crude (light) touch fibers from the head synapse with first-order neurons in the trigeminal ganglion. From the trigeminal ganglion, first-order axons travel to the pons, where they synapse with second-order neurons in the sensory nucleus of cranial nerve V. From the sensory nucleus of cranial nerve V, second-order axons form the dorsal trigeminal tract, which has both crossed and uncrossed fibers. The second-order fibers terminate in the ventral posteromedial nucleus of the thalamus. Third-order axons from the ventral posteromedial nucleus subsequently terminate in the postcentral gyrus of the cerebral cortex.

After leaving the dorsal root ganglion, crude touch and pressure fibers from the extremities and trunk enter the dorsal white column on the ipsilateral side and bifurcate (see Figure 28-12). One branch immediately enters the dorsal gray horn and synapses with second-order neurons. The other branch ascends for up to 10 spinal segments before synapsing with the second-order neurons in the dorsal horn. Second-order axons from both branches cross over and enter the ventral white column, forming the ventral spinothalamic tract, which ascends to the thalamus and synapses with third-order neurons in the ventral posterolateral nucleus. Tertiary axons travel through the internal capsule to the postcentral gyrus.

Owing to the branching arrangement of the first-order fibers from the trunk and extremities, injuries to the spinal cord rarely result in the total loss of these two sensations. Each cerebral cortex receives both crossed and uncrossed pressure and light-touch fibers from the face; as a result, damage to the postcentral gyrus on one side does not result in loss of pressure and crude touch sensations to the face, even though these sensations are lost on the trunk and extremities of the contralateral side.[2,10,11,17]

Vibratory Sense, Proprioception, and Discriminatory Touch

Proprioceptive fibers from muscles of the face involved in facial expression and mastication synapse in cell bodies located in the mesencephalic nucleus of the midbrain. Little is known about the rest of the pathway.

Fibers from the trunk and extremities carrying proprioceptive, vibratory, and discriminatory (fine) touch sensations synapse with neuron cell bodies in the dorsal root ganglion. From the dorsal root ganglion, first-order axons enter the dorsal white column and immediately ascend to the medulla (Figure 28-13). The fibers are somatotopically organized in the white columns. Axons from the lumbar and sacral parts of the spinal cord travel medially in the fasciculus gracilis, and fibers from the cervical and thoracic areas of the cord are located laterally in the fasciculus cuneatus of the dorsal white column of the spinal cord. Each fasciculus terminates in

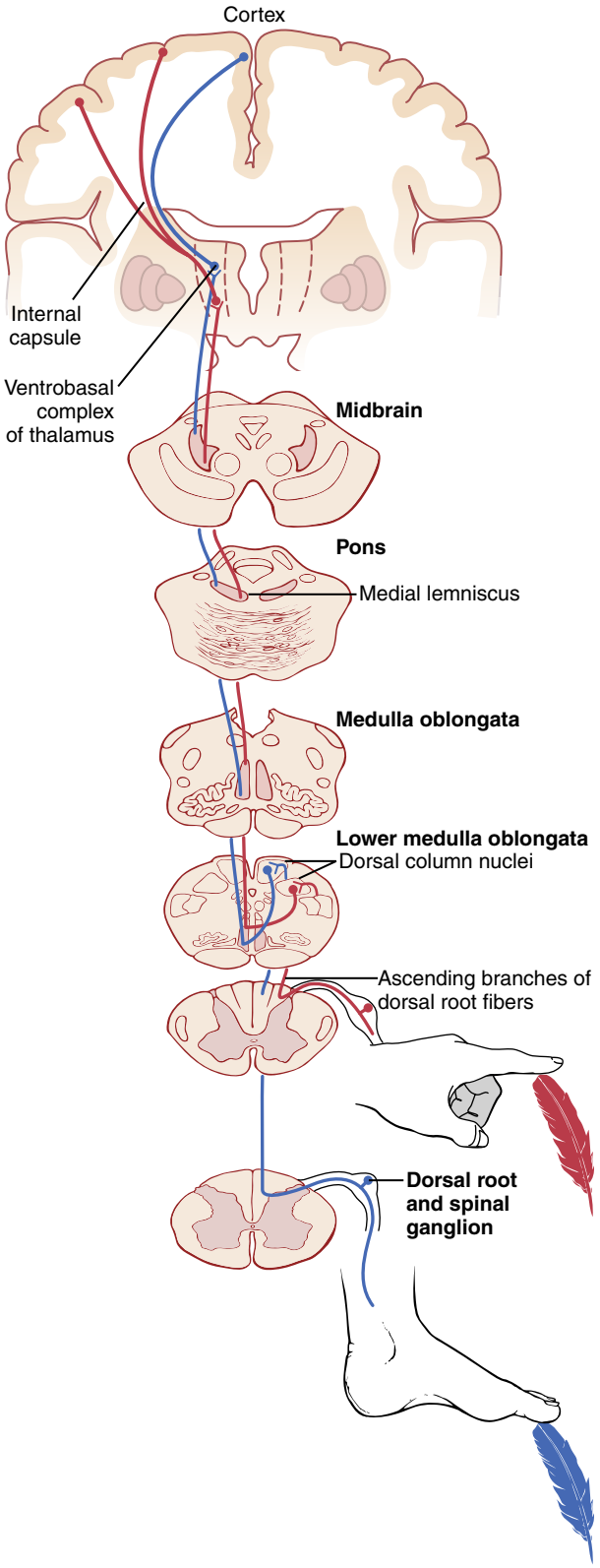

FIGURE **28-13** Vibration, proprioception, and fine tactile sensations travel via the dorsal column–medial lemniscal system. (From Hall JE. *Guyton and Hall Textbook of Medical Physiology*. 12th ed. Philadelphia: Saunders; 2011:474.)

its respective medullary nucleus; for example, the fasciculus gracilis terminates in the nucleus gracilis. Second-order axons decussate after leaving their medullary nucleus and form a bundle termed the *medial lemniscus*, which terminates in the ventral posterolateral thalamic nucleus. Third-order fibers from the ventral posterolateral nucleus terminate in the postcentral gyrus.[2,10,11,17]

There are important distinctions to be made between the *dorsal column medial lemniscal system* and the *anterolateral system*. The differences actually determine the types of sensory information that can be transmitted by the two systems. The dorsal column medial lemniscal system is composed of large myelinated fibers with a high degree of spatial orientation that is maintained from their origin in the dorsal root to their termination in the thalamus. Therefore, sensations that must be transmitted rapidly with a high degree of localization to the stimulus travel via the dorsal column. The anterolateral system on the other hand is composed of smaller myelinated nerve fibers with less spatial orientation. Hence the anterolateral system transmits a wider variety of sensations, at a slower velocity, and with less specificity than the dorsal column system.[16] A summary of the different sensations transmitted between the two systems is shown in Box 28-1.

Pupillary light and accommodation reflexes are mediated through the Edinger-Westphal nucleus and cranial nerve III. Pupillary dilation is produced by postganglionic sympathetic fibers from the superior cervical ganglion that travel with branches of the internal carotid artery to the radial muscle of the iris.[2,10,11,17]

BOX **28-1**

Sensations Transmitted Through the Dorsal Column–Medial Lemniscal System and Anterolateral System

Dorsal Column–Medial Lemniscal System

- Touch sensations requiring high degree of localization of the stimulus
- Touch sensations requiring transmission of fine gradations of intensity
- Phasic sensations, such as vibratory sensations
- Sensations that signal movement against the skin
- Position sensations from the joints
- Pressure sensations related to fine degrees of judgment of pressure intensity

Anterolateral System

- Pain
- Thermal sensations, including both warmth and cold sensations
- Crude touch and pressure sensations capable only of crude localizing ability on the surface of the body
- Tickle and itch sensations
- Sexual sensations

From Hall JE. *Guyton and Hall Textbook of Medical Physiology*. 12th ed. Philadelphia: Saunders; 2011:573.

MOTOR PATHWAYS

Motor, or efferent, pathways transmit information from the brain to the voluntary muscles of the body, to smooth and cardiac muscles, and to some glands. The corticospinal tracts supply the voluntary muscles of the trunk and extremities; nine cranial nerves supply the voluntary muscles of the head and neck. Autonomic preganglionic fibers arise in the brain and spinal cord and transmit efferent signals to smooth muscle, cardiac muscle, and some glands (lacrimal, bronchial).

Corticospinal Tract

The corticospinal tract originates in large, upper motor neurons located in the precentral gyrus of the frontal lobe (Figure 28-14).

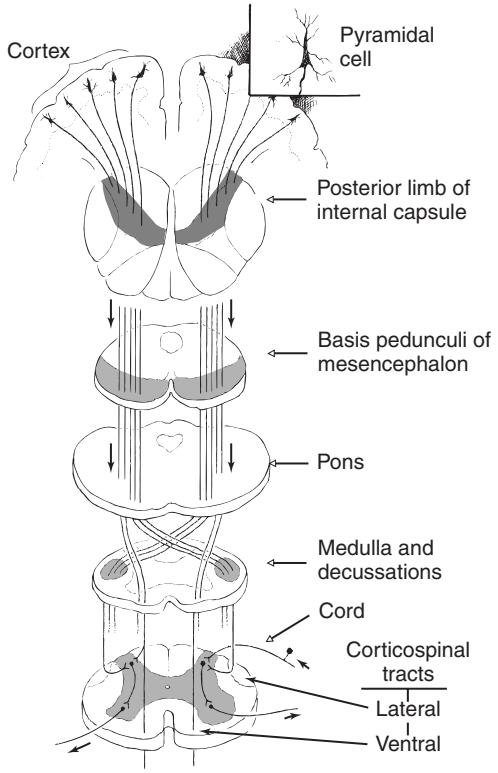

FIGURE **28-14** Corticospinal tracts. (Modified from Guyton AC. *Basic Neuroscience: Anatomy and Physiology*. 2nd ed. Philadelphia: Saunders; 1991:212.)

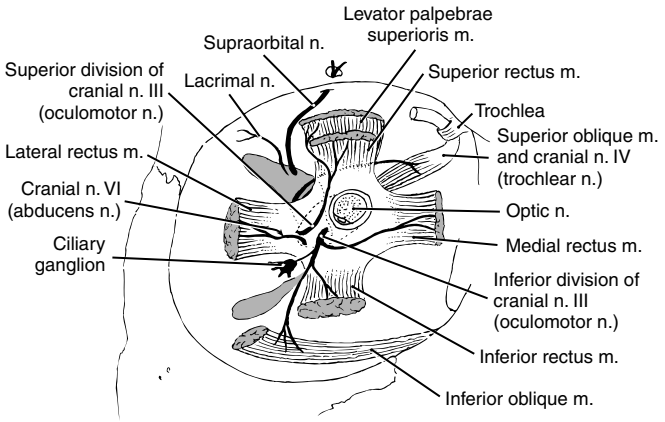

FIGURE **28-15** Frontal view of the posterior orbit with its motor nerves and the extraocular muscles. *n.*, Nerve; *m.*, muscle.

These neurons are arranged in a specific manner. Neurons supplying voluntary muscles of the head are found in the precentral gyrus near the lateral fissure of Sylvius, and those innervating the legs and feet are found in an area of the gyrus near the median longitudinal fissure. All parts of the body are represented in the gyrus. However, areas that perform complex movements (such as the hands when writing, typing, or playing the piano) have a larger area in the gyrus than other parts of the body not involved in intricate movements. Many of the upper motor neurons are pyramid shaped.

Axons travel from the pyramidal cells through the internal capsule, the major pathway for ascending and descending fibers between the cortex and other sites in the CNS. The internal capsule has three parts: the anterior limb, the posterior limb, and the genu, which lies between the anterior and posterior limbs. Fibers in the internal capsule are highly organized. Motor fibers to all parts of the body except the face are located in the anterior limb and part of the posterior limb. Fibers supplying the face are located in the genu. From the internal capsule, the axons travel through the midbrain (basis pedunculi) to the medulla, where approximately 90% of the fibers decussate, forming the pyramids of the medulla. The corticospinal tract is frequently called the *pyramidal tract*, either because of the shape of the upper motor neurons or because of the site at which the fibers decussate in the medulla. The fibers that cross over form the lateral corticospinal tract. Axons from the lateral corticospinal tract continue their descent to the spinal cord. At each level of the cord, some fibers leave the lateral corticospinal tract and enter the ventral horn gray matter, where they synapse with lower motor neurons. The fibers that do not decussate (approximately 10%) in the medulla continue to the spinal cord as the ventral corticospinal tract. The ventral corticospinal tracts cross over before synapsing with lower motor neurons in the gray matter. Axons from the lower motor neurons travel in the spinal nerves to innervate voluntary muscle.

A few corticospinal tract neurons are located anterior to the precentral gyrus. Axons from these neurons have an inhibitory effect on the lower motor neurons because they prevent them from discharging excessively. Damage to these suppressor fibers can stimulate the lower motor neurons either to overfire, resulting in hyperreflexia, or to discharge simultaneously, causing spasticity. Damage to the corticospinal tract anywhere along its route to the spinal cord can cause upper motor neuron paralysis. If the injury occurs above the decussation in the medulla, the paralysis is on the opposite side of the body. Paralysis occurs on the same side of the body if the damage occurs below the medulla. With upper motor neuron paralysis, reflexes are intact, but suppressor-fiber activity is impeded. As a result, hyperreflexia is present, and the upper motor neuron paralysis is spastic. Damage to lower motor neuron cell bodies in the ventral horn or ventral root fibers produces lower motor neuron paralysis, a flaccid type of paralysis. Cerebral palsy and amyotrophic lateral sclerosis are diseases that affect the corticospinal tracts.

Motor Innervation to the Head

Upper motor neurons whose axons supply the voluntary muscles of the head are found in the precentral gyrus next to the lateral fissure of Sylvius. The cell bodies, whose axons supply the extrinsic muscles of the eye, are located in the middle frontal gyrus. Axons from both areas form the corticobulbar tracts, which travel through the genu of the internal capsule to the brainstem, where they synapse with neurons located in nuclei spread throughout the brainstem. Axons from these neurons form many of the cranial nerves.

Axons originating from neurons located in the midbrain form the oculomotor and trochlear nerves (Figure 28-15). The oculomotor nerve innervates most of the external muscles of the eye (inferior oblique and the inferior, medial, and superior rectus muscles), along with the levator palpebrae superioris muscle, which raises the upper eyelid. The trochlear nerve innervates the external oblique muscle of the eye. Three other groups of nuclei have neurons whose axons form the trigeminal, abducens, and facial nerves. The trigeminal nerve innervates part of the soft palate and all of the muscles of mastication. The abducens innervates the lateral rectus muscle of the eye, and the facial nerves supply all the muscles involved in facial expression.

Axons from neurons located in medullary nuclei form the glossopharyngeal, vagal, accessory, and hypoglossal nerves. Both the glossopharyngeal and vagal nerves arise from the ambiguous

nucleus. The glossopharyngeal nerve supplies the stylopharyngeal muscle of the pharynx, and the vagal nerve innervates the muscles of the throat involved in swallowing and phonation. All of the tongue muscles are supplied by the hypoglossal nerve. The accessory nerve innervates the trapezius and sternocleidomastoid muscles of the neck. With the exception of the facial and hypoglossal nerves, the remaining nerves receive information from both the right and the left corticobulbar tracts. The nuclei of facial nerve fibers to the upper part of the face receive axons from the left and right corticobulbar tracts; the facial nerve nuclei whose fibers supply the lower part of the face receive fibers only from the contralateral corticobulbar tract. The nuclei from the origin of the hypoglossal nerves receive innervation from only the contralateral corticobulbar tract.[2,10,11,17]

Subcortical Motor Areas

Several motor areas in the brain are outside the cerebral cortex. For the most part, these are relatively primitive motor areas that have a modulating influence on motor function. Included in the subcortical motor areas are the basal ganglia, the nucleus of Luys, the red nucleus (nucleus ruber), the substantia nigra, and the reticular formation.

The basal ganglia lie deep within the cerebral hemispheres at the level of the internal capsule. They are composed of three nuclei: the globus pallidus, the putamen, and the caudate, which are collectively termed the *corpus striata*. The globus pallidus and the putamen are sometimes termed the *lentiform nucleus*. The globus pallidus makes up the paleostriatum, and the other two nuclei are part of the neostriatum.

The globus pallidus receives input from the motor cortex and from the other basal ganglia; it sends fibers to the subcortical motor areas. The globus pallidus is connected to the thalamus by two tracts, the ansa lenticularis and the lenticular fasciculus, which merge as they enter the thalamus to form the thalamic fasciculus. The thalamus forms a feedback process by sending fibers to the caudate nucleus and motor cortex. In this way, the motor activity of the basal ganglia can be influenced by the motor cortex without the presence of direct connections between the two structures. Dopamine, an important neurotransmitter in the basal ganglia, is produced in the substantia nigra of the midbrain and then travels by axonal transport to the caudate nucleus and the putamen.

The subthalamic nucleus of Luys is located in the diencephalon and is connected to other subcortical motor areas. Lesions in this nucleus result in a suppression of motor activity.

Three motor areas are located in the midbrain: the red nucleus, the substantia nigra, and the reticular formation. The red nucleus is located at the level of the corpora quadrigemina and gives rise to the crossed rubrospinal tract. When stimulated, this tract excites alpha and gamma flexor motor neurons and inhibits extensor motor neurons. The reticular formation consists of a diffuse collection of neurons found throughout the brainstem and into the diencephalon. Two major tracts arise from the reticular formation. One tract is the uncrossed medial reticulospinal tract, which excites alpha and gamma extensor motor neurons and inhibits flexor motor neurons when stimulated. The second tract is the lateral reticulospinal tract, which contains crossed and uncrossed fibers and activates alpha and gamma flexor motor neurons and inhibits extensor motor neurons when stimulated.

Lesions in the subcortical motor areas produce diseases characterized by disturbed muscle tone and dyskinesia (abnormal involuntary movements). In Parkinson disease, the globus pallidus and substantia nigra are affected. Huntington chorea involves atrophy of the caudate nucleus and putamen, as well as degeneration of cortical neurons. Other diseases that involve subcortical motor nuclei include athetosis, dystonia, ballismus, and Sydenham chorea.

NEUROANESTHESIA

Neuroanesthesia must take into account the unique set of circumstances each individual case represents. Comorbidities, pathology to be addressed, positioning, side of surgery, surgical approach, and procedure to be applied are all factors that must be clearly understood and fully addressed to administer a successful neuroanesthetic. Compounding the complexity is the constantly changing landscape of neurosurgical procedures, both cranial and spine. Providing competent neuroanesthesia in this environment demands thorough preparation and a degree of communication between surgeon and anesthesia not seen in other anesthesia environments.

A comprehensive anesthetic plan for each individual patient can only be instituted by thoughtful placement of each patient within the matrix of considerations discussed above. What follows will give a broad overview of the effects of anesthetic agents on cerebral blood flow (CBF), cerebral metabolic rate of oxygen consumption ($CMRO_2$), and intracranial pressure (ICP). The remainder of this chapter provides a general discussion of the preoperative, intraoperative, and immediate postoperative care associated with common intracranial surgical procedures.

Effects of Anesthetic Agents on Cerebral Physiology

CBF, cerebral blood volume (CBV), ICP, $CMRO_2$, and cerebral compliance all must be considered in concert with pharmacologic principles in the design of a neurosurgical anesthetic regimen (Table 28-4).

Inhalation Agents

All anesthetic agents influence ICP by decreasing cerebrovascular resistance through cerebrovascular dilation and by dose-dependent impairment of autoregulation, producing increases in ICP and CBV and a decrease in $CMRO_2$. The changes in ICP are generally greater in patients who have an underlying increase in ICP.[18,19] The potent inhalational agents decrease mean arterial pressure (MAP) and increase ICP, reducing cerebral perfusion pressure (CPP).[20-22] Isoflurane produces the greatest increases in CBF and ICP, followed by sevoflurane and desflurane.[18,23-25]

CBF in humans is unaltered with isoflurane-inspired concentrations of 0.6 to 1.1 minimum alveolar concentration (MAC); however, 1.6 MAC isoflurane doubles CBF. Animal studies have shown that isoflurane may enhance the carbon dioxide (CO_2) reactivity of the cerebral vessels. Cerebral autoregulation is impaired with concentrations exceeding 1 MAC.[26,27] $CMRO_2$ is depressed with isoflurane, as with all potent inhalation anesthetics, and progressive metabolic depression occurs with concentrations of isoflurane greater than 1 MAC until the electroencephalograph (EEG) becomes isoelectric at approximately 2.5 MAC.[28,29] These properties suggest that clinically relevant doses may provide a neuroprotective effect against ischemic insults, as demonstrated in human studies of critical regional CBF during carotid clamping.[30] Although strong experimental data support a neuroprotective potential of several anesthetic agents, consistent long-term protection by either agent has not been demonstrated. Unfortunately, there is a lack of clinical studies to support the use of any one anesthetic agent over the others. Proposed mechanisms related to the neuroprotective effect of inhalation anesthetic agents include activation of ATP-dependent potassium channels, up-regulation of nitric oxide synthase, reduction of excitotoxic stressors and cerebral metabolic rate, augmentation of peri-ischemic cerebral blood

TABLE 28-4 Effects of Anesthetics on Cerebral Dynamics

Drug	Cerebral Blood Flow	$CMRO_2$	Intracranial Pressure	Cerebral Perfusion Pressure
Inhalation				
Nitrous oxide	↑	↑↓	0/↓	↓
Sevoflurane	↑	↓	↑	↓
Isoflurane	↑	↓	↑	↓
Desflurane	↑	↓	↑	↓
Intravenous				
Barbiturates	↓↓	↓↓	↓↓	0/↓
Etomidate	↓↓	↓↓	↓	0
Propofol	↓	↓	↓	↓
Ketamine	↑	↑	↑↑	↓
Benzodiazepines	↓	↓	↓	0/↓
Dexmedetomine	↓	0/↓	0	0/↓
Morphine	0/↓	0/↓	↓	↑↓
Fentanyl	0/↓	0/↓	↓	0/↓
Alfentanil	0/↓	0/↓	↓	↓
Sufentanil	0/↓	0/↓	↓	↓
Remifentanil	0/↓	0/↓	↓	↓

From Zaglaniczn KL, Aker J, eds. *Clinical Guide to Pediatric Anesthesia*. Philadelphia: Saunders; 1999:176. Sakabe T, Matsumoto M. Effects of anesthetic agents and other drugs on cerebral blood flow, metabolism, and intracranial pressure. In: Cottrell JE, Young WL, eds. Cottrell and Young's Neuroanesthesia 5th ed. St Louis: Mosby; 2010: 78-95.
$CMRO_2$, Cerebral metabolic rate of oxygen.

flow and up-regulation of antiapoptotic factors including mitogen-activated protein kinases.[31] Activation of intracellular signaling cascades that lead to altered expression of protective genes also may be involved.[32] The high concentrations of isoflurane necessary for abolishing cortical activity have no toxic effect on cerebral metabolic pathways.[29,33] The majority of human studies show that inspired concentrations of isoflurane of less than 1% have minimal effect on ICP and that any increase in ICP is attenuated by mild hyperventilation. An exception to this generalization is that some patients with malignant brain tumors may show increases in ICP despite prior hyperventilation, particularly if computed tomography shows a midline shift.[34-36]

Desflurane is unique among the potent inhalation agents in that its low blood/gas solubility facilitates a rapid emergence, which may be useful for immediate postoperative neurologic evaluation. Desflurane has effects on EEG, CBF, and $CMRO_2$ similar to those of isoflurane. Young[37] and Ornstein et al.[38] compared the effects of desflurane and isoflurane on CBF at two concentrations, 1 MAC and 1.5 MAC, in an air-oxygen mixture during hypocapnia and reported no difference between isoflurane and desflurane at the two different MAC levels. Holmström and Akeson[39] reported that desflurane was associated with more CBF than isoflurane at the same depth of anesthesia. However, the results of ICP studies are not as definitive. Muzzi et al.[40] reported that desflurane 1 MAC in an air-oxygen mixture with an arterial CO_2 tension ($PaCO_2$) of 26 mmHg resulted in sustained increases in ICP until the dura was incised. The physiologic effects of sevoflurane are similar to those of other inhalation anesthetics, but some consider sevoflurane less vasoactive than isoflurane or desflurane.[41] In summary, all potent inhalational agents are known to increase CBF, CBV, and ICP. Mild hyperventilation attenuates these dose-dependent increases in ICP.

The use of nitrous oxide (N_2O) in intracranial procedures continues to be a controversial area of clinical practice. N_2O can produce increases in CBF, $CMRO_2$, and ICP. The effect of N_2O on cerebral dynamics varies widely and is influenced by what drugs are coadministered, the doses of each, and body temperature. Concomitant hyperventilation or the administration of one of several intravenous anesthetics (barbiturates, propofol, benzodiazepines, opioids) can reduce the increases in CBF and $CMRO_2$ during N_2O administration. However, the combination of N_2O and volatile anesthetics behaves much differently. Administering a volatile anesthetic in low doses (below 1 MAC) may decrease CBF and $CMRO_2$. The addition of 50% N_2O with less than 1 MAC of the volatile anesthetic produces increases in both CBF and $CMRO_2$. The cerebral vasodilation produced by N_2O is greater when increasing doses (greater than 1 MAC) of the volatile anesthetic are administered. N_2O may increase CBF by 100% or more at approximately 0.5 MAC. N_2O appears to produce nonuniform changes in CBF, increasing flow in anterior regions and decreasing flow in posterior brain regions. N_2O is not thought to affect CBV or CSF dynamics.[42-46]

Many clinicians have advocated that N_2O should no longer be administered in neurosurgical patients. But vast clinical experience of N_2O in thousands of neurosurgical patients, with little documentation of adverse neurologic events, argues against N_2O as having major neurotoxic effects during limited exposure. Typically, only very small amounts of N_2O are broken down in the body, but when used on long cases (over 12 hours), substantial accumulation of metabolic breakdown products may occur. These metabolites have been associated with megaloblastic anemia, leukopenia, impaired fetal development, and a depressed immune system. Circumstances in which the practitioner should consider eliminating N_2O are listed in Box 28-2.

Nitrous oxide (N_2O) is more soluble than nitrogen and expands closed-gas spaces. Its use should be restricted in patients with an intracranial or intravascular air compartment such as pneumocephalus.[47] Some practitioners abandon N_2O before closure of the dura to attenuate the development of iatrogenic pneumocephalus.

Intravenous Agents

Propofol is a popular induction and maintenance agent for neurosurgical patients. It is very useful in patients with intracranial

BOX 28-2

Considerations for Eliminating Nitrous Oxide

Nitrous oxide should be eliminated:
- In the presence of intracranial air (recent craniotomy, craniofacial trauma)
- When signal quality during intraoperative evoked potential monitoring is inadequate
- When the patient has clinical evidence of moderate to severe increases in ICP
- When a "tight-brain" is clinically appreciated during the intraoperative period
- When a case longer than 8 hours is anticipated

ICP, Intracranial pressure.

pathologic conditions, provided that hypotension is prevented. The cerebral effects are a dose-dependent reduction in CBF and $CMRO_2$. The reductions are usually in the 40% to 50% range. CPP may decrease because of reductions in blood pressure after bolus induction doses; however, the reduction in CBF appears to be independent of systemic hemodynamic changes.[48,49] They are most likely due to the metabolic depressant effect and cerebral vasoconstriction.[50,51] Reductions in systemic blood pressure produce corresponding reductions in CPP.

Etomidate reduces $CMRO_2$ and CBF in normal brains and in situations of reduced intracranial compliance. It produces a reduction in ICP without reducing CPP. Etomidate, like other CNS depressants, appears to reduce metabolic rate and produce cerebral vasoconstriction, which accounts for the reduction in ICP.[52-54] Major disadvantages include a high incidence of myoclonia, thrombophlebitis, nausea, vomiting, and suppression of the adrenocortical response to stress.[54,55] Many clinicians feel that etomidate should be avoided in brain-injured patients. Although it is considered as an induction drug of choice in situations of hemodynamic compromise, prolonged adrenal insufficiency is a major concern. Adrenal insufficiency is of special concern in critically ill patients, with sepsis and traumatic brain injury. Etomidate should be replaced by an amnestic dose of a benzodiazepine in combination with an opioid or ketamine to facilitate endotracheal intubation. If etomidate is used, empirical adrenal replacement therapy for at least 24 hours should be considered.[52]

Dexmedetomidine is gaining popularity in neuroanesthesia and neurocritical care practice. This presynaptic α_2-adrenergic receptor agonist offers a unique "cooperative sedation," anxiolysis, and analgesia with no respiratory depression.[56] Dexmedetomidine produces a dose-dependent sedation that resembles natural sleep. Sleep patterns differ from the classic gamma-aminobutyric acid (GABA) receptor agonists such as propofol. Patients do not experience respiratory depression and are readily arousable.[57] An advantage of this type of sedation is that procedures requiring "wake-up" tests can be more readily accomplished compared with usual anesthetic regimens.[58] Dexmedetomidine does not interfere with electrophysiologic monitoring, thereby allowing brain mapping during awake craniotomy and microelectrode recording during implantation of deep-brain stimulators. Motor and somatosensory evoked potentials are maintained when added to a desflurane and remifentanil technique. Decreases in the amplitude of motor evoked potentials may occur at high doses.[59,60] Bispectral index (BIS) values are decreased in a dose-dependent manner to a greater extent than with propofol.[61]

Dexmedetomidine does not change cerebral metabolism ($CMRO_2$). Cerebral blood flow (CBF) is decreased due to cerebral vasoconstriction. This suggests uncoupling between cerebral metabolism and flow because of decreases in central catecholamine turnover. Effects on intracranial pressure are not clinically significant.[62,63]

The central sympatholytic effects also result in an antishivering action, hypothermia, and a reduction in the neuroendocrine stress response to surgery. A reduction in postoperative agitation and emergence delirium in children and adults is an increasingly used clinical action. A neuroprotective effect has been proposed, but benefits in head-injured patients remain to be clarified.[62] Analgesic- and anesthetic-sparing effects are well documented and are produced at both the brain and spinal cord level. The greatest utilization of dexmedetomidine outside the neurosurgical intensive care environment is for the awake craniotomy.

Opioid-based anesthetic techniques are popular for neurosurgical procedures because they provide a steady hemodynamic course and predictable emergence. The synthetic opioids produce dose-related reductions in CBF (decrease to 25 mL/100 g/min) and $CMRO_2$ (40% to 50%).[64-67] Later investigations in patients after acute head injury or in those undergoing supratentorial craniotomy noted increases in ICP and decreases in CPP after administration of induction doses of fentanyl, sufentanil, and alfentanil.[68] These opioid-induced changes in ICP have been suggested to occur secondarily to an autoregulatory response to decreases in MAP.[69]

Fentanyl decreases the resistance to CSF absorption and results in a 10% reduction in CBV.[55,64] Sufentanil is 5 to 10 times more potent than fentanyl and has the highest therapeutic index of the clinically used opiates. Of the synthetic opiates, alfentanil produces the greatest decreases in MAP and CPP.[55,64] Remifentanil is the latest available compound of the 4-anilidopiperidine derivatives. It is characterized by an ultrashort duration of action and a metabolism independent of both hepatic and renal functions. Its main drawback is a lack of residual analgesia and the risk of postoperative hyperalgesia.[70] Meperidine should probably be avoided in the neurosurgical patient, because its metabolite, normeperidine, is a well-known convulsant.

Judiciously titrated doses of naloxone reverse opioid-induced respiratory depression and normalize both CBF and $CMRO_2$. The abrupt reversal of opioid-induced respiratory depression should be avoided in neurosurgical patients. Naloxone administered in this fashion is associated with hypertension, cardiac dysrhythmias, pulmonary edema, and intracranial hemorrhage.[71,72]

The benzodiazepines are useful anesthetic adjuncts used for their anxiolytic, anticonvulsant, and amnestic effects. Benzodiazepines produce a dose-dependent decrease in $CMRO_2$ and reductions in CBF; however, their effects on ICP are minimal.

Flumazenil, the benzodiazepine-specific antagonist, has no effect on cerebral dynamics when administered alone. High-dose midazolam anesthetic in the canine was associated with rebound increases in CBF and ICP to values greater than baseline when abrupt reversal was accomplished with flumazenil.[73] Flumazenil may produce seizures when large doses are administered.

Ketamine has had limited popularity in neuroanesthesia. The dissociative mechanism of action and resultant stormy emergence from anesthesia are undesirable after neurosurgical procedures. The primary advantage of ketamine is the stable hemodynamic course in the face of hypovolemia that may occur in the head-injured patient with multisystem trauma. Ketamine is known to produce untoward alterations in cerebral physiology, increasing CBF by 60% to 80% and elevating ICP. Ketamine also increases the resistance to CSF reabsorption, which over time may increase

ICP beyond that produced by increases in CBF alone. Cerebral metabolic rate is unchanged, but regional differences may exist.

A renewed interest in ketamine has been prompted because of its noncompetitive antagonism of the glutamine NMDA receptor. Similar compounds have been demonstrated to afford some degree of neuroprotection. Ketamine is a profound analgesic that has a preference for skin, bones, and joint pain. Analgesia occurs with subanesthetic doses, and it is widely used for sedation in combination with low doses of benzodiazepines, propofol, and other analgesics.[74] The effect on glucose utilization varies by brain region. The response of cerebral vessels to carbon dioxide is left intact. For these reasons ketamine has traditionally been thought to be contraindicated in patients with a head injury or an increased ICP.

Recently, however, it has been noted that ketamine can be used safely in neurologically impaired patients under conditions of controlled ventilation, coadministration of a GABA receptor agonist such as midazolam or propofol, and avoidance of nitrous oxide.[75] Trauma patients with multiple injuries may still benefit from the favorable cardiovascular effects while avoiding untoward neurologic adverse actions. Ketamine produces atypical anesthesia; thus EEG patterns also differ fron standard anesthetics. On loss of consciousness and onset of analgesia, ketamine induces a transition from alpha to theta waves (slow waves with moderate to high amplitude) on the EEG. Alpha waves do not reappear until after consciousness returns and analgesia is lost. Ketamine alone does not decrease the bispectral index (BIS) even when patients are unconscious.[76] Several researchers have in fact noted an increase in BIS levels when ketamine is added to a propofol, fentanyl, or sevoflurane anesthetic. Ketamine does not alter auditory evoked potentials (AEPs), mid-latency auditory evoked potential (MLAEP), or A-line autoregressive index monitors based on MLAEPs.

Nondepolarizing neuromuscular relaxants do not appear to have clinically significant direct effects on CBF or $CMRO_2$, provided MAP is not altered after administration.[77] The depolarizing agent succinylcholine in select circumstances may produce transient elevations in ICP, CBF, and $CMRO_2$.

Upper motor neuron disease may alter the peripheral nerve–stimulating response of nondepolarizing neuromuscular relaxants. Generally, the twitch response shows relative resistance to muscle relaxants on the hemiparetic or hemiplegic side, compared with the unaffected side or respiratory muscles.[78,79] Decreased sensitivity to nondepolarizing muscle relaxants is most exaggerated in the first 3 weeks of upper motor neuron disease. Therefore, monitoring neuromuscular blockade is preferentially performed on the unaffected side. Patients on chronic anticonvulsant therapy may be more resistant to long-acting nondepolarizing muscle relaxants.[80] Patients receiving chronic phenytoin therapy have an increased dosage requirement and reduced duration of action for the nondepolarizing neuromuscular relaxants, with the exception of atracurium and cisatracurium.

Succinylcholine indirectly increases intracranial pressure (ICP), and therefore concern has always existed as to the appropriateness of its use in certain neurosurgical procedures and in patients with brain pathology and ICP. Research conducted in animals shows a small and transient rise of 10 to 15 mmHg for 5 to 8 minutes after administration.[81] The rise is associated with an increased cerebral blood flow, muscle spindle afferent activity, and electroencephalogram arousal. Fasciculation of the neck muscles causing jugular vein stasis appears to be a factor. The ICP effects are blocked by pretreatment with a small dose of nondepolarizing relaxant. In clinical practice, the administration of succinylcholine is preceded by an anesthetic induction agent that lowers ICP, so that may help counteract this effect as well. Nevertheless, the routine use of succinylcholine in neurosurgery has declined. It remains widely used, with nondepolarizing relaxant and lidocaine pretreatment, for emergency procedures requiring rapid airway control via rapid sequence induction As mentioned previously, succinylcholine is contraindicated in patients with neurologic or denervated muscle because of the potential for life-threatening hyperkalemia. Succinylcholine should be avoided in patients with cerebrovascular accident, upper and lower motor neuron lesions, coma, encephalitis, and closed head injury and after severe burns and prolonged bedrest.[82]

The availability of suitable nondepolarizing alternatives such as rocuronium (1 mg/kg intubating dose) facilitates endotracheal intubation within 60 to 90 seconds and avoids the known complications attendant on the administration of succinylcholine.

Antihypertensives

β-Adrenergic antagonists have great utility for the control of the inotropic and chronotropic effects of sympathetic stimulation that attend laryngoscopy, endotracheal intubation, and endotracheal extubation. Esmolol is a rapid-onset, short-acting selective β_1-adrenergic receptor antagonist. Administration of 0.5 to 1 mg/kg 2 minutes before laryngoscopy and endotracheal intubation attenuates the predictable increases in heart rate and blood pressure. Its effects on ICP are thought to be negligible. Labetalol is a selective α_1-adrenergic antagonist and nonselective β_1- and β_2-adrenergic antagonist (ratio of β-blockade to α-blockade is 7:1 for intravenous preparation). Labetalol spares presynaptic α_2-receptors; consequently, released norepinephrine produces further inhibition of catecholamine release via a negative feedback from the stimulation of β_2-receptors. Labetalol and esmolol may be preferred for the control of emergence hypertension after intracranial procedures. In one study, patients treated with labetalol as compared with esmolol experienced a higher incidence of bradycardia in the immediate postoperative period.[83,84]

The smooth muscle relaxants sodium nitroprusside and nitroglycerin produce increases in CBV and ICP. Sodium nitroprusside is a direct-acting cerebrovasodilator, increasing CBV after dilation of cerebral capacitance vessels.[77,85] Deliberate hyperventilation and the administration of a barbiturate may attenuate the cerebrovasodilation. Most contemporary neuroanesthesiologists consider nitroglycerin and sodium nitroprusside to be potent dilators of capacitance vessels and unsafe in patients with abnormal elastance. If a patient is on a tenuous portion of the pressure-volume curve, the dramatic rise in CBV caused by nitroglycerin or nitroprusside use would be catastrophic, resulting in spatial exhaustion and intracranial hypertension.[86]

INTRACRANIAL PRESSURE

In its simplest definition, *intracranial pressure* refers to the supratentorial CSF pressure. The supratentorial pressure may be measured within the lateral ventricle or within the subarachnoid space over the convexity of the cerebral cortex. CSF pressure may vary markedly in different areas within the cranium, and similarly, CSF pressure in the cranial subarachnoid space may differ from that in the spinal subarachnoid space. In individuals free of neurologic pathology in the recumbent position, the CSF pressure measured at the lumbar cistern accurately reflects ICP. However, many factors, including the assumption of the upright position, can alter the relationship between cranial and spinal CSF pressures. In addition, in the presence of intracranial mass lesions, infratentorial CSF pressure (as measured in the cisterna magna or lumbar cistern) often decreases, whereas supratentorial pressure increases.

Therefore, the measurement of supratentorial CSF pressure is a useful clinical concept.[21,87]

Determinants of Intracranial Pressure

The brain is enclosed within a rigid container, and because the brain is not compressible, any increase in total intracranial volume produces an accompanying increase in ICP (Monro-Kelly doctrine). Increased ICP may have a detrimental effect on the well being of the brain. The intracranial contents consist of the brain (12%), intracellular water (78%), CSF (approximately 75 mL), and blood (approximately 50 mL), for a combined volume of approximately 1200 to 1500 mL.[88] The brain is surrounded by the dura mater and rigidly encased in the bone of the calvaria and skull base. In the strictest sense, the intracranial space, volume, and pressure are defined by the limits of the encasing bone. However, should the skull become disrupted, the remaining intracranial contents may be subject to the potential for abnormal pressure accumulation because of the restrictions imposed by an intact dura mater. The same dural restrictions also may contribute to regional ICP gradients in patients with intracranial mass lesions and an intact cranial vault.[89] Intracranial hypertension may lead to global reductions in CPP (CPP = MAP − ICP) from compression-induced ischemia or may produce shifting of intracranial contents, resulting in compression of the brain against the falx, the tentorium, or the foramen magnum.

The ICP is approximately 5 to 15 mmHg in adults; lower values are recorded in children and infants. This pressure is determined by the relationship between the volume allowed by the structures that limit intracranial volume and the actual volume of the intracranial space. Because of the normal elastance of the intracranial contents, individuals without intracranial pathology maintain normal ICP despite transient increases that develop with coughing or during a Valsalva maneuver. Small increases in the intracranial volume do not produce abrupt increases in ICP. This normal elastance exists because the limits of the intracranial contents have not been reached.

Once a growing mass, blood or tumor, has increased intracranial volume to its limit, dramatic increases in ICP may occur.[90] This relationship is depicted in Figure 28-16. Although this ICP-volume curve is commonly used to explain these relationships, Todd et al.[91] suggest that the x-axis be relabeled as the "volume of the growing mass," because this axis does not really represent total intracranial volume. The initial portion of the ICP curve is relatively flat because the total intracranial volume does not change with early periods of bleeding or tumor growth. This portion of the curve reflects the phenomenon of spatial compensation. As the mass (blood or tumor) increases, the volume of the intracranial compartments must decrease to maintain normal ICP. In most cases, the CSF compartment decreases; that is, CSF is absorbed by the arachnoid granulations or shunted to the spinal subarachnoid space to compensate for the increasing intracranial volume. Compensation is exhausted when the CSF compartment cannot decrease further in size and total intracranial volume increases, accounting for the increase in ICP. Once volume compensation has reached exhaustion, the subsequent increasing ICP has a direct relationship with a reduction in cerebral perfusion and an increased herniation risk (see Figure 28-16).[92]

Measurement of Intracranial Pressure

The current gold standard for ICP monitoring is the intraventricular catheter. Although it is highly invasive, it allows for drainage of CSF to lower ICP. As with any indwelling catheter, there can be insertion problems and safeguards against infection are necessary. It is usually zeroed daily, with the jugular foramen projected at the tragus as the reference level. Intraparenchymal probes are a popular method of measuring ICP as well. They are easy to use and transport and are zeroed when inserted. Infection problems are minimal. The microsensor transducer and the fiber optic transducer are the most widely available.[93] Older methods such as epidural and subarachnoid probes are largely obsolete. The primary reasons for monitoring ICP are trauma and subarachnoid hemorrhage, although other indications exist. A Glasgow Coma Scale score of 7 or less in a comatose patient is the classic indication. A ventriculostomy catheter and other brain monitors are depicted in Figure 28-17.[94-96]

Intracranial Hypertension

Intracranial hypertension occurs with a sustained increase in ICP above 20 to 25 mmHg.[97] Intracranial hypertension develops with expanding tissue or fluid mass, interference with normal CSF absorption, excessive CBF, or systemic disturbances promoting brain edema. Often, multiple factors are responsible for the development of intracranial hypertension. For example, tumors in the posterior fossa usually produce some degree of brain edema and readily obstruct CSF flow by compressing the fourth ventricle.[98]

Although many patients with intracranial hypertension are initially asymptomatic, all eventually develop characteristic signs and symptoms, including headache, nausea, vomiting, papilledema, focal neurologic deficits, altered ventilatory function, decreasing consciousness, seizures, and coma. When ICP exceeds 30 mmHg, CBF progressively decreases, and a vicious cycle is established: ischemia produces brain edema, which in turn increases ICP, and further precipitates ischemia. If this cycle remains unchecked, progressive neurologic damage or catastrophic herniation may result.[21,98,99] A consistent increase in intracranial pressure above 20 mmHg must be treated.

When intracranial hypertension is caused by hematoma, contusion, tumor, hygroma, hydrocephalus, or pneumatocephalus, surgical treatment is indicated. In the absence of a surgically treatable condition, ICP may be controlled by correcting the patient's position, temperature, ventilation, hemodynamics, and drainage of CSF. Other first-tier options include controlled hypocapnea (hyperventilation; $Paco_2$ 30-35 mmHg). On average, CBF decreases by 4% for every 1 mmHg decrease in $Paco_2$. Hyperosmolar therapy (mannitol, hypertonic saline) and induced arterial hypertension (CPP concept) are also used.

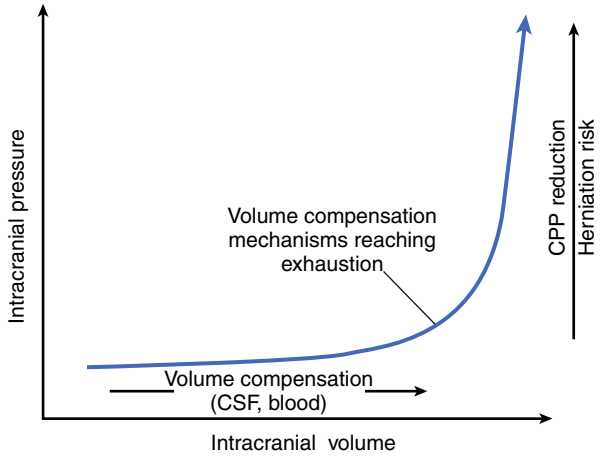

FIGURE **28-16** The intracranial pressure-volume relationship. (From Miller RD, et al, eds. *Miller's Anesthesia*. 7th ed. Philadelphia: Churchill Livingstone; 2010:2046.)

When autoregulation of cerebral blood flow is compromised, hyperoncotic treatment aimed at reducing vasogenic edema and intracranial blood volume may be applied. When intracranial hypertension persists, second-tier treatments may be indicated. These include forced hyperventilation ($Paco_2$ less than 25 mmHg), barbiturate coma, or experimental protocols such as tris buffer, indomethacin, or induced hypothermia. The last resort is emergent bilateral decompressive craniectomy. These interventions are discussed later.[93]

Intracranial Pressure Reduction

The major methods of treating elevated ICP are listed in Box 28-3. Selective application of these methods often results in ICP reduction accompanied by clinical improvement. A patent airway, adequate oxygenation, and controlled ventilation provide the foundation for neuroresuscitative care in acute intracranial hypertensive states. Frequently, overlap occurs among causes of increased ICP, and this may necessitate simultaneous application of a number of different therapeutic modalities.[68]

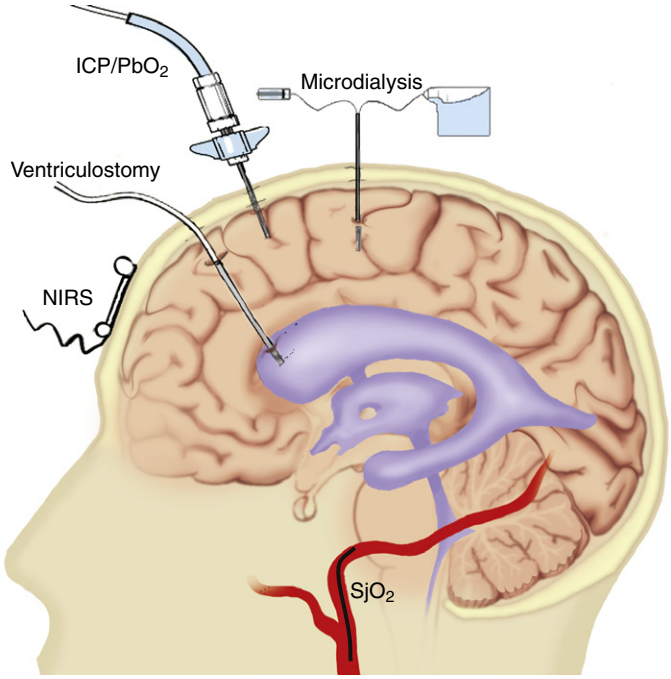

FIGURE **28-17** Schematic of available intracranial monitoring, with near-infrared oximetry (NIRS), intracranial pressure (ICP, either via ventriculostomy or parenchymal probe), brain tissue oximetry (PbO_2), microdialysis, and jugular venous oximetry (SjO_2). (From Miller RD, et al, eds. *Miller's Anesthesia*. 7th ed. Philadelphia: Churchill Livingstone; 2010:2904.)

Hyperventilation

Lowering $Paco_2$ increases cerebrovascular resistance, reducing CBV and ICP. It must be kept in mind that controlled hyperventilation is more a rescue maneuver than a standard treatment. The reactivity of cerebral vessels to changes in $Paco_2$ is an important physiologic control system. When the physiologic control is intact, hyperventilation lowers $Paco_2$, resulting in respiratory alkalosis and subsequent vasoconstriction. When vasoconstriction is pronounced, intracranial blood volume will decrease and lower ICP. This is particularly important in known low-CBF conditions, such as severe traumatic brain injury (TBI) or vasospasm. To avoid cerebral ischemia, $Paco_2$ should be lowered to approximately 30-35 mmHg. The vasoconstrictive effect on cerebral arterioles lasts only 11 to 20 hours because the pH of the CSF rapidly equilibrates to the new $Paco_2$ level. When hypocapnea is to be monitored by end-tidal capnometry, as is usually the situation in the operating room, the $Paco_2$ is approximately 2-5 mmHg higher than end-tidal carbon dioxide ($ETco_2$) readings although many conditions can affect this gradient. Compared with autoregulation of CBF, CO_2 reactivity is usually maintained even in the traumatized brain. When CO_2 reactivity is lost, a poor prognosis is probable.[100]

Cerebrospinal Fluid Drainage

Intracranial hypertension may be reduced by a surgical CSF diversion. The long-term effectiveness of this therapeutic alternative depends on the cause of the increased ICP. When brain edema produces elevation of ICP, CSF drainage may provide only transient abatement of intracranial hypertension. If external drainage is continued in this circumstance, ventricular collapse can occur and prevent further venting of CSF. Successful chronic control of high ICP caused by hydrocephalus can be achieved with implanted CSF shunts.[68,93,100]

Surgical Decompression

Surgical decompression may be used for uncontrollable increases in ICP. Internal decompression involves the excision of brain tissue, reduction in ICP, and reduction of the potential for brainstem

BOX 28-3

Methods for the Treatment of Elevated Intracranial Pressure

- Apply mild hyperventilation on demand ($Paco_2$ 30 to 35 mmHg)
- Optimize sedation and analgesia to allow for ventilatory control
- Administer diuretics (osmotic mannitol 0.25-1 g/kg IV) (may repeat once if serum osmolarity less than 320 mOsm/kg and patient is euvolemic) or furosemide
- Perform cerebrospinal fluid drainage (if available)
- Avoid overhydration; target normovolemia
- Elevate patient's head 15 degrees; position to improve cerebral venous return; avoid neck-vein compression
- Insert intracranial pressure monitor such as a ventricular catheter or parenchymal probe; tissue oxygen partial pressure, $AVDo_2$, and CBF monitoring recommended
- Optimize hemodynamics: mean arterial pressure, central venous pressure, pulmonary capillary wedge pressure, heart rate, and cerebral perfusion pressure; consider antihypertensive therapy as needed
- Administer corticosteroids (avoid with traumatic brain injuries)
- Surgical decompression; consider decompressive craniectomy if hematoma is present
- Cerebral vasoconstriction such as propofol
- Consider mild hypothermia

$AVDo_2$, Arteriovenous difference in oxygen content; *CBF*, cerebral blood flow; *IV*, intravenous; *$Paco_2$*, partial pressure of arterial carbon dioxide.

displacement or herniation. External decompression involves excision of the skull overlying the site of either an epidural or a subdural hematoma. Decompressive surgery is generally considered to be a last resort in patients with persistent, intractable increases in ICP.[54]

Hypothermia

Hypothermia may assist in uncontrollable increases in ICP by decreasing $CMRO_2$ 7% for each degree centigrade decrease in core body temperature. Temperature is lowered by convective cooling to a bladder temperature of 35° to 36° C for 48 hours after trauma or hemorrhage.[101]

Pharmacologic Manipulation of Intracranial Pressure

Diuretics

Loop diuretics (furosemide, bumetanide, ethacrynic acid) produce a general diuresis, decrease the rate of CSF production, and decrease cerebral edema. Osmotic diuretics are effective in decreasing the water content of the brain. Mannitol is the most widely used osmotic diuretic for acute control of intracranial hypertension. Rapid administration of mannitol may produce vasodilation, increases in CBF, a transient rise in ICP, and a transient increase in circulating blood volume. Increases in circulating blood volume may prove to be detrimental to patients with underlying cardiac dysfunction. Prior administration of intravenous furosemide may minimize these potential complications. Decreases in ICP begin shortly after mannitol administration and may continue for up to 6 hours. The typically prescribed dose of mannitol is 0.25 to 1 g/kg. Continued use of mannitol may produce hyperosmolality and electrolyte imbalance, which may be attenuated with concurrent administration of a loop diuretic.[102]

Hypertonic saline has an osmotic effect on the brain because of its high tonicity and ability to effectively remain outside the blood-brain barrier. Like mannitol, hypertonic saline produces an osmolar gradient causing shrinkage of brain tissue and reduction in ICP. It also increases circulating blood volume, MAP, and CPP. The ICP reduction is seen for approximately 2 hours and may be maintained for longer periods by using a continuous infusion of hypertonic saline. The ICP reduction is thought to be caused by a reduction in water content in areas of the brain with intact blood-brain barrier, such as the nonlesioned hemisphere and cerebellum. Most comparisons with mannitol suggest almost equal efficacy in reducing ICP, but there is a suggestion that mannitol may have a longer duration of action. Results from studies directly comparing hypertonic saline with standard treatment in regard to safety and efficacy are inconclusive. However, the low frequency of side effects and a definite reduction of ICP observed with use of hypertonic saline in these studies are very promising. Systemic effects include transient volume expansion, natriuresis, hemodilution, immunomodulation, and improved pulmonary gas exchange. Adverse effects include electrolyte abnormalities, cardiac failure, bleeding diathesis, and phlebitis.[103]

Corticosteroids

Glucocorticoids penetrate the blood-brain barrier and decrease edema associated with mass lesions. Steroids have been in use for neurosurgical patients for decades. They are commonly used for primary and metastatic brain tumors to decrease vasogenic cerebral edema.

Increased ICP decreases over 2 to 5 days with treatment. The most commonly used regimen is intravenous dexamethasone, 4 mg every 6 hours. Despite many years of use the CRASH (Corticosteroid Randomization After Significant Head injury trial) results showed that steroids were harmful in TBI. They may be given in spinal cord trauma. There is no indication for steroids with intracranial hypertension after TBI. Classical indications, such as perifocal edema surrounding intracranial tumors or edema associated with cerebral abscess, remain valid.[104]

Barbiturates

Barbiturate coma, hypothermia, or decompressive craniectomy should be considered for intracranial hypertension refractory to initial medical management. Barbiturate coma is used to reduce refractory ICP by decreasing $CMRO_2$ scavenging free radicals, preventing convulsions, and reducing the hyperthermic response to ischemia. Barbiturates induce hypotension, which at times may be very difficult to treat.[105] Volume expansion should be the first-line treatment to maintain systemic blood pressure, although intravenous pressors may be used. The cerebral metabolic rate cannot be lowered further after burst suppression is achieved by barbiturates; theoretically, ICP will be at its lowest barbiturate-induced level when burst suppression is achieved.[106] Patients may be kept in burst suppression–induced barbiturate coma for hours to days. Although routine use of barbiturates has not been effective in reducing morbidity or mortality after severe head injury, beneficial reductions in ICP are produced. A disadvantage is the inability to perform neurologic assessments during the coma.[107]

NEUROPHYSIOLOGIC MONITORING

Great use is made of neurophysiologic brain monitoring. It is important to confer with the surgeon prior to surgery to determine which neurophysiologic monitoring is to be used and to plan the anesthetic in a manner that optimizes the results of the required monitoring.

Intraoperative monitoring (IOM) is used routinely to asses the nervous system during procedures that present significant risk of brain, spinal cord, or nerve injury. Intraoperative testing is used to identify nerves and to define brain regions and structures for resection. There is significant improvement in patient outcomes with monitoring. The Therapeutics and Technology Subcommittee of the American Academy of Neurology concluded that the following are useful and noninvestigational: (1) EEG, compressed spectral array, and somatosensory evoked potentials (SSEPs) in carotid endarterectomies and brain surgeries that potentially compromise cerebral blood flow; (2) brainstem auditory evoked response and cranial-nerve monitoring in surgeries performed in the region of the brainstem or inner ear; and (3) somatosensory evoked monitoring performed for surgical procedures potentially involving ischemia or mechanical trauma of the spinal cord.[108] Motor evoked potentials monitoring is common during spine surgery and has a good correlation to postoperative motor outcome. The novel technique of motor evoked potential monitoring using transcranial electrical stimulation allows reliable assessment of the functional integrity of the corticospinal and corticobulbar tracts while the patient is under general anesthesia.[109]

Surgical procedures that commonly use intraoperative monitoring are shown in Box 28-4. Intracranial posterior fossa cases commonly use brain auditory evoked potentials (BAEPs), somatosensory evoked potentials (SSEPs), and cranial nerve electromyography (EMG) monitoring. Typical applications are cerebellopontine angle and skull base tumor resection, brainstem vascular malformation and tumor resection, and microvascular

BOX **28-4**

Surgical Procedures Commonly Using Intraoperative Monitoring

- Epilepsy surgery
- Cerebral tumor and vascular malformation resection
- Intracranial aneurysm clipping
- Movement disorders electrode placement
- Mapping nerves, tracts, and nuclei during brainstem and cranial base surgery
- Ear and parotid surgery near facial nerve
- Thyroid and aortic arch surgery near laryngeal nerve
- Carotid endarterectomy
- Carotid balloon occlusion
- Endovascular spinal and cerebral procedures
- Spinal deformity correction
- Spinal fracture stabilization
- Spinal tumor resection
- Cervical myelopathy decompression
- Lumbar stenosis decompression and fusion
- Tethered cord and cauda equina procedures
- Dorsal root entry zone surgery
- Brachial and lumbosacral plexus surgery
- Peripheral nerve surgery
- Cardiac and aorta procedures

Adapted from Nuwer MR. Clinical neurophysiology: intraoperative monitoring. In: Daroff et al, eds. *Bradley's Neurology in Clinical Practice*. 6th ed. Philadelphia: Saunders; 2012:440.

decompressions. Intracranial supratentorial procedures include resections for epilepsy, tumors, and vascular malformations as well as for aneurysm clipping. These use multimodality monitoring with a combination of EEG and SSEP monitoring together with functional cortical localization with direct cortical stimulation and electrocorticography (ECoG). Surgery of the carotid, aorta, or heart may use EEG to monitor hemispheric function or assess the need for shunting or adequacy of protective hypothermia. SSEPs for also used these vascular cases.

Spinal surgery is the most common setting for IOM. Procedures include cervical diskectomy and fusion for myelopathy, stabilization for deformities such as scoliosis, resection of spinal column or cord tumors, and stabilization of fractures. Both SEP and MEP often are used to assess the posterior columns and corticospinal tract functions. The use of MEP depends on the case, since it usually requires total intravenous anesthetic and incurs some movements during surgery. As a result, some spinal cases still are done with SEP alone. In cases involving pedicle screw placement, EMG is monitored to detect screw misplacement. Spinal cord monitoring also is used for cardiothoracic procedures of the aorta that jeopardize spinal perfusion. Peripheral nerve monitoring is carried out for cases risking injury to the nerves, plexus, or roots. Testing also can determine which segments of a nerve are damaged when performing a nerve graft.

When SSEP monitoring is used for spinal cord surgery the risk of paraplegia was 60% less among the monitored cases when compared with historical and contemporaneous controls. That amounted to 1 case out of every 200 that did not have paraplegia when monitoring was used. To improve even further, multimodality monitoring combining SSEPs with MEPs and others is now standard for many spinal procedures. The expectation is that the rate of postoperative neurologic deficits will be reduced even further.[110]

Electroencephalography

The EEG recorded from the scalp is a summation of the excitatory and inhibitory postsynaptic potentials produced in the pyramidal layer of the cerebral cortex. EEG activity requires about 50% of the total oxygen consumed by the brain; the remaining 50% is needed to maintain cellular integrity. When oxygen delivery is compromised, slowing of EEG activity ensues.

Changes in EEG frequency and amplitude may be caused by administration of anesthetic drugs and changes in anesthetic depth. Low doses of potent inhalation agents with N_2O produce an active EEG. Steady-state anesthesia, regardless of the agent used, usually produces a stable EEG pattern. It is worth noting that deep levels of anesthesia and cerebral ischemia produce similar EEG changes. In both cases, fast activity is replaced by slower, larger EEG waveforms. Boluses of anesthetic drugs may produce large EEG changes indistinguishable from those seen during ischemia. The EEG provides information about the overall electrical functioning of the cerebral cortex but not much about the subcortical brain, spinal cord, or cranial and peripheral nerves.[110]

Somatosensory Evoked Potentials

An evoked potential differs from the EEG mainly in two ways: (1) the EEG is a random, continuous signal that arises from the ongoing activity of the outer layers of the cortex, and an evoked potential is the brain's response to a repetitive stimulus along a specific nerve pathway, and (2) EEG signals range from 10 to 200 millivolts (mV). Evoked potentials are smaller in amplitude (1, 5, 20 microvolts), requiring precise electrode positioning and special techniques (signal averaging) to extract the specific response from the underlying EEG "noise." The technique of signal averaging has been further developed in computer processing. The technique now used applies a stimulus repeatedly—preferably at randomized intervals—and records the evoked response over the corresponding area of the brain, averaging out mathematically the change over the number of stimuli.[111]

SSEP can be used for detecting localized injury to specific areas of the neural axis by assessing cortically generated waves, or it can serve as a nonspecific indicator of the adequacy of cerebral oxygen delivery.[110]

Although anesthetics alter the generation and transmission of SSEP, suppression of muscle artifact by neuromuscular blocking drugs and the ability to use much higher stimulus intensity in the anesthetized patient allow rapid production of waves that are reproducible, although they differ from those found in the awake patient. Early components of SSEP are generally resistant to anesthetic depression. Etomidate and ketamine both increase the amplitude of scalp-recorded waves by 200% to 600%. Volatile anesthetics and N_2O depress the SSEP waveform in a dose-dependent manner. Avoiding changes in inhaled gas concentration and bolus injection of hypnotic drugs during periods of risk minimizes difficulties in determining whether waveform changes are due to surgical manipulation.[112] The effects of anesthetics on somatosensory evoked potentials are shown in Table 28-5.

Hypothermia increases SSEP latency. Latency increases about 3 milliseconds with every decrease in temperature of 2° C to 3° C. This amount of change is suggestive of neural injury. Hyperthermia suppresses SSEP amplitude, with the amplitude being only 15% of that at normothermia.[112-115]

Reproducible, very-short-latency waves of the trigeminal system are produced by stimulation of the lip at 2 to 4 Hz (512 stimuli). This modality of evoked potential is abnormal in patients with posterior fossa masses in the region of cranial nerve V or in symptomatic hydrocephalus.[116] This modality of evoked

TABLE 28-5 Effects of Anesthetics on Somatosensory Evoked Potentials

Drug	Latency	Amplitude
Isoflurane	↑	↓
Sevoflurane	↑	↓
Nitrous oxide	↑	↓
Desflurane	↑	↓
Fentanyl	Slight ↑	Slight ↓
Propofol	↑	No change
Ketamine	↑	↑
Etomidate	↑	↑
Dexmedetomidine	No change	No change

potential monitoring may be useful in patients with large posterior fossa tumors that cause severe cranial nerve VIII dysfunction and make brainstem auditory evoked response (BAER) monitoring impossible.[112]

BAER assesses only brainstem function, although long-latency cortical waves can be assessed to evaluate cortical function. BAER has been used extensively in patients at risk of brain injury during intracranial surgery, despite the extremely small amount of neural tissue assessed and the resistance of BAER to oxygen deprivation when compared with other neural monitors such as the EEG or SSEP waves.[112,117]

Compared with SSEPs, intraoperative factors other than surgical brain damage are relatively unlikely to seriously alter the BAER. BAER waveforms are resistant to both intravenous and inhalational drugs.[112] Fentanyl in large doses does not alter BAER.[112,118] Propofol (2 mg/kg, followed by an infusion) increases the latency of waves I, III, and V without a change in the amplitudes, but it completely suppresses middle-latency auditory waves.[112,119] N_2O produces a linear decrease in BAER amplitude from 10% to 40%[112,120]; N_2O at doses of 33% reduces the wave amplitude without altering latency.[112,121,122]

BAER waves are easily identifiable at more frequently used levels of hypothermia (29° C), although latencies are delayed by about 33%.[123] BAER latency is inversely related to temperature over the range of 36° C to 42° C, with a decrease in amplitude as temperature increases.[112,124]

BAER appears to be a sensitive monitor to the auditory apparatus in response to direct injury.[112] The auditory apparatus includes the cochlear hair cells, spiral ganglion, eighth cranial nerve, cochlear nuclei, superior olivary complex, lateral lemnisci, inferior colliculus, and medial geniculate thalamic nuclei.[110] Some have recommended BAER monitoring be undertaken in all patients at risk of brainstem injury, even if the primary disease causes hearing on the affected side to decrease below the functional level.[112] Some also consider BAER clinically useful and probably approaching standard of care for microvascular decompression procedures and acoustic tumor surgery.[110]

Aggressive intraoperative monitoring does not guarantee prevention of neurologic injury, because all parts of the brain are not assessed using currently available monitoring.[112] Except when the entire brainstem is at risk, there will likely be a high incidence of cases in which BAERs are unaffected intraoperatively, yet significant impairment in motor function or consciousness occurs postoperatively.[110]

Electromyography (EMG) monitoring is frequently used for facial nerve monitoring. Generally, two types of EMG activity are monitored. The first involves active stimulation of the nerve for localization and the second, spontaneous EMG activity initiated by irritation or manipulation of the nerve. It has been noted that in the presence of light anesthesia, spontaneous EMG activity caused by slight movements may become apparent and mimic neuronal irritation.[110]

The effects of muscle relaxants on EMG monitoring have not been adequately studied.[110,112] The degree of neuromuscular blockade should be maintained at a light level until response of the respective muscles (orbicularis oris and orbicularis oculi) is verified.[110] Chronically injured facial nerves may show greater sensitivity to the effects of neuromuscular blockade, suggesting lower levels of neuromuscular blockade should be used.[125] Some do not paralyze patients during the time EMG monitoring is used. Facial nerve monitoring is considered the standard of care for acoustic tumor surgery and during other surgery that risks facial nerve function.[110]

The motor component of cranial nerves III, IV, X, XI, and XII also can be monitored using EMG.[110,126,127] Whereas some consider the use of EMG monitoring of cranial nerves other than VII not widespread or universally accepted,[110] recent interest in skull-base surgery has spurred EMG monitoring for lower cranial nerve preservation. Some recent evidence suggests EMG monitoring proved to be a safe tool for the intraoperative identification and localization of the lower cranial nerves, contributing to their anatomic and functional preservation. The predictive value of standard neurophysiologic parameters for functional outcome, however, is limited.[128]

There is great interest in intraoperative use of motor evoked potentials (MEPs) because of the theoretic limitations of SSEPs in monitoring motor function.[110] MEPs assess function of the motor cortex and descending tracts. The peripheral response of the MEP is recorded by measuring the compound muscle action potential.[112] The motor cortex is stimulated by electrical or magnetic stimulation. Both volatile anesthetics and neuromuscular blocking drugs suppress these responses.[112,129,130]

Evoked potentials may be affected by various anesthetics. Neuromuscular blockade resulting in a 70% or less reduction in the height of the response to ulnar nerve stimulation is compatible with MEP monitoring.[110,131] A combination of N_2O-narcotic anesthetic and a stable level of neuromuscular blockade, such as that provided by an infusion of neuromuscular blocking agent, has been advocated to provide a stable response.[112] Some authors recommend that N_2O be kept to less than 50% or not used if monitoring of MEPs is vital to safe spinal surgery.[132,133] Total intravenous anesthesia using infusions of propofol in combination with a narcotic allow stable MEP recordings. Total intravenous anesthesia with ketamine also has been recognized as being compatible with stable MEP readings.[110,134]

MEP responses produced by electrical stimulation of the spinal cord are resistant to the effects of anesthesia and require no special anesthetic considerations other than the need for muscle relaxants to prevent gross movements.[110] Recommended monitoring modalities and anesthestic techniques for various surgical produres are shown in Table 28-6.

ANESTHETIC CONSIDERATIONS FOR SPECIFIC PROCEDURES

Supratentorial Surgery

Intracranial masses may be congenital, neoplastic (benign, malignant, or metastatic), infectious (abscess or cyst), or vascular (hematoma or malformation). Most but not all anesthetics

TABLE 28-6 Recommended Monitoring Modalities and Anesthetic Regimens for Surgical Procedures

	MONITORING MODALITIES					ANESTHETIC RECOMMENDATION	
			ELECTROMYOGRAPHY				
Type of Procedure	Somatosensory Evoked Potentials	Transcranial Motor Evoked Potentials	Free Run	Stimulated	Auditory Brainstem Responses	Volatile (Inhalational Anesthetics)	Total Intravenous Anesthesia
Spine Skeletal							
Cervical	•	•	•				•
Thoracic	•	•	•	•			•
Lumbar instrumentation	•		•	•		•	
Lumbar disc			•	•		•	
Head and Neck							
Parotid			•	•		•	
Radical neck			•	•		•	
Thyroid			•	•		•	
Cochlear implant			•	•		•	
Mastoid			•	•		•	
Neurosurgery							
Spine							
Vascular	•	•					•
Tumor	•	•					•
Posterior Fossa							
Acoustic neuroma			•	•	•	•	
Cerebellopontine	•	±	•	•	±		•
Vascular	•	•	•		±		•
Supratentorial							
Middle cerebral artery aneurysm		•					•
Tumor in motor cortex	•	•					•

Adapted from Jameson LC, Sloan TB, et al. Monitoring of the brain and spinal cord. *Anesthesiol Clin*. 2006;24:777.
• Recommended for most surgeries; ± recommended for some procedures (depending on specific location of pathology).

can be used safely in patients with cerebral lesions. Important considerations are the effects of the agent on ICP, CPP, CBF, $CMRO_2$, promptness of return of consciousness, drug-related protection from cerebral ischemia or edema, blood pressure control, and compatibility with neurophysiologic monitoring techniques.[135]

Most craniotomy surgery in the United States today is performed after a propofol induction of anesthesia with intubation of the trachea after administration of a nondepolarizing relaxant. Maintaining anesthesia is commonly accomplished with a volatile agent (often isoflurane) and a narcotic, such as fentanyl, sufentanil, alfentanil or remifentanil, in various combinations.[135]

Preoperative Evaluation

The clinical signs of a supratentorial mass include seizures, hemiplegia, and aphasia. The clinical signs of infratentorial masses include cerebellar dysfunction (ataxia, nystagmus, dysarthria) and brainstem compression (cranial nerve palsies, altered consciousness, abnormal respiration). When ICP increases, frank signs of intracranial hypertension also can develop.[98]

Preanesthetic evaluation should attempt to establish the presence or absence of intracranial hypertension. Computed tomography or magnetic resonance imaging (MRI) data should be reviewed for evidence of brain edema, midline shift greater than 0.5 cm, and ventricular size. A neurologic assessment should evaluate the current mental status and any existing deficits. Anticonvulsant therapy and medications prescribed for control of ICP (corticosteroids, diuretics) should be reviewed. Laboratory evaluation should rule out corticosteroid-induced hyperglycemia and electrolyte disturbances that may develop secondary to diuretic therapy. For anticonvulsants, amount, time of last dose, and blood levels should be noted.

The decision regarding the amount and timing of the premedication administration should be made only after a thorough patient evaluation. Benzodiazepines produce respiratory depression and hypercapnia. Premedication should be omitted in patients with a large mass lesion, a midline shift, and abnormal ventricular size. Opioids are universally avoided in the preoperative period. If premedication is desired in those patients deemed appropriate, careful titration of intravenous midazolam may begin once the patient has been delivered to the preoperative holding area. In an attempt to help control ICP in patients with mass lesions, the head of the bed should be elevated 15 to 30 degrees during transport to the preoperative holding area and the operating room. Due diligence to all existing hospital recommendations for prophylactic antibiotics given at the appropriate time and in the appropriate amount should be performed.

TABLE 28-7 Cerebral Oxygenation Monitoring

Monitor	Abbreviations	Comments
Jugular bulb oximetry	$Sjvo_2$	Invasive; monitors global not focal ischemia and hypoxia; < 50% desaturation suggests inadequate delivery or excessive consumption; > 75% suggests hyperemia or stroke
Transcranial Doppler monitoring	rso_2	Noninvasive; monitors flow within the Circle of Willis; temporal bone thickness may prevent monitoring; ratio > 3 may be indicative of vasospasm; ratio < 3 suggests hyperemia
Brain tissue oxygen tension	Pbo_2	Invasive; reserved for global head injuries; simultaneously estimates tissue oxygen tension and ICP; normal values 20-45 mmHg; pathologic reading < 15 mmHg
Near-infrared spectroscopy	NIRS	Noninvasive; estimates brain tissue saturation; concerns with reliability and specificity; may be best used as a trend monitor for flow

Adapted from Miller RD, et al, eds. *Miller's Anesthesia: Expert Consult.* 7th ed. Philadelphia: Churchill Livingstone; 2009:2905-2907.
ICP, Intracranial pressure.

Intraoperative Monitoring

Routine monitors for supratentorial procedures include continuous electrocardiography, cuff measurement of blood pressure, precordial stethoscope, monitoring of the fraction of inspired oxygen, pulse oximetry, temperature, peripheral nerve stimulation, end-tidal CO_2 ($ETco_2$) monitoring, and indwelling urinary catheterization. For patients with ischemic heart disease, use of a modified V_5 ECG lead is recommended. An arterial line placed either before or immediately after anesthetic induction provides for uninterrupted blood pressure monitoring and easy access for blood sampling for laboratory analysis. SSEPs may be assessed. Methods for cerebral oxygenation monitoring are listed in Table 28-7.[136-138]

Fluid Management

Tissues within the CNS are subject to water movement governed by the blood-brain barrier. The pore size in the blood-brain barrier is only one tenth that of the periphery, at 0.7 to 0.9 nm.[139] There is a fundamental difference between capillaries within the CNS and the peripheral capillaries. The blood-brain barrier remains impermeable to both ions and proteins. The number of ions represents a greater magnitude in determining the net movement of water than the number of plasma proteins. There can be little doubt that osmolarity is the primary determinant of water movement across the intact blood-brain barrier.[140,141]

Normovolemia is the goal during intracranial surgery. Preoperative fluid deficits and intraoperative blood and fluid losses must be adequately replaced during neurosurgical procedures. Judicious fluid administration minimizes the occurrence of cerebral edema and increased ICP, reduced CPP, and worsened cerebral ischemia. In most neurosurgical patients, fluids that contain sodium in a concentration similar to that of serum (e.g., lactated Ringer's solution or 0.9% saline) are administered in a volume sufficient for maintaining peripheral perfusion but avoiding hypervolemia (0.5 to 1 mL/kg/hr). Traditionally, less fluid was given than would be administered for nonneurologic surgery, although current recommendations indicate that patients should be kept isovolemic, isotonic, and isooncotic.[142-145] Glucose-containing or hypoosmolar solutions such as lactated Ringer's solution should be avoided. The use of isoosmolar crystalloids is widely accepted and can be justified on a scientific basis.[141,146,147]

Hyperglycemia induces marked detrimental cerebrovascular changes during both ischemia and reperfusion.[148] Multiple studies have demonstrated that hyperglycemia before and during an episode of global cerebral ischemia will exacerbate the neurologic injury.[149]

Hyperglycemia-enhanced ischemic injury is due to several factors including a rise in lactate production and concomitant tissue acidosis.[150-152] Another theory suggests that hyperglycemia enhances ischemic injury by attenuating an increase in adenosine.[150,153,154] Yet another theory suggests that hyperglycemia significantly worsens the degree of acute blood-brain barrier disruption that occurs during ischemia.[150,155] It is also thought that hyperglycemia is associated with a significantly reduced CBF and increased heterogeneity of regional CBF during the postischemic period.[150,156-159]

Fluid therapy is most challenging during prolonged surgical procedures or in the surgical management of multiple traumas. If tissue trauma is severe or if hemorrhage has been prolonged, patients develop a marked reduction in functional extracellular volume as a result of the internal redistribution of fluids (third-space losses). Although the extent of tissue manipulation in most routine neurosurgical procedures is small, third-space fluid losses during prolonged surgery and in patients with severe associated systemic trauma can be sufficient to decrease intravascular volume, reduce peripheral perfusion, and impair renal function. The sequestered extracellular fluid can be cautiously replaced with 0.9% saline. In the absence of diuretic therapy, a urinary output of 0.5 to 1 mL/kg/hr suggests adequate replacement, as do hemodynamic stability and cardiac filling pressures within the normal range. Hematocrit should be kept above 28%.[135]

Anesthetic Induction and Maintenance

Although induction of anesthesia for patients undergoing craniotomy can be performed with various agents, a smooth and gentle induction of general anesthesia is more important than the drug combination used. No evidence indicates that one technique or set of drugs is better than another. A reasonable induction sequence would combine preoxygenation, propofol (1 to 2 mg/kg), and a nondepolarizing muscle relaxant. No evidence suggests that any of the induction agents is superior. The hemodynamic response to intubation may be blunted with the administration of fentanyl (10 to 15 mcg/kg total dose) or lidocaine (1.5 mg/kg) administered 3 minutes before laryngoscopy. The dose of these induction agents may need to be adjusted according to the patient's age and physical status. Whatever agents are selected, the induction should be accomplished without the development of sudden hypertension or hypotension.

The head typically is elevated from 15 to 30 degrees to facilitate venous and CSF drainage. The head also may be turned to the side to facilitate exposure. Excessive neck flexion may impede jugular venous drainage and increase ICP. Because of the flexion-extension-rotation of the head in combination with head fixation in a pinion headrest, the use of an armored or reinforced endotracheal tube (ETT) is recommended to avoid kinking of the tube once positioning is accomplished. The ETT follows the position of the chin. With extension of the neck, the chin and ETT move

cephalad; with neck flexion, the chin and ETT move caudad. The anesthesia circuit connections must be firmly secured by simultaneously pushing and twisting to seat the plastic connectors. The risk of unrecognized disconnections may be increased because the operating table is usually turned 90 to 180 degrees away from the anesthetist, and both the patient and the breathing circuit are almost completely covered by surgical drapes.[98]

Maintenance of anesthesia may be accomplished with an oxygen-air-opioid technique, a selected potent inhalation agent, or oxygen-air and a continuous infusion of propofol. After endotracheal intubation, mechanical hyperventilation is begun, decreasing $ETCO_2$ to 30 to 35 mmHg, confirmed through arterial blood gas analysis. The patient should be covered with blankets or a forced-air warming blanket to maintain core body temperature.

An opioid-based anesthetic technique with air in oxygen with low-dose (less than 1%) isoflurane is a popular choice. Incremental administration of fentanyl, sufentanil, alfentanil, or an infusion of remifentanil is acceptable. Sufentanil as a 0.5 to 1 mcg/kg loading dose, followed by either incremental boluses (not to exceed 0.5 mcg/kg/hr) or an intravenous infusion of 0.25 to 0.5 mcg/kg/hr in combination with less than 1% isoflurane in oxygen may be used. Sufentanil administration should be discontinued approximately 45 minutes before the end of surgery to ensure that the patient awakens promptly. The primary advantage of remifentanil is rapid awakening. If the patient experiences hypertension or tachycardia near the end of surgery, the practitioner should consider giving either labetalol or esmolol, not additional opioids.[160]

A volatile agent (isoflurane, desflurane, or sevoflurane) with little or no opioid supplementation also can be used for maintenance of anesthesia. If isoflurane is used, the concentration should remain less than 1%. Hyperventilation in combination with less than 1% isoflurane generally results in stable intracranial dynamics.[160]

N_2O may be used in an anesthetic regimen if it is deemed desirable. However, if the patient is suspected to have a pneumocephalus or the potential for air embolism exists, N_2O use is contraindicated. N_2O expands both the pneumocephalus and the air embolus. A tension pneumocephalus acts like an expanding mass lesion. A large air embolus can cause cardiovascular collapse.[160]

Hyperventilation is an important adjunct to any neuroanesthetic technique. Hypocapnia decreases ICP before opening of the dura and attenuates the vasodilation produced by the volatile anesthetic agents. Optimal hyperventilation during surgery would yield a $PaCO_2$ of 30 to 35 mmHg. Diuretics, when indicated, may be timed just before or after the cranial vault is opened to facilitate surgical exposure.

Skeletal muscle relaxation prevents patient movement at inappropriate times. It may decrease ICP by relaxing the chest wall, decreasing intrathoracic pressure, and facilitating venous drainage. In choosing an agent for muscle relaxation, the length of the procedure and the effect of the drug on ICP should be considered.[160]

Emergence

Arguably, in no other anesthetic situation is careful attention to appropriate planning for the emergence from anesthesia as important as in neurosurgical brain tumor surgery. Sudden emergence from anesthesia can result in uncontrolled hypertension. Delirium with coughing and straining on the endotracheal tube should be avoided. In a patient with a compromised blood-brain barrier, this stormy emergence can produce devastating consequences. Late emergence from anesthesia can result in a confusing diagnostic picture with possible intracranial hematoma, acute hydrocephalus, or other diagnoses masked by the residual anesthesia.[92]

The goal for emergence is control. A controlled emergence focuses on regulation of blood pressure, ICP, and CBF. Controlled emergence also accounts for the preexisting pathophysiology, the surgical trauma, the length of the procedure, and appropriate management of the airway.[92]

Emergence from anesthesia begins when the surgical pathology has been addressed. Collaboration with the surgeon is essential. Prior to closing the dura, the appropriate levels of postoperative blood pressure can be determined. The $PaCO_2$ should be allowed to return to a normal level. Blood pressure can then be raised to 120% of the normal baseline level prior to closing of the dura. Hypertension is considered a frequent occurrence of the postoperative period.[134,161,162] Tachycardia associated with hypertension "invariably" results from emergence excitement.[163] By raising the blood pressure and the $PaCO_2$ prior to dural closure, the ability of the brain to withstand such challenges can be directly assessed by the surgeon.[92]

Once the dura has been closed, the blood pressure is maintained at baseline levels throughout the remainder of the closure.

There is strong support for the notion that sympatholytic drugs should be used to decrease blood pressure during emergence.[164] Studies have shown that during the first hour after craniotomy for supratentorial lesions, the arteriovenous oxygen content difference is low, suggesting a state of cerebral luxury perfusion.[165,166] This event coincides with a high level of mean arterial blood pressure. Accordingly, it is supposed that this correlation is caused by changes in the mean blood pressure and impaired autoregulation. This may be deleterious, because it enhances blood-brain barrier leakage, provoking edema and hemorrhage.

A relationship between hypertension and postoperative hematoma formation exists.[167] The parameters for these events for each individual patient are unknown. Normal autoregulation of CBF maintains adequate perfusion at mean blood pressures ranging from 50 to 150 torr,[168] but the effects on autoregulation of combinations of anesthetic agents over a prolonged case and under varying temperatures are unknown.[149] Labile hypertension and unstable blood pressure during the perisurgical period may contribute to intracerebral hemorrhage remote from the site of the initial neurosurgical procedure.[169] Given the evidence, and without the need to volume expand and maintain the patient in a hyperdynamic manner, it would seem prudent to institute some form of blood pressure control to provide the most controlled emergence possible.

Judicious titration of short-acting antihypertensives (esmolol, labetalol) has great clinical utility in controlling blood pressure during emergence. When access to the patient is regained, the use of anesthetic gases is discontinued, and the muscle relaxant is reversed. Intravenous lidocaine (1.5 mg/kg) can be given just before suctioning for cough suppression before extubation. Rapid awakening facilitates immediate neurologic assessment and can generally be expected after a pure opioid-N_2O technique. Delayed awakening may result from residual opioid or remaining end-tidal concentrations of potent inhalation agent. After extubation, the patient is transported to the intensive care unit postoperatively for continued monitoring of neurologic function.[164]

Awake Craniotomy

In a small percentage of patients—those in whom a seizure focus may be suppressed during general anesthesia or may be adjacent to an area of eloquent cortical function—awake craniotomy may be necessary.[170] Sources feel awake craniotomy is the most reliable method to ensure neurologic integrity in the presence of

cerebral gliomas that infiltrate or come close to the especially sensitive areas of the brain. Awake craniotomy allows for localization of eloquent cortical areas by electrical stimulation and of epileptic foci through cortical recordings. Continuous monitoring of the functional integrity of the brain in awake patients is inherently protective while surgical removal of the gliomatous tissue is performed.[171] Anesthetic techniques may vary, depending on whether the procedure is for tumor removal or seizure treatment.

Patient Selection

To minimize the risk of intraoperative complications, contraindications for awake craniotomy include developmental delay, lack of maturity, an exaggerated or unacceptable response to pain, a significant communication barrier, and a failure to obtain patient consent. Only those patients with the ability to clearly understand risks and benefits and who, in the opinion of the neurosurgeon and the anesthesia team, will cooperate during surgery should be considered as candidates for an awake craniotomy.[170] Seizure management should be optimized with acceptable levels of antiepileptic medications verified.

Patient Teaching

The single most important element in the successful awake craniotomy is a highly motivated, well-informed patient. Each step of the procedure is discussed with the patient and family. Special emphasis is paid to prolonged surgical procedure, positioning, head immobility, pain anxiety, monitoring, noise, seizure management, and any individual considerations.

Anesthesia Induction and Maintenance

Upon arrival to the holding area, an intravenous line is established. Preanesthesia medications are administered; they may include antibiotics, steroids, antiemetic prophylaxis, and anticonvulsants as indicated.

In the operating room suite, application of noninvasive monitoring is completed. Last-minute questions are addressed, and the patient is induced with propofol. Some sources use either dexmedetomidine singly or in combination with propofol.[172] After satisfactory general anesthesia is established, a laryngeal mask airway (LMA) is placed, with patient ventilation controlled using a continuous propofol infusion. Invasive monitoring is established (arterial line, central line, urinary catheter). The scalp is anesthetized with 0.5% bupivacaine and the head placed in a pinion head holder. The patient is carefully positioned with all bony surfaces padded and the patient carefully secured to the table to minimize a sense of falling when the table is moved during the awake phase of the surgery. Frameless stereotaxis registration is accomplished. Depending on the preoperative radiographic edema findings, hypertonic saline or mannitol is given. During the draping, an area is constructed around the patient's face such that the face may be clearly seen and accessed. A light is introduced under the drapes to keep the patient from darkness. During the scalp opening, spontaneous ventilation is established. Prior to the bone flap removal, the LMA is removed and verbal contact established.

Awake Phase

All sedation is stopped. All issues regarding patient comfort and concerns are addressed prior to the incision of the dura. Conversation with the patient is confined to the surgeon and one member of the anesthesia team. Stimulation of eloquent areas is carried out with results noted. Any seizures are controlled with propofol, or cold saline is available if needed.[173] Following the stimulation and mapping, volumetric surgical removal of the tumor or seizure focus is accomplished with interval monitoring. Upon completion of the surgical removal and requisite monitoring, propofol sedation may be restarted and titrated to patient preference. Sedation is discontinued upon conclusion of surgery. The most common complications associated with awake craniotomy are pain, seizures, nausea, and confusion.[174,175]

BOX 28-5

Clinical Situations Contributing to the Occurrence of Venous Air Embolism

- Patient positioning (seated, prone, steep Trendelenburg)
- Transfusion therapy
- Intravenous therapy
- Central venous catheterization
- Hepatic surgical procedures
- Urologic surgical procedures
- Posterior spinal procedures
- Epidural or caudal catheter insertion
- Bone marrow harvesting
- Laparoscopy
- Radical pelvic surgery
- Obstetric gynecologic procedures
- Thoracic procedures
- Orthopedic procedures
- Cardiac surgery
- Head and neck surgery

Posterior Fossa Surgery

Neuropathology within the posterior fossa may impair control of the airway, respiratory function, cardiovascular function, autonomic function, and consciousness. The major motor and sensory pathways, the primary cardiovascular and respiratory centers, the reticular activating system, and the nuclei of the lower cranial nerves are all concentrated in the brainstem. All of these structures are contained in a tight space with little room for edema, tumor, or blood.

Venous Air Embolus

In addition to the previously mentioned monitoring modalities, monitoring during posterior fossa surgery requires consideration of patient position and the potential for venous air embolus (VAE). Clinical situations that contribute to the occurrence of VAE are listed in Box 28-5. Air also may be entrained from the cranial pin sites of the Mayfield head holder and from improperly connected vascular lines (arterial, central, and intravenous).

The occurrence of VAE depends on the development of a negative pressure gradient between the operative site and the right side of the heart. As the gradient between the cerebral veins and the right atrium increases, the potential for air entry increases. The estimated incidence of VAE during neurosurgical procedures ranges from 5% to 50%, with an increased incidence in the sitting position.[176,177] A recent systematic review of 4806 patients undergoing sitting position neurosurgery noted a 39% rate of VAE for posterior fossa surgery and 12% for cervical procedures.[178]

As the venous pressure at wound level is usually negative, air can be entrained. This air may follow any of four pathways. Most commonly it passes through the right heart into the pulmonary circulation, diffuses through the alveolar-capillary membrane, and appears in expelled gas. It also may pass through a

pulmonary-systemic shunt such as in a patient with a patent foramen ovale (paradoxical air embolism). It may collect at the superior vena cava–right atrial junction. Lastly, rarely it may traverse through lung capillaries into the systemic circulation.[179,180]

The physiologic consequences of VAE depend on both the volume and the rate of air entrainment. In the canine model, large cumulative doses of air produce sudden cardiac arrest and death; smaller cumulative doses produce less profound physiologic consequences, including increased pulmonary artery and central venous pressure, decreased cardiac output with accompanying hypotension, progressive hypotension, and dysrhythmias.[181] Despite the potentially devastating effects of VAE, a retrospective review of neurosurgery patients who had appropriate monitoring for the detection of VAE found that VAE contributed to patient morbidity or mortality in only six instances (0.4%).[182-184]

Paradoxical Air Embolism

Paradoxical air embolism (PAE) develops with the entry of air into the systemic circulation. Individuals with an existing anatomic connection between the right and left sides of the heart (atrial or ventricular septal defect, probe-patent foramen ovale) are at risk. A patent foramen ovale may exist in 30% to 35% of the population.[185] If right-sided heart pressures exceed left-sided pressures (a situation that may occur in fluid-restricted neurosurgical patients), systemic air may embolize and enter the arterial circulation through a probe-patent foramen ovale.

Patients who require the sitting position should be carefully evaluated with echocardiograms if the history suggests the presence of an intracardiac defect (presence of heart murmur) or probe-patent foramen ovale. The presence of a probe-patent foramen ovale may be elicited with the injection of contrast material before, during, and after the patient produces a Valsalva maneuver. If the condition is identified, the surgical procedure should be accomplished in an alternative position.[186]

Detection of Venous Air Embolus

The entrainment of air into the vascular system is usually of little consequence, because the lungs serve as effective blood filters.[187] Small bubbles of air are absorbed into the blood or enter the alveoli, where they are eliminated. However, the efficient filtering capacity of the lung may be breached by a large bolus of air. Air enters the venous circulation as small bubbles that pass through the right side of the heart, entering the pulmonary arterioles. A reflexive sympathetic pulmonary vasoconstriction is produced after the release of endothelial mediators, which are ultimately responsible for the clinical manifestations (pulmonary hypertension, hypoxemia, CO_2 retention, increased dead-space ventilation, and decreased ET_{CO_2}). The continued entry of air produces an airlock within the right ventricle, producing right ventricular failure and decreased cardiac output. Altered ventilation-perfusion relationships parallel the hemodynamic changes. Obstructed pulmonary blood flow increases dead-space ventilation, resulting in decreased ET_{CO_2}. The entry of a large volume of air in the alveoli may be detected by the sudden appearance of end-tidal nitrogen. Studies indicate that entrapement of small amouts of air less than 0.5 mL/kg will manifest as a decreased ET_{CO_2} , increased end-tidal nitrogen (ETN_2), oxygen desaturation, altered mental status, and wheezing. Moderate amounts of entrapped air, approximately 0.5 to 2.0 mL/kg, will produce difficulty breathing, wheezing, hypotension, ST changes, peaked P waves, jugular venous distention, myocardial and cerebral ischemia, bronchoconstriction, and pulmonary vasoconstriction. Large quantities of air entrapement greater than 2.0 mL/kg result in chest pain, right-sided heart failure, and cardiovascular collapse.[188]

The selection of appropriate monitoring for the detection of VAE is based on the various sensitivities of the available monitoring modalities (Table 28-8).[187] Precordial Doppler monitoring can detect air entrainment at rates as small as 0.0021 mL/kg/min.[189] The Doppler probe is affixed over the right side of the heart along the right sternal border between the third and sixth intercostal spaces. Proper positioning over the right atrium is confirmed if a change in Doppler signal is elicited when a 10-mL bolus of saline is injected rapidly into a previously placed right central venous catheter.[189-191] Placement of a right atrial catheter affords the means for diagnosis and recovery of intravenous air and also reflects cardiac preload. When a right atrial catheter is placed, it is recommended that either radiographic confirmation or ECG confirmation of proper placement of the catheter tip be obtained.[191] Advantages and disadvantages of selected monitors for detection of VAE are noted in Table 28-8.

Capnography complements the capabilities of the Doppler device, because small, hemodynamically insignificant air emboli detected with the Doppler device can be differentiated from emboli that may produce arterial hypotension.

Transesophageal echocardiography (TEE) is the most sensitive method of air embolism detection, but it is also the most expensive. With TEE, it is possible to observe both cardiac contractility and air bubbles as they pass through the heart.[192] TEE is also capable of detecting PAE in the heart. The detection of a "millwheel" murmur via precordial or esophageal stethoscope is a late sign of air entrainment.

Treatment of Venous Air Embolus

Detection of VAE should prompt certain crucial steps (Box 28-6). The surgeon should be notified, and N_2O should be immediately discontinued, 100% oxygen delivered, and the right atrial catheter aspirated.[193] The surgeon should flood the surgical field with irrigation or pack the area with saline-soaked sponges. A Valsalva maneuver or bilateral compression of the jugular veins for 5 to 10 seconds increases the cerebral venous pressure and induced bleeding. The addition of positive end-expiratory pressure also slows air entry. However, 10 to 15 cm H_2O may be required to effectively elevate venous pressure when the head is elevated. The head should be lowered to decrease air entrainment. This may be accomplished by placing the operating table in Trendelenburg position. If air entrainment continues, the anesthetist should ask for an assistant. A second pair of hands allows simultaneous jugular vein compression and central catheter aspiration.[194,195]

Supportive therapy is required for hemodynamic compromise. Administration of ephedrine, 10 to 20 mg intravenously, and an intravenous fluid bolus improves the blood pressure. If these measures do not restore blood pressure, additional vasopressors (epinephrine) may be required.

Anesthetic agent and technique may influence the rate of air entrainment and the resulting physiologic consequences. The anesthetist should recall the role N_2O may play in the patient at risk for VAE, because N_2O is known to increase the volume of embolized air. Munson and Merrick[193] demonstrated that the expansion of an intravascular air bubble is proportional to the delivered concentration of N_2O. A 50% concentration doubles the initial air-bubble volume, and a 70% concentration quadruples the air-bubble volume. General endotracheal anesthesia with controlled ventilation is thought to be protective in patients experiencing VAE.

TABLE 28-8 Monitors for Detection of Venous Air Embolism

Monitor	Advantages	Disadvantages
Precordial Doppler ultrasonography	Most sensitive noninvasive monitor Earliest detector (before air enters pulmonary circulation)	Not quantitative May be difficult to place in obese patients, patients with chest wall deformity, or patients in the prone/lateral positions False-negative result if air does not pass beneath ultrasonic beam (about 10% of cases) Useless during electrocautery IV mannitol may mimic intravascular air
Pulmonary artery (PA) catheter	Quantitative, slightly more sensitive than $ETCO_2$ Widely available Placed with minimum difficulty in experienced hands Can detect right-atrial pressure greater than pulmonary capillary wedge pressure	Small lumen, less air aspirated than with right-atrial catheter Placement for optimal air aspiration may not allow pulmonary capillary wedge pressure measurement Nonspecific for air
Capnography ($ETCO_2$)	Noninvasive Sensitive Quantitative Widely available	Nonspecific for air Less sensitive than Doppler ultrasound, PA catheter Accuracy affected by tachypnea, low cardiac output, chronic obstructive pulmonary disease
End-tidal nitrogen (ETN_2)	Specific for air Detects air earlier than $ETCO_2$	May not detect subclinical air embolism May indicate air clearance from pulmonary circulation prematurely Accuracy affected by hypotension
Transesophageal echocardiography (TEE)	Most sensitive detector of air Can detect air in left side of heart, aorta	Invasive, cumbersome Expensive Must be observed continuously Not quantitative May interfere with Doppler ultrasonography

From Cottrell JE, Young WL, eds. *Cottrell and Young's Neuroanesthesia*. 5th ed. Philadelphia: Mosby; 2010:210.

BOX 28-6

Therapy for Venous Air Embolism

- Notify surgeon on detection (flood surgical field with saline and wax bone edges)
- Discontinue nitrous oxide administration; administer 100% oxygen
- Perform a Valsalva maneuver or compression of jugular veins
- Aspirate air from atrial catheter
- Support blood pressure with volume and vasopressors
- Reposition patient in left lateral decubitus position with a 15-degree head-down tilt if blood pressure continues to decrease
- Modify the anesthetic as needed to optimize hemodynamics
- Postoperative follow-up should include ECG, chest x-ray, and arterial blood gases with oxygen as needed

ECG, Electrocardiogram.

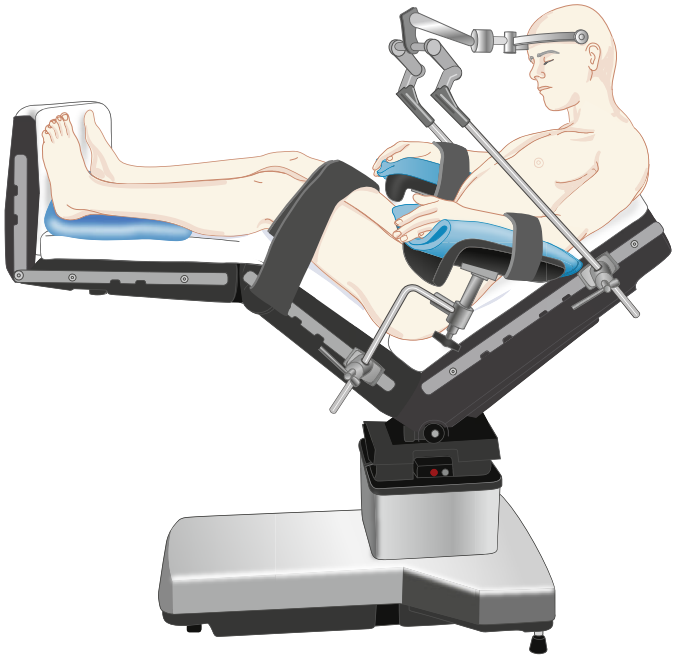

FIGURE **28-18** Representation of a patient properly positioned for seated posterior fossa operation with the knees at heart level and the neck not hyperflexed. (From Miller RD, et al, eds. *Miller's Anesthesia*. 7th ed. Philadelphia: Churchill Livingstone; 2010:1163.)

Surgical Positioning

Although most posterior fossa explorations may be performed with the patient in either the lateral or prone position, the sitting position (Figure 28-18) is occasionally preferred because the enhanced CSF and venous drainage facilitates surgical exposure. The use of this position, however, has declined dramatically because of the potential for serious complications.[196,197] The patient is semirecumbent in the standard sitting position with the back elevated to 60 degrees and the legs elevated (with the knees flexed) to the level of the heart. The latter is important for preventing venous pooling and reducing the risk of venous thrombosis. The head is fixed in a three-point head holder with the neck in flexion, and the arms remain at the sides with the hands resting on the lap.[98]

Careful positioning is essential to prevent iatrogenic injury. Pressure points such as the elbows, ischial spines, and forehead must be protected with foam padding. Excessive neck flexion has

BOX **28-7**

Postoperative Considerations with Posterior Fossa Surgery

- Cranial nerve dysfunction
- Central apnea
- Loss of upper airway control and patency
- Altered level of consciousness
- Altered cardiomotor function
- Cardiac dysrhythmias

Adapted from Miller RD, et al, eds. *Miller's Anesthesia*. 7th ed. Philadelphia: Churchill Livingstone; 2009:2073.

been associated with swelling of the upper airway (venous obstruction) and, rarely, quadriplegia resulting from compression of the cervical spinal cord and decreased cervical cord perfusion when the neck is elevated above the heart. Preexisting cervical spinal stenosis probably predisposes to the latter injury.[98]

Anesthetic Induction, Maintenance, and Emergence

Increased ICP, although common in patients with supratentorial lesions, is less common in patients with posterior fossa lesions. Obstructive hydrocephalus is more typical because CSF outflow is occluded at the level of the aqueduct of Sylvius or fourth ventricle. This can be readily identified preoperatively by magnetic resonance imaging or computed tomography and may be corrected before definitive surgical intervention with the placement of a ventricular catheter. Premedication is contraindicated in patients with obstructive hydrocephalus.

Induction should be slow and deliberate to avoid changes in cerebral perfusion and increased ICP. Because the head is generally flexed and fixed in this position, a wire-reinforced ETT may prevent intraoperative kinking. These tubes may become permanently kinked if the patient is lightly anesthetized and bites the tube. Intravenous fluid administration during posterior fossa surgery should be limited to the infusion of deficit and maintenance quantities of a balanced salt solution. Major volume resuscitation can be accomplished with the infusion of blood, colloid, or crystalloid solutions.

Emergence from anesthesia should be as smooth and gentle as possible. The intraoperative use of opioids facilitates a smooth emergence without significant coughing and bucking. The administration of lidocaine 1.5 mg/kg intravenously decreases the airway irritation of the ETT.[194]

The decision to remove the ETT should be made after the anesthetic course and surgical procedure are reviewed. Intraoperative air embolism may be followed by the development of pulmonary edema. Although this condition is self-limiting, continued mechanical ventilation is the treatment of choice. Consideration also must be given to the possibility of cranial nerve damage during the operative procedure. Provided the patient is safely extubated, continued vigilant observation is essential because airway compromise may develop after injury to cranial nerves IX, X, and XI (Box 28-7).

Pituitary Surgery

Approximately 10% of intracranial neoplasms are found in the pituitary gland and come to clinical attention because of their mass effects or the hypersecretion of pituitary hormones. These tumors are rarely metastatic and produce local symptoms via bone invasion, hydrocephalus, and compression of a cranial nerve (most often the optic nerve). Frontotemporal headache and bitemporal hemianopsia are the most common nonendocrine symptoms of enlarging pituitary lesions. Nonsecreting pituitary tumors account for approximately 20% to 50% of lesions in this area and are classified as *chromophobe adenomas*.[197,198]

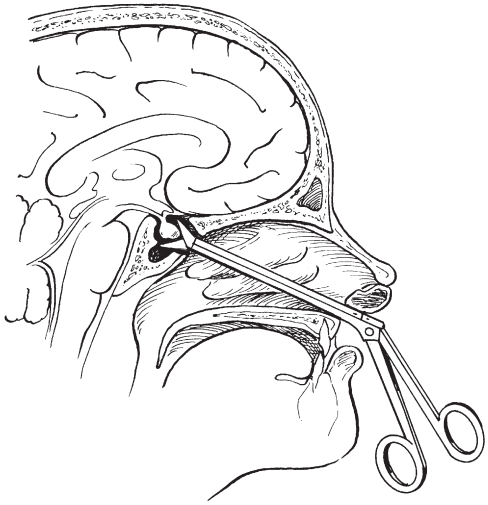

FIGURE **28-19** Transsphenoidal approach to the pituitary gland. (From Black JM, Hokanson Hawks JH. *Medical-Surgical Nursing: Clinical Management for Positive Outcomes*. 8th ed. St. Louis: Saunders. 2009:1829.)

Tumors that secrete excess growth hormone produce acromegaly. Increased growth hormone increases the size of the skeleton, particularly the bones and soft tissues of the hands, feet, and face. The enlarged facial structures may increase the likelihood of difficult intubation. Excess growth hormone also may contribute to the development of coronary artery disease, hypertension, and cardiomyopathy. Hyperglycemia is also a common finding, reflecting a growth hormone–induced glucose intolerance.[199]

Surgical Approach

Medical and surgical therapies exist for both functional and nonfunctional pituitary tumors. Transsphenoidal surgery (Figure 28-19) offers several advantages over the intracranial approach. Statistically, morbidity and mortality rates are reduced because of a decrease in blood loss and less manipulation of brain tissue. In addition, the risk of inducing panhypopituitarism and the incidence of permanent diabetes insipidus are both reduced. For patients with large tumors (greater than 10 mm), tumors of uncertain type, and tumors that have substantial extrasellar (beyond the sella turcica) extension, the transsphenoidal approach is inadequate, and a bifrontal intracranial approach is required for successful removal.[199] Current trends are moving toward endoscopic approaches to the pituitary tumor. Less invasive approaches, such as the transnasal approach combined with endoscopic resection of tumor, have been performed. The endoscopic technique entails less morbidity and a shorter hospital stay than the traditional approach.[200]

Preoperative Evaluation

Patients undergo transsphenoidal operations for the treatment of hypersecreting pituitary tumors. Clinical symptoms of pituitary tumors include amenorrhea, galactorrhea, Cushing disease, and acromegaly.

Each preoperative condition has its own constellation of systemic disorders and accompanying effects on intracranial dynamics that must be considered when an anesthetic technique is

selected. Pituitary tumors can damage decussating optic fibers, producing blindness in the temporal half of the visual field of both eyes (bitemporal heteronymous hemianopsia). Occasionally, an aneurysm of one of the internal carotid arteries may produce nasal hemianopsia on the affected side. Patients who have Cushing disease also may be affected by hypertension, diabetes, osteoporosis, obesity, and friability of skin and connective tissue. Patients who have acromegaly may have hypertension, cardiomyopathy, diabetes, and osteoporosis, as well as cartilaginous and soft-tissue hypertrophy of the larynx and enlargement of the tongue, complicating intubation of the trachea. Patients who have panhypopituitarism may exhibit hypothyroidism, requiring preoperative thyroid supplementation.

The transsphenoidal approach usually necessitates the head and back be elevated 10 to 20 degrees. The patient's head is supported by a three-point pin head holder and centered within a C-arm fluoroscopy unit for radiographic control during surgery. The patient's arms are placed at the sides and padded so that injury to the ulnar nerves is avoided. The patient's airway is shared with the surgeon; therefore, great attention must be directed to the proper securing of the ETT and anesthesia circuit to prevent unintended extubation and anesthesia-circuit disconnect. Hyperventilation is avoided after anesthetic induction, because reductions in ICP result in retraction of the pituitary into the sella, making surgical access difficult. The anesthetist should also consider the potential for massive hemorrhage, because the carotid arteries lie adjacent to the suprasellar area and may be inadvertently injured.

When the resection involves the suprasellar area, postoperative endocrine dysfunction may occur, namely, diabetes insipidus. Diabetes insipidus that occurs after most transsphenoidal procedures is usually self-limited and resolves within a week to 10 days.[196] Although the onset is usually on the first or second postoperative day, diabetes insipidus may develop during the perioperative period or in the immediate recovery period. Intraoperative diagnosis is made with the sudden onset of diuresis. The diagnosis may be confirmed with concurrent urine and serum osmolalities. If diabetes insipidus persists or if it becomes difficult to match urinary losses, the patient may receive aqueous vasopressin (Pitressin) or desmopressin (1-deamino-8-D-arginine vasopressin [DDAVP]). Intravenous DDAVP is longer acting and is not associated with the coronary vasoconstriction that follows administration of aqueous vasopressin.

Anesthetic Induction, Maintenance, and Emergence

After anesthetic induction and intubation, the ETT is typically moved to the left corner of the patient's mouth and secured to the chin with adhesive and tape. A right-angled ETT may be effective because such tubes are pre-bent and curve along the mandible when exiting the mouth. The esophageal stethoscope and temperature probe are inserted and secured on the lower left as well, leaving the upper lip totally exposed. An orogastric tube is placed, aspirated, and then put to gravity drainage during the procedure. The oropharynx is then packed with moist cotton gauze. The eyes are first taped closed and then covered with cotton-padded adhesive patches to prevent corneal abrasion and seepage of cleansing solution and blood into the eyes.

Propofol, an opioid (fentanyl, sufentanil, alfentanil, or remifentanil), and a neuromuscular relaxant (either succinylcholine or a nondepolarizing neuromuscular relaxant for intubation, followed by a selected nondepolarizing agent), with a combination of air and oxygen is a commonly used anesthetic combination for this procedure. Isoflurane may be added in low concentrations for blood pressure control; alternatively, it may be used as the primary anesthetic drug.

The topical use of cocaine and the oral and nasal submucosal injection of local anesthetic solutions containing epinephrine help constrict gingival and mucosal vessels and dissect the nasal mucosa away from the cartilaginous septum. Epinephrine use may produce hypertension or dysrhythmias or both. Cocaine interferes with the intraneuronal uptake of catecholamine and can augment both the hypertensive and dysrhythmogenic properties of epinephrine. The use of epinephrine is relatively safe if (1) ventilation is adequate, (2) epinephrine is given in combination with lidocaine instead of saline, (3) epinephrine concentrations of 1:100,000 to 1:200,000 are used, and (4) total dose does not exceed 10 mL of 1:100,000 solution in 10 minutes for a 70-kg adult. A total dose of 200 mg of cocaine should not be exceeded. Persistent dysrhythmias may require treatment with lidocaine or possibly a β-blocker. Hypertension may be controlled with an increased concentration of the selected inhalation agent or with small intravenous doses of labetalol, or esmolol.[201,202]

In some cases, it may be necessary to insert a catheter into the lumbar subarachnoid space to facilitate the injection of preservative-free saline to delineate the suprasellar margins or for prevention of CSF leak postoperatively. If air is injected, N_2O must be discontinued from the anesthetic mixture because of rapid diffusion into the air present in the closed cranial vault.[202]

Emergence from anesthesia should be conducted as described for the previously discussed procedures. Intravenous lidocaine, 1.5 mg/kg given approximately 3 minutes before suctioning and extubation, decreases coughing, straining, and hypertension. Postoperatively, patients should be responsive to commands in the recovery room. Steroid therapy is continued throughout this period and tapered over time, if appropriate.

Cerebrovascular Surgery

Cerebral Aneurysms

Interventional neuroradiology is often the approach of first choice for the management of intracranial aneurysms. Aneurysm coiling or occlusion of the proximal arteries and obliteration of the aneurysm sac is the preferred therapy for many lesions.[203] The International Subarachnoid Aneurysm Trial and subsequent studies have shown this approach to have several advantages over craniotomy with clipping although recurrence may be higher.[204]

Cerebral aneurysms are abnormal, localized dilations of the intracranial arteries. They are classified as berry or saccular, mycotic, traumatic, fusiform, neoplastic, or atherosclerotic. Rupture of a saccular aneurysm is a leading cause of subarachnoid hemorrhage (SAH).[205]

Approximately 6 million people in North America have cerebral aneurysms, with approximately 25,000 to 30,000 new cases of SAH occurring annually. The peak age for rupture of a cerebral aneurysm is 55 to 60 years. A slight female predilection also exists, with aneurysmal rupture occurring in three women for every two men.[206]

More than 40% of patients with SAH die or develop significant and lasting neurologic disabilities before they receive any treatment. A small bleed occurs in approximately 50% of patients and is often tragically ignored or misdiagnosed. Even in patients who receive prompt care, only half remain functional survivors; the remainder die or develop serious neurologic deficits.[207]

Aneurysms may arise at any point in the circle of Willis. Most aneurysms are broad based and located in the middle cerebral

TABLE 28-9 Modified Hunt and Hess Classification for Subarachnoid Hemorrhage

Score	Neurologic Finding	Mortality (%)
0	Unruptured aneurysm	0-2
1	Asymptomatic or minimal headache and slight nuchal rigidity	2-5
2	Moderate to severe headache, nuchal rigidity, but not neurologic deficit other than cranial nerve palsy	5-10
3	Drowsiness, confusion, or mild focal deficit	5-10
4	Stupor, mild or severe hemiparesis, possibly early decerebrate rigidity, vegetative disturbance	20-30
5	Deep coma, decerebrate rigidity, moribound appearance	30-40

Adapted from Cottrell JE, Young WL, eds. *Cottrell and Young's Neuroanesthesia*. 5th ed. St Louis: Mosby; 2010:219.

system. Traumatic aneurysms develop as a result of direct trauma to an artery, with injury to the wall.

Mirror aneurysms of the internal carotid system are common, and other combinations of locations occur. The site of the bleeding aneurysm is best located by computed tomography studies, evidence of vasospasm in the immediate vicinity, and lobulation of the aneurysm wall on angiographic studies.[205]

Diagnosis of Subarachnoid Hemorrhage

SAH produces an abrupt, intense headache in 85% of patients, and transient loss of consciousness may be seen in up to 45% of patients. Nausea and vomiting, photophobia, fever, meningismus, and focal neurologic deficits are not uncommon. The severity of a SAH can be graded clinically with the use of classifications such as Hunt and Hess (Table 28-9). Although surgical mortality rates vary somewhat among institutions, patients with a neurologic grade I SAH generally undergo surgical clipping with a low mortality rate (less than 5%), whereas grade V patients generally do not survive.[207] Unruptured cerebral aneurysms are commonly detected on brain imaging performed for reasons unrelated to the aneurysms.[208]

General Considerations

Hypertension often accompanies acute SAH and is postulated to develop secondary to autonomic hyperactivity, which may increase transmural pressure in the aneurysmal sac. *Transmural pressure* is defined as the differential pressure between MAP and ICP and represents the stress applied to the aneurysm's wall (Figures 28-20 and 28-21).[207]

Increases in blood pressure directly increase the transmural pressure and the likelihood of bleeding; conversely, reductions in blood pressure reduce transmural pressure and may compromise perfusion. Caution should be exercised when purposefully reducing transmural pressure because cerebral autoregulation may be impaired after SAH, and a reduction in blood pressure may induce or aggravate cerebral ischemia, particularly if vasospasm is present. To balance these opposing concerns, many neurosurgeons attempt to maintain systolic blood pressure between 120 and 150 mmHg before clipping the aneurysm.[203,207]

ECG changes are common after SAH and have been reported to occur in 50% to 80% of patients. The most common changes involve the T wave or the ST segment, but other changes such as

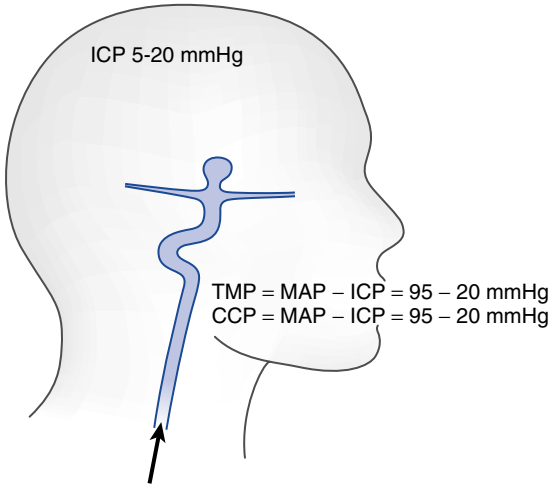

FIGURE 28-20 Determinants of transmural pressure (TMP) and cerebral perfusion pressure (CPP). Both are determined by the difference between mean arterial pressure (MAP) and intracranial pressure (ICP) and are therefore numerically identical. (From Cottrell JE, Young WL, eds. *Cottrell and Young's Neuroanesthesia: Expert Consult*. 5th ed. Philadelphia: Mosby; 2010:226.)

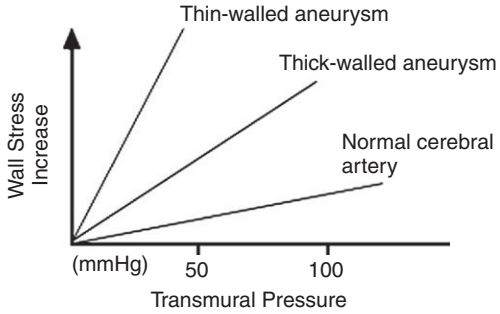

FIGURE 28-21 Aneurysm wall stress.

the presence of a U wave, QTc interval (interval corrected for heart rate) prolongation, and dysrhythmias may be present. Whether such changes in the ECG represent myocardial injury has long been debated. In the majority of patients, these changes do not appear to be associated with adverse neurologic or cardiac outcomes.[207,209]

Rebleeding from a previously ruptured aneurysm is a life-threatening complication. The incidence of rebleeding is approximately 50% in the first days after SAH, and rebleeding is associated with an 80% mortality rate.[210] The chance of rebleeding from an unsecured aneurysm declines over time; by 6 months, the risk stabilizes at approximately 3% per year. Approaches used to decrease the risk of rebleeding include early surgical clipping, the use of antifibrinolytic agents, and blood pressure control.[207,211]

Vasospasm

Cerebral vasospasm, a delayed and sustained contraction of cerebral arteries, continues to be a leading cause of morbidity and mortality in patients with SAH after aneurysm rupture.[205] Vasospasm is reactive narrowing of cerebral arteries after SAH. Approximately one in four patients who have a SAH will develop vasospasm. Although arterial narrowing may be detected with angiography in 60% of patients, only half of these patients develop clinical symptoms. The accompanying neurologic deterioration, arising from impaired cerebral perfusion, ischemia, and secondary infarction of the brain, peaks between the fourth and ninth day after SAH and resolves

over the next 2 to 3 weeks.[211] Angioplasty, either mechanical (balloon) or pharmacologic (intraarterial vasodilators), may be used as a treatment. Angioplasty ideally is done in patients who already have had the symptomatic aneurysm surgically clipped and for patients in the early course of symptomatic ischemia to prevent hemorrhagic transformation of an ischemia region. A balloon catheter is guided under fluoroscopy into the vasospastic segment and inflated to distend the constricted area mechanically. It also is possible to perform a "pharmacologic" angioplasty by direct intraarterial infusion. There is the greatest experience with intraarterial papaverine, or calcium channel blockers. Vasospasm and the ensuing delayed ischemic deficit are thought to result from several factors. Vasospasm is initiated by the release of oxyhemoglobin, one of the blood breakdown products. However, the exact mechanism of cerebral vasospasm after SAH is not completely understood. The mechanism involves multifactorial processes and chemicals such as free radicals, lipid peroxidation, and the release of endothelin-1. Past studies on vasospasm have demonstrated prolonged smooth-muscle contraction in affected arteries. Hypertrophy, fibrosis, wall degeneration, and inflammatory changes were also observed.[205,212,213]

Successful treatment of vasospasm depends on maintaining adequate CPP. This is accomplished by expanding intravascular volume (which augments blood pressure and cardiac output), avoiding hyponatremia, and preserving relative hemodilution (hematocrit approximately 32%).[213] Because of the risk of rebleeding, both hypertension and hypervolemia are used with caution in the period preceding surgical correction.

Pharmacologic vasodilation of spastic vessels has been ineffective because vasospasm involves a structural alteration in the vessel wall rather than just a spastic contracture or failure of relaxation of the smooth muscle cells in the media of the vessels. Nimodipine is commonly used to prevent vasospasm after neurologic trauma or hemorrhage. Nimodipine is the only calcium channel blocker shown to reduce morbidity and mortality from vasospasm. Various agents are being tested as means to prevent or ameliorate vasospasm, including magnesium sulfate, statins, and an endothelin antagonist.[214] Cerebral vasospasm is frequently the cause of poor outcomes after successful surgical or endovascular treatment.

Currently, the most consistently effective regimen to prevent and treat ischemic neurologic deficits due to cerebral vasospasm uses hypervolemia, hypertension, and hemodilution. It is referred to as triple-H therapy. The rationale behind induced hypervolemia and hypertension is that in subarachnoid hemorrhage, the ischemic areas of the brain have impaired autoregulation and thus CBF depends on perfusion pressure. The CBF depends on the intravascular volume and mean arterial blood pressure. Sufficient intravenous fluids are given to raise the CVP to 10 mmHg. Hypervolemia is generally achieved with infusions of colloids (e.g., 5% albumin) as well as crystalloids. Hemodilution, the last component of the triple-H therapy, has the goal of keeping the hematocrit between 27% and 30%. Hypertension often results from the fluid loading; however, vasopressors are sometimes needed. The most widely used vasopressors are dopamine, dobutamine, and phenylephrine. Hypertensive, hypervolemic therapy may induce a vagal response and profound diuresis, requiring administration of large amounts of intravenous fluids. Atropine (1 mg intramuscularly every 3 to 4 hours) may be given to maintain the heart rate between 80 and 120 beats/min, and aqueous vasopressin (Pitressin) 5 units intramuscularly may be administered to maintain the urine output at less than 200 mL/hr.

With this regimen, often only small amounts of vasopressor drugs are required. The blood pressure is titrated to a level necessary to reverse the signs and symptoms of vasospasm or to a maximum of 160 to 200 mmHg systolic in the patient whose aneurysm has been clipped. If the aneurysm has not been clipped, the systolic blood pressure is increased to only 120 to 150 mmHg. The elevated blood pressure must be maintained until the vasospasm resolves, usually in 3 to 7 days. Response to therapy can now be monitored noninvasively with transcranial Doppler (TCD). Improvement in vasospasm may be associated with a decrease in flow velocity, so angiography may be necessary.[215]

Timing of Surgery

There was debate in the past about the timing of surgical intervention. Early surgery has been shown to carry higher procedural morbidity and mortality. The presence or absence of vasospasm on angiographic studies has often been a major determinant. Nevertheless, early surgery prevents devastating rebleeding and enables aggressive hypervolemia/hypertension/hemodilution (triple-H) therapy for cerebral vasospasm. Current evidence supports that either conventional open surgery or endovascular treatment should be performed as soon as possible after the onset of subarachnoid hemorrhage (SAH) unless contraindicated. A good outcome achieved with early operation (within 24 to 48 hours) in patients who are neurologically intact (grades I or II), regardless of whether vasospasm has been demonstrated. Such emergency intervention decreases the likelihood of rebleeding. Only 53% of grade III patients achieve a good outcome after early surgery; this indicates that the gross neurologic condition preoperatively is the best prognostic indicator of intact survival.[205] In the first few days after hemorrhage, the brain is swollen, soft, hyperemic, and prone to contusion and laceration. Practice was guided for many years by The International Cooperative Study on the Timing of Aneurysm Surgery. This multicenter study demonstrated that SAH patients who underwent surgery on posthemorrhage days 4 to 10 had worse outcomes than patients treated on days 0 to 3 and days 11 to 14. It was concluded that patients who present with SAH on days 4 to 10 should have aneurysm surgery delayed until after day 10. Since the introduction of interventional neuroradiology techniques, practitioners have come to believe that coiling of ruptured aneurysms can be performed safely on patients who arrive on posthemorrhage days 4 to 10, and treatment need not be delayed until after day 10, as the results of the Timing of Aneurysm Surgery Study initially suggested.[210,216]

Impaired autoregulation may decrease cerebral tolerance to brain retraction. Although removal of a subarachnoid clot probably decreases the incidence and severity of delayed arterial narrowing, clearly, operative management may be hazardous. In more severely injured patients (grades III through V), surgery is often delayed in anticipation of resolution of vasospasm and improvement in neurologic status.[205,210,216] Currently, most neurovascular surgeons elect to operate within 3 or 4 days of the bleed in good-grade patients to minimize the chances of a devastating rebleed.[217,218]

As mentioned above, endovascular coiling has been used increasingly for treating SAH secondary to aneurysm rupture.[204,219-221]

Preoperative Evaluation

The baseline neurologic status must be ascertained. The level of consciousness may vary from perfect alertness to deep coma and is an important prognostic factor for the postoperative state. Evidence of increased ICP should be elicited preoperatively so it can be managed appropriately. Focal motor and sensory signs may indicate intracerebral extension of SAH, vasospasm, or cerebral edema.[207]

Pulmonary complications, such as pneumonia, neurogenic pulmonary edema, and atelectasis, are not uncommon. Patients often have an increased risk of aspiration because of their depressed level of consciousness, and measures should be taken to reduce gastric

acidity and volume preoperatively. The use of prophylactic hypervolemia also increases the likelihood of pulmonary edema.[207]

The hemodynamic status of the patient should be assessed, with particular attention paid to the relationship between neurologic deterioration and blood pressure changes. Continuous arterial blood pressure monitoring is essential. Serious dysrhythmias or evidence of ventricular dysfunction should be diagnosed preoperatively so appropriate monitoring and management can be instituted.[222]

The syndrome of inappropriate antidiuretic hormone and diabetes insipidus can occur in patients with subarachnoid hemorrhage.

The presence of blood in the subarachnoid space may produce a 1° C to 2° C elevation of body temperature. Temperature elevation increases cerebral oxygen requirements and therefore should be treated to prevent an increase of cerebral ischemia.[207,211,223]

Preoperative sedation is rarely necessary in these patients. Depression of ventilation associated with opioids and benzodiazepines may result in hypercapnia, with resultant increases in CBF and ICP. Additionally, the reduced level of consciousness preoperatively and postoperatively may make clinical assessment difficult. Preoperative anxiety is not a problem in patients with a depressed level of consciousness (grades III through V), so sedation is not required. In awake patients, a reassuring preoperative visit usually allays anxiety. If preoperative sedation is considered necessary, the best choice is probably a small dose of a benzodiazepine (midazolam), with continued observation after its administration.[224-226]

Anesthetic Induction, Maintenance, and Emergence

Maintaining adequate intravascular volume requires two large-bore intravenous cannulas. Intraoperative monitoring includes continuous ECG (V_5), arterial pressure monitoring, peripheral nerve stimulator, central venous pressure monitoring, EEG, ET_{CO_2} monitoring, pulse oximetry, and monitoring of temperature and fluid balance.[227]

Intraoperative neurophysiologic monitoring during intracranial aneurysm surgery is standard practice. It is an important adjunct to surgical inspection and intraoperative angiography to detect cerebral ischemia. Somatosensory evoked potentials (SSEPs), particularly median and posterior tibial nerve SSEPs, are commonly monitored during anterior circulation procedures. Dural monitoring with SSEPs and brainstem auditory evoked responses (BAERs) are preferred for posterior circulation and aneurysm surgeries. There is a significant correlation between alterations in electrical signals and regional cerebral blood flow (rCBF), with transient electrophysiologic changes generally corresponding to good outcomes and permanent changes corresponding to postoperative deficits. Electroencephalography (EEG) is also commonly used. Prior to temporary clip application, the neuroanesthesia team titrates brain protective anesthetics to achieve burse suppression on EEG. Burst suppression helps decrease metabolic demand so that the cerebral tissue can better tolerate induced ischemia such as during temporary clipping.[25]

The anesthetic induction should be slow and deliberate. The anesthetic depth should be sufficient to avoid the hypertensive responses that accompany laryngoscopy and endotracheal intubation. Anesthesia is induced with titrated doses of propofol. The addition of an opioid (5 to 10 mcg/kg of fentanyl or 1 to 2 mcg/kg of sufentanil) and intravenous lidocaine (1.5 mg/kg) further blunts the patient's response to the sympathetic stimulation of laryngoscopy and intubation. An additional dose of opioid or propofol is required for the placement of the three-point pin head holder. Prior injection of local anesthetic minimizes the associated sympathetic stimulation. Epinephrine should not be included with the local anesthetic because delayed absorption (up to 30 minutes after injection) may produce significant increases in blood pressure. Isoflurane may be introduced after hyperventilation before laryngoscopy to increase the depth of anesthesia. Ventilation is controlled with administration of 100% oxygen to achieve a Pa_{CO_2} of 35 to 40 mmHg with normal intracranial compliance. Mild hyperventilation (Pa_{CO_2} of 30 to 35 mmHg) is instituted when intracranial compliance is impaired.[207]

Succinylcholine produces moderate increases in ICP.[228-230] Elevation of serum potassium sufficient to produce lethal dysrhythmias has been reported in comatose, nonparetic, head-injured patients and in patients after SAH who received succinylcholine. Alternatively, intubation can be accomplished with 1 mg/kg of rocuronium.

The patient is placed in one of several positions, depending on the site of the aneurysm. Aneurysms that arise from the anterior part of the circle of Willis require that the patient be supine for a frontotemporal approach. The lateral position for a temporal approach is required for aneurysms that arise from the posterior aspect of the basilar artery. Aneurysms that arise from the vertebral artery or from the lower basilar artery require a sitting or prone position for a suboccipital approach. Aneurysms that arise from the anterior communicating artery are usually approached from the right and those from the middle cerebral and posterior communicating arteries are approached from the side on which the aneurysm is located.[231]

Anesthesia is maintained with air and oxygen or N_2O in oxygen, with incremental titrated dosages of an opioid (fentanyl, alfentanil, or sufentanil), or an infusion of remifentanil and a muscle relaxant. Isoflurane also may be added in inspired concentrations not to exceed 1%. Patients who have intracranial aneurysms may require induced hypertension or hypotesion to rebleeding and counteract vasospasm.[232] In addition, controlled hypotension is commonly used intraoperatively to make aneurysms softer and more pliable at the time of clipping, as well as to minimize blood loss if aneurysmal rupture occurs at this time.[209] Sodium nitroprusside and an inhalation anesthetic agent are the drugs most widely used for induction or hypotension.[232]

The safe limit of controlled hypotension has not been definitively established. Because autoregulation is maintained to a MAP of 50 to 60 mmHg, some argue that this limit should not be exceeded. In addition, because patients with poor-grade aneurysms may not have intact autoregulation, some argue that a lower limit of 60 mmHg should be adopted. Limits of autoregulation are shifted to higher pressures in patients with preexisting hypertension, so decreases in MAP should probably be limited to no more than 40% of preoperative values.[207]

Rather than induce hypotension to facilitate clip ligation of the neck of the aneurysm, many neurosurgeons now routinely use temporary proximal occlusion of the parent vessel.[233]

The use of mild intraoperative hypothermia has been advocated for cerebral protection during periods of temporary occlusion.[234] Deliberate mild hypothermia was first used in 1955 as an intraoperative technique to ameliorate new neurologic deficits after cerebral aneurysm clipping. Subsequently, it was also used after neonatal asphyxia, head trauma, and cardiac arrest. The Intraoperative Hypothermia for Aneurysm Surgery Trial (IHAST II) was a randomized, control trial designed to evaluate the effectiveness of mild hypothermia in decreasing neurologic deficits after aneurysm surgery. Intraoperative hypothermia did not improve the neurologic outcome after craniotomy among good-grade patients with aneurysmal subarachnoid hemorrhage.[235]

At the conclusion of the anesthetic procedure, patients with good-grade aneurysms may be extubated in the operating room, although care must be exercised so that coughing, straining,

hypercarbia, and hypertension are avoided. Propofol, lidocaine, or small doses of fentanyl may be used for short-term anesthesia as the procedure is being finished and for reducing the hemodynamic responses to extubation. Although the residual depressant effects of opioids may be reversed with judicious titrated dosages of naloxone, larger doses of naloxone can be hazardous in that they may cause sudden, violent awakening of the patient and marked increases in systemic blood pressure. Endotracheal tubes should be retained in patients with poor-grade aneurysms and in those who have had intraoperative complications; these patients will probably require postoperative ventilation.[211]

Postoperative Care

Postoperative care is directed at the prevention of vasospasm via the maintenance of intravascular volume expansion and moderate hypertension (MAP of 80 to 120 mmHg). Changes in the level of consciousness and development of focal neurologic deficits are usually early signs of vasospasm. These clinical signs should be aggressively managed with hypertension, hypervolemia, and hemodilution. Dopamine may be used for blood pressure support. Computed tomography should be used for ruling out other causes of neurologic deterioration, including rebleeding, infarction, and hydrocephalus.[211]

Aneurysmal Rupture

Intraoperative aneurysmal rupture can be catastrophic. An abrupt increase in blood pressure during or after induction of anesthesia may indicate that an aneurysm has bled. The use of 1 to 2 mg/kg of propofol or 0.5 to 1 mcg/kg of sodium nitroprusside decreases the transmural pressure of the aneurysm, although hypotension can be detrimental at this juncture. Intraoperative aneurysmal rupture necessitates maintaining the MAP between 40 and 50 mmHg or lower to facilitate surgical control of the neck of the aneurysm or the parent vessel. Alternatively, one or both carotid arteries may be compressed for up to 3 minutes to produce a bloodless field. Blood that is lost should be continuously replaced with blood, blood products, or colloid solution so that intravascular volume is maintained.[211]

Although barbiturates have been used for protection against focal cerebral ischemia, their efficacy has not been demonstrated in this clinical situation.[236]

Interventional Neuroradiology

Treatment of aneurysms by an interventional neuroradiology procedure presents some special anesthestic considerations. These include maintaining immobility during procedures to facilitate imaging, rapid recovery from anesthesia at the end of procedures to facilitate neurologic examination and monitoring, or to provide for intermittent evaluation of neurologic function during procedures, managing anticoagulation, treating and managing sudden hemorrhage or vascular occlusion, manipulating systemic or regional blood pressures, and guiding the management of the patients during transport to and from the radiology suites. Both general and intravenous sedation are used; however, general anesthesia is preferred because the procedures can be long and manipulation of blood pressure and respiration may be necessary. The patient is prepared in a manner similar to that for open intracranial aneurysm clipping. Anesthesia considerations and management are also the same; however, if an intracranial emergency occurs during the procedure, several steps should be taken. Box 28-8 outlines the management of intracranial emergencies.[203] Anesthetic considerations for select interventional neuroradiology procedures are noted in Table 28-10.

BOX 28-8

Management of Intracranial Catastrophes*

Initial resuscitation

- Communicate with endovascular therapy team
- Assess need for assistance; call for assistance
- Secure the airway; ventilate with 100% O_2
- Determine whether problem is hemorrhagic or occlusive (see text)
  - *Hemorrhagic:* Immediate heparin reversal (1-mg protamine for each 100 units of heparin given) and low normal mean arterial pressure
  - *Occlusive:* Deliberate hypertension, titrated to neurologic examination, angiography, or physiologic imaging studies; or to clinical context

Further resuscitation

- Head up 15° degrees in neutral position, if possible
- $Paco_2$ manipulation consistent with clinical setting, otherwise normocapnia
- Mannitol 0.5 g/kg, rapid IV infusion
- Titrate IV agent to electroencephalogram burst suppression
- Passive cooling to 33°-34° C
- Consider ventriculostomy for treatment or monitoring of increased ICP
- Consider anticonvulsants (e.g., phenytoin or phenobarbital)

From Lee CZ, Young WL. Anesthesia for endovascular neurosurgery and interventional neuroradiology. Anesthesiol Clin. 2012 Jun; 30(2):127-47.

*These are only general recommendations and drug doses that must be adapted to specific clinical situations and in accordance with a patient's preexisting medical condition. In some cases of asymptomatic or minor vessel puncture or occlusion, less aggressive management may be appropriate.

ICP, Intracranial pressure.

Arteriovenous Malformation

Arteriovenous malformations are congenital intracerebral networks in which arteries flow directly into veins. Patients with these malformations generally are younger than those with aneurysms. They may have bleeding or seizures or, less commonly, ischemia resulting from "steal" from normal areas or occurring with high-output congestive heart failure. The anesthetic problems parallel those associated with patients undergoing aneurysm surgery. Notably, arteriovenous malformations do not autoregulate their blood flow. The operation is likely to be longer and bloodier than that of aneurysm clipping. Surgery may be preceded by an attempt at embolization by the neuroradiologist to diminish the risk of surgery. The neurologic examination should be repeated after embolization to document new deficits that otherwise might be attributed to anesthesia and surgery.

Head Trauma

Head injuries are a contributory factor in up to 50% of deaths resulting from trauma. Most patients with head trauma are young, and many (10% to 40%) have associated intraabdominal injuries, long-bone fractures, or both. The significance of a head injury is dependent not only on the extent of the irreversible neuronal damage at the time of injury but also on the occurrence of any secondary insults. Additional insults include systemic factors such as hypoxemia, hypercapnia, and hypotension; the formation and expansion of an epidural, subdural, or intracerebral hematoma; and sustained intracranial hypertension (Box 28-9). Studies suggest that sustained increases in ICP of approximately 60 mmHg result in irreversible brain edema. Surgical and anesthetic

TABLE 28-10 Interventional Neuroradiologic Procedures and Primary Anesthetic Considerations

Procedure	Possible Anesthetic Considerations
Therapeutic embolization of vascular malformation	
Intracranial AVMs	Deliberate hypotension, postprocedure NPPB
Dural AVM	Existence of venous hypertension; deliberate hypercapnia
Extracranial AVMs	Deliberate hypercapnia
Carotid cavernous fistula	Deliberate hypercapnia, postprocedure NPPB
Cerebral aneurysms	Aneurysmal rupture, blood pressure control*
Ethanol sclerotherapy of AVMs or venous malformations	Brain swelling, airway swelling, hypoxemia, hypoglycemia, intoxication from ethanol, cardiorespiratory arrest
Balloon A&S of occlusive cerebrovascular disease	Cerebral ischemia, deliberate hypertension, concomitant coronary artery disease, bradycadia, hypotension
Balloon angioplasty of cerebral vasospasm secondary to aneurysmal SAH	Cerebral ischemia, blood pressure control*
Therapeutic carotid occlusion for giant aneurysms and skull base tumors	Cerebral ischemia, blood pressure control*
Thrombolysis of acute thromboembolic stroke	Postprocedure ICH (NPPB), concomitant coronary artery disease, blood pressure control*
Intraarterial chemotherapy of head and neck tumors	Airway swelling, intracranial hypertension
Embolization for epistaxis	Airway control

From Lee CZ, Young WL. Anesthesia for endovascular neurosurgery and interventional neuroradiology. Anesthesiol Clin. 2012 Jun;30(2):127-47.
*Blood pressure control refers to deliberate hypo- or hypertension.
A&S, Angioplasty and stenting; *AVM*, arteriovenous malformation; *ICH*, intracerebral hemorrhage; *NPPB*, normal perfusion pressure breakthrough; *SAH*, subarachnoid hemorrhage.

BOX 28-9

Peripheral Sequelae of Head Trauma

- Hemodynamic instability
- Abnormal breathing patterns
- Bone fractures
- Pneumothorax
- Airway obstruction
- Aspiration
- Hypoxia
- Adult respiratory distress syndrome
- Neurogenic pulmonary edema
- Electrocardiographic changes
- Hematologic
- Disseminated intravascular coagulation
- Endocrinologic
- Cervical spine injury
- Maxillofacial injuries

Adapted from Pasternack JJ, Lanier WL. Diseases affecting the brain. In: Hines RL, Marscall KE, eds. *Stoelting's Anesthesia and Co-Existing Disease*. 6th ed. Philadelphia: Saunders; 2012:218-254.

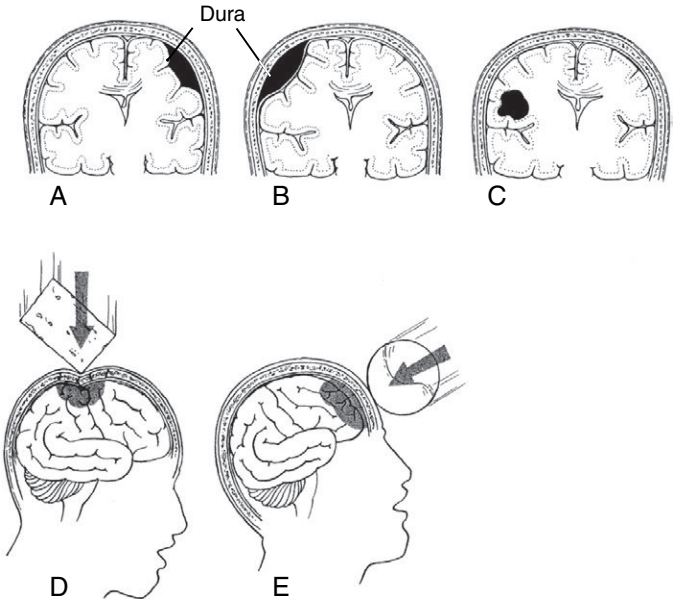

FIGURE 28-22 **A,** Subdural hematoma. **B,** Epidural hematoma. **C,** Intracerebral hematoma. **D,** Direct head injury resulting in depressed skull fracture and compression injury. **E,** Blow to skull resulting in tearing of blood vessels. Shaded areas on skull represent cerebral contusion. (From Black JM, Hokanson Hawks JH. *Medical-Surgical Nursing: Clinical Management for Positive Outcomes*. 8th ed. St. Louis: Saunders; 2009:1934-1936.)

management of these patients is directed at preventing secondary insults.[98] Types of cerebral hematomas and mechanisms of head injuries are illustrated in Figure 28-22.

Preoperative Management

Emergency therapy for head injury should begin before hospital admission, because a large proportion of deaths occur in the prehospital phase. Therapy is based on prevention of secondary brain injury resulting from hypoxia, hypercapnia, hypotension, and expanding intracranial masses.

Airway Management

Measures to ensure airway patency, adequacy of ventilation and oxygenation, and the correction of systemic hypotension should be instituted simultaneously with neurologic evaluation. Airway obstruction and hypoventilation are common. Up to 70% of head-injured patients have concurrent hypoxemia, which may be complicated by pulmonary contusion, fat emboli, or neurogenic pulmonary edema. All patients must be assumed to have a cervical spine injury (10% incidence) until disproved by radiography. Axial traction to maintain the head in a neutral position should be used during airway instrumentation. Fiberoptic intubation may be preferred for airway management in some cases. Patients with obvious hypoventilation, absence of the gag reflex, or a persistent total score below 7 on the Glasgow Coma Scale (see Table 19-5) require tracheal intubation and hyperventilation. A modified coma scale for infants is given in Table 28-11 and outlines response patterns seen after neurologic injuries. All other patients

TABLE 28-11 Modified Coma Scale for Infants

Response	Score
Eye Opening	
Spontaneous	4
To speech	3
To pain	2
None	1
Verbal Response	
Coos, babbles	5
Irritable cries	4
Cries to pain	3
Moans to pain	2
None	1
Motor Response	
Normal spontaneous movement	6
Withdraws to touch	5
Withdraws to pain	4
Abnormal flexion	3
Abnormal extension	2
None	1

should be carefully observed for deterioration. Table 28-12 summarizes respiratory patterns seen with various neurologic injuries. The Glasgow Coma Scale score generally correlates well with the severity of injury and outcome.[98]

When intubation is indicated, the oral route provides the most efficient means of safely securing the airway. Whenever possible, a modified, rapid-sequence endotracheal intubation should be performed; that is, it should be preceded by a period of 100% oxygen administration and hyperventilation supplemented by continuous cricoid pressure.[237-239] Nasal intubation should be avoided in the presence of suspected basilar skull fracture, bleeding diathesis, suspected upper-airway foreign body, or severe facial fractures.[237] If a difficult intubation is anticipated, awake intubation, fiberoptic techniques, or tracheostomy may be necessary.

Cardiovascular Assessment

Multisystem trauma often accompanies head injury. Hypotension results from intravascular loss from associated injuries. These injuries must be identified and treated early in the resuscitative period. Fluid resuscitation is facilitated by the administration of isotonic fluid, either normal saline or lactated Ringer's solution, or colloids if blood is not readily available. Glucose in water should not be used because it decreases serum osmolarity and can aggravate cerebral swelling. The ideal replacement fluid, of course, is blood. Because the cerebral vessels are already dilated from hypotension, rapid restoration of the normal arterial pressure precipitates brain swelling. It is extremely valuable to insert an ICP monitor during resuscitation for the monitoring of both systemic arterial pressure and ICP.[235] Dysrhythmias and ECG abnormalities in the T wave, U wave, ST segment, and QT interval are common after head injuries but are not necessarily associated with cardiac injury.[98] Some guidelines for blood pressure management in select neurosurgical emergencies are noted in Table 28-13.

Coagulopathies

Chronic Subdural Hematoma. Bridging veins run between the dura and the surface of the brain. A subdural hematoma develops when these veins tear and leak blood, usually as the result of a head injury. A collection of blood then forms over the surface of the brain. In a chronic subdural collection, the problem is not discovered immediately, and blood leaks from the veins slowly over time. A subdural hematoma is more common in the elderly because normal brain shrinkage occurs with aging that stretches and weakens the bridging veins. Thus these veins are more likely to break in the

TABLE 28-12 Respiratory Patterns with Head Trauma

Pattern	Description	Location of Injury and Other Causes
Cheyne-Stokes respiration	Regular increase in the rate and depth of breathing that peaks and is followed by a decreasing rate and depth of breathing, which progresses to apnea; then the cycle repeats itself	Bilateral dysfunction of cerebral hemispheres Midbrain and upper pons
Central neurogenic hyperventilation	Deep, rapid, and regular pattern of breathing	Low midbrain and upper pons Increased intracranial pressure with head trauma
Apneusis breathing	A pause at full inspiration occurs; may see prolonged inspiratory pause alternating with prolonged expiratory pause	Mid and low pons Hypoglycemia, anoxia, and meningitis
Cluster breathing	Periodic breathing with frequent apneic episodes	Low pons and high medulla
Ataxic breathing	Irregular breathing with shallow, deep respirations and irregular apneic episodes; usually slow	Medulla

From Drain CB, Odom-Forren J, eds. *Perianesthesia Nursing: A Critical Care Approach*. 5th ed. St. Louis: Saunders; 2009:574.

TABLE 28-13 Guidelines for Blood Pressure Management in Common Neurologic Conditions

Diagnosis	Recommendation
Acute ischemic stroke	Keep <180/110 mmHg if thrombolysis Treat only BP >220/120 if no thrombolysis
Intracerebral hemorrhage	Keep SBP <180 and MAP <130 mmHg (ideal SBP <160 and MAP <110 mmHg)
Subarachnoid hemorrhage	Keep SBP <160 mmHg before aneurysm treated Do not lower BP after aneurysm treated
Traumatic brain injury	Keep adequate MAP to maintain CPP >60 mmHg

Adapted from Rabinstein AA. Principles of neurointensive care. In: Daroff et al, eds. *Bradley's Neurology in Clinical Practice*. 6th ed. Philadelphia: Saunders; 2012:814.
BP, Blood pressure; *CPP*, cerebral perfusion pressure; *MAP*, mean arterial pressure; *SBP*, systolic blood pressure.

elderly, even after a minor head injury. Rarely, a subdural hematoma can occur spontaneously. Risks include head injury, old age, chronic use of aspirin or antiinflammatory drugs such as ibuprofen, anticoagulant medication, chronic heavy alcohol use, or many diseases associated with blood-clotting problems.[240]

A recent study of 713 emergency referrals documented over 90 days evaluated the effect of antithrombotic therapy on neurosurgical emergency referral. Of the 713 patients, 174 (24.4%) were discovered to have intracranial or spinal hemorrhage, and 75 (43.1%) of these were on antithrombotic therapy. Seventeen of the 75 (22.6%) had no documented indication for antithrombotic therapy (all of these were on aspirin therapy), and 9 of the 29 on warfarin (31%) had an INR (international normalized ratio [prothrombin time]) in excess of 3.5 on presentation.[241]

The key elements in dealing with coagulation abnormalities in patients presenting for emergent/urgent neurosurgery are (1) identify the coagulopathy, (2) implement a plan that allows for optimum coagulation status given the comorbidities of the patient, and (3) time the period of optimum coagulation to coincide with the conclusion of surgery and the immediate postoperative period.

The coincidence of coagulopathy and chronic subdural hematoma requires correction of coagulation to facilitate surgery.[242] Forty-two percent of 114 patients presenting for drainage of chronic subdural hematoma were found to have coagulation disorders before surgery. Addressing coagulopathies in the geriatric population is a situation best addressed by a multidisciplinary approach. The primary problem in this population has to do with limited vascular space that may not be able to accommodate the volume of blood products necessary for reversal in an urgent/emergent fashion. For example, studies suggest that 10 to 17 mL/kg of fresh frozen plasma is necessary to reverse coumadin toxicity.[243]

This may not be a reasonable option in the face of imminent surgery. The Mayo Clinic asked seven experts on clinical stroke, neurologic intensive care, and hematology to address three scenarios for dealing with reversal of warfarin in patients with intracranial hemorrhage. All experts agreed that anticoagulation should be urgently reversed, but how to achieve it varied from the use of prothrombin complex concentrates only (three experts), to recombinant factor VIIa only (two experts), to recombinant factor VIIa along with fresh frozen plasma (one expert), to prothrombin complex concentrates and fresh frozen plasma (one expert).[244] Although a universally accepted treatment remains to be identified, the options available provide anesthesia providers with a number of options for treating warfarin toxicity that limit the fluid loads associated with fresh frozen plasma.

The broadening use of recombinant factor VIIa in treating active or impending bleeding in brain injury has led some to conclude that the compartmentalized mode of action of recombinant factor VIIa, along with its good safety profile and Intracerebral Hemorrhage Trial results, provide encouraging data to justify its off-label use in selected patients in the presence of any coagulopathy.[245]

Reversal of clopidogrel, aspirin, or aspirin plus clopidogrel may be addressed by platelet administration. Alternatively, recombinant factor VIIa has been shown to reverse the inhibitory effects of aspirin or aspirin plus clopidogrel and could be useful for bleeding complications or when acute surgery is needed during treatment with these antiplatelet drugs.[246]

Severe brain injury initiates the outpouring of tissue thromboplastin and activation of the complement system, causing disseminated intravascular coagulopathy and fibrinolysis and precipitating the development of adult respiratory distress syndrome. Early recognition of abnormal prothrombin and partial thromboplastin times is crucial. Prompt therapy with fresh frozen plasma, cryoprecipitate, whole blood, and if necessary, platelets may abort the development of disseminated intravascular coagulopathy.[239,240]

Increased Intracranial Pressure

The clinical appreciation of elevated ICP is difficult in unconscious patients. Therefore, initial therapy is directed toward lowering ICP or at least toward preventing further increases in ICP. Simple maneuvers such as using a head-up tilt of 15 to 20 degrees to keep the head in the midline position and not rotated to either side (to ensure jugular vein patency), avoiding overhydration, maintaining normovolemia, and maintaining normal (rather than increased) arterial pressure all help control ICP.[238]

In patients in whom intracranial hypertension is suspected, whether from an epidural or subdural hematoma or from diffuse brain swelling, emergency treatment directed at reducing ICP is the rational course. Ideally, a definitive study for identifying the cause of clinical deterioration is performed before therapy. The first and most rapidly effective therapy is hyperventilation. In a patient with multiple trauma and reduced blood volume, care must be taken during controlled ventilation to avoid increasing the intrathoracic pressure, decreasing venous return, and producing secondary hypotension. Corticosteroids (dexamethasone or methylprednisolone) are of little benefit and likely are detrimental in trauma, and these drugs must not be relied on to lower the ICP rapidly.[247]

Although mannitol effectively lowers the ICP minutes after administration, its use remains controversial. The drug is indicated, however, when either elevated ICP or a mass and herniation are responsible for the patient's deteriorating state. The risk of increasing the size of a hematoma is negligible compared with the disastrous effects of untreated progressive uncal herniation. If decompression of transtentorial herniation is delayed, secondary hemorrhage into the brainstem can occur and cause irreversible neurologic deficit. Once mannitol is given and the ICP is reduced, the specific intracranial disorder must be identified as soon as possible if a recurrence of the patient's deterioration is to be prevented.[247]

Animal and human studies have demonstrated that hypertonic saline has clinically desirable physiologic effects on CBF, ICP, and inflammatory responses in models of neurotrauma.[248] Some studies suggest that 23.4% hypertonic saline is a safe and effective treatment for elevated ICP in patients after traumatic brain injury.[249,250]

Mannitol therapy for raised ICP may have a beneficial effect on mortality when compared with pentobarbital treatment, but a detrimental effect on mortality when compared with hypertonic saline in treating increased ICP in head-injury patients.[251]

Neurodiagnostic Evaluation

The choice between operative and medical management of head trauma is based on radiographic and clinical findings. Patients should be stabilized before any computed tomography or angiographic studies are performed. Critically ill patients should be closely monitored during such studies. Restless or uncooperative patients may require general anesthesia if these diagnostic examinations are to be accomplished. Sedation without control of the airway should be avoided because of the risk of further increases in ICP from hypercapnia or hypoxemia. In the event of neurologic deterioration before completion of these studies, intravenous administration of mannitol should be considered.[98] Reductions of $Paco_2$ levels may, by decreasing CBF, allow better angiographic studies. The introduction of computed tomography and MRI has greatly facilitated neuroradiologic diagnosis. Serial computed tomography is an aid in predicting the outcome of patients with severe head injury. New findings after the initial study are associated with poorer outcomes.[252]

Intraoperative Management

Operative treatment is reserved for depressed skull fracture, depressed fractures associated with underlying brain injury, and evacuation of epidural, subdural, and some intracerebral hematomas.[253]

Monitoring during anesthesia is generally similar to that for other mass lesions associated with intracranial hypertension. Intra-arterial and central venous (or pulmonary artery) pressure monitoring should be established if it is not already present, but it should not delay surgical decompression in a rapidly deteriorating patient.[98,240]

Anesthetic Induction, Maintenance, and Emergence

Intubation must be accomplished as expeditiously as possible with the use of small, incremental doses of propofol, rocuronium (assuming the airway can be instrumented), lidocaine, and labetalol (as needed for the treatment of systemic hypertension), with concurrent cricoid pressure. Hyperkalemia may be induced with succinylcholine in a patient with closed-head injury without paresis; therefore, use of this drug should be avoided.[254] Intracranial damage is usually associated with hypertension. The true state of hydration may be realized for the first time after induction, when catastrophic hypotension may occur if fluid replacement is inadequate or barbiturate dosage is excessive.

Ventilation should be controlled. A $Paco_2$ of 25 to 30 mmHg promotes brain relaxation for surgical exposure without producing ischemia from hypocapnic vasoconstriction. A higher $Paco_2$ (30 to 35 mmHg) is recommended for patients who require burr holes for evacuation of chronic subdural hematomas, particularly after decompression, because a slack brain may encourage recurrence.[253]

If the patient is unconscious in the absence of a drug overdose, the ICP is probably elevated. In this case, a barbiturate and an opioid in combination with oxygen (or air in oxygen) and a muscle relaxant are appropriate. A similar technique is indicated in the patient who has a computed tomography scan that demonstrates obliteration of basal cisterns, dilation of the fourth or lateral ventricles, or a midline shift of 10 mm.[253]

Although hyperventilation attenuates the increase in ICP when inhalation anesthetics are used, in patients with head injury, cerebral vasoconstriction in response to hypocapnia is not a dependable indicator. The introduction of inhalation agents in such patients may increase ICP and exacerbate the formation of edema. The administration of inhalation anesthetics in low inspired concentrations may have a role in the treatment of intraoperative hypertension.[253]

Patients who have chronic subdural hematoma and are alert and responsive may have burr holes placed for evacuation of accumulated blood under local anesthesia with sedation. Depressed skull fractures also may be elevated while the patient is awake and under local anesthesia with sedation. This technique must be used cautiously when the patient placed in the three-point pin head holder has a full stomach.[253]

Fluid replacement should be accomplished with glucose-free solutions. Hypovolemia results in systemic hypotension, an unstable anesthetic course, and (by decreasing cerebral oxygen delivery) increased cerebral vasodilation. Rheologic conditions are optimal at hematocrit levels of 30% to 32%.[239]

The decision of whether to extubate the trachea at the conclusion of the surgical procedure depends on the severity of the injury, the presence of concomitant abdominal or thoracic injuries, preexisting illnesses, and the preoperative level of consciousness. A recent study noted that up to 54.5% of patients had an adverse event after surgery.[254] Occurrence of nausea, vomiting, and respiratory and cardiac problems was significantly more likely than in patients undergoing routine surgical procedures. Young patients who are conscious preoperatively may be extubated after the removal of a localized lesion, whereas patients with diffuse brain injury should remain intubated. Moreover, persistent intracranial hypertension requires continued paralysis, sedation, hyperventilation, and possibly a pentobarbital infusion postoperatively.[98]

SUMMARY

Anesthesia management of the neurosurgical patient continues to be one of the most challenging clinical issues encountered by the nurse anesthetist. Advances in surgical approaches to tumors, vascular lesions, and trauma necessitate constant reappraisal of the important role of anesthesia care in improving a patient's long-term outcome. Intraoperative monitoring modalities new to neurosurgical procedures remain to be definitively evaluated. Interventional radiologic approaches are now a primary therapy for several neurologic disorders, and anesthesia management presents many new challenges in caring for these patients. As clinical practice evolves, it is both exciting and satisfying to meet the demands of this area of anesthesia practice.

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Renal Anatomy, Physiology, Pathophysiology, and Anesthesia Management

CHAPTER 29

◆ *Joanne Donnelly and Sandra Maree Ouellette*

The kidneys are paired organs that lie retroperitoneally on both sides of the vertebral column. They function to excrete the end products of bodily metabolism and thereby control the concentration of constituents of body fluids. A rich blood supply to these vital organs, coupled with the physiologic processes of filtration, reabsorption, secretion, and excretion, maintains homeostasis of the fluid that bathes each cell. For management of anesthetized patients to be optimal, clinicians must be familiar with physiologic mechanisms that allow the kidneys to control the body's intracellular and extracellular environments.

This chapter addresses the effect of anesthesia and surgery on both the normal and the diseased kidney. After a discussion of the anatomic structure and physiologic mechanisms of the kidney, the effects of anesthesia on normal renal function are addressed. Pathophysiologic mechanisms associated with acute and chronic renal failure follow. Preoperative renal assessment and anesthetic considerations for patients with impaired renal function are emphasized, and pertinent anesthetic considerations for common urologic procedures are identified.

STRUCTURE OF THE KIDNEY

The kidneys are bean-shaped, reddish-brown organs located in the posterior part of the abdomen on both sides of the vertebral column (Figure 29-1). These organs extend from the 12th thoracic vertebra to the 3rd lumbar vertebra; each weighs approximately 125 to 170 g in men and 115 to 155 g in women. Each kidney is about 11.25 cm long, 5 to 7.5 cm wide, and 2.5 cm thick. The right kidney's position is slightly lower than the left because of hepatic displacement. The kidneys and their vessels are embedded in fatty tissue (perirenal fat) and enclosed in renal fascia. Renal fascia and large vessels hold the kidneys in position (see Figure 29-1).

The anterior and posterior surfaces, upper and lower poles, and lateral margin of the kidney have convex contours. The medial margin is concave because of the presence of the hilus (recessed fissure). Structures that enter or leave the kidney through the hilus include the renal artery and vein, nerves, lymphatics, and ureters.

A longitudinal section of the kidney reveals two distinct regions—the outer cortex and the inner medulla (Figure 29-2). The medulla is divided into 8 to 18 triangular wedges called *pyramids*. The base of each pyramid is directed toward the renal cortex, and the apexes converge toward the renal pelvis. Pyramids have a striated appearance because they contain the loop of Henle and collecting ducts of the nephron. The apex of each pyramid, called the *papilla*, is composed of many collecting ducts, and those papillary ducts empty into a cup-shaped structure known as the *minor calyx*. Several minor calyces join to form major calyces, which come together as the renal pelvis. The renal pelvis is the major reservoir for urine. Ureters connect the renal pelvis to the bladder. [1]

Nephron

The functional unit of the kidney is the nephron. Approximately 1,250,000 of these units are present in each kidney. The shape of the nephron is unique, unmistakable, and admirably suited for its function. Each area of the nephron is selective with regard to its performance. Nephrons hold the filtrate that has been filtered from the blood. End products of metabolism are excreted, and metabolically important substances such as water are reabsorbed as needed.

The nephron (Figure 29-3) begins in the cortex at the glomerulus and ends where the tubule joins the collecting duct at the papilla. The glomerulus is a tuft of capillaries derived from the afferent arteriole. Blood is brought to the glomerulus by the afferent arteriole; blood that is not filtered returns to the circulation by way of the efferent arteriole (see Figure 29-3). The filtrate from the glomeruli enters the Bowman capsule, or capsula glomeruli, flows through a tortuous tube, or proximal convoluted tubule, and then goes to the loop of Henle, distal convoluted tubule, and collecting duct.

The nephron, which changes in shape and direction as it follows its course, is contained partly in the renal cortex and partly in the medulla (Figure 29-4). The cortex contains the Bowman capsule, glomerulus, and proximal and distal tubules. The thin, descending loop of Henle comes from the proximal tubule and extends toward the pyramid. The descending loop of Henle eventually bends on itself and forms an enlarged, ascending loop of Henle. The ascending limb joins the distal convoluted tubule.[1]

The kidneys have two kinds of nephrons: cortical nephrons, which extend only partially into the medulla, and juxtamedullary nephrons, which lie deep in the cortex and extend deep into the medulla. One fifth to one third of the nephrons are juxtamedullary and play an important role in concentration of urine.

Renal Blood Supply

To understand how the kidneys function, it is essential to understand their blood supply. The kidneys are highly vascular. Although they represent only 0.5% of body weight, they receive 1100 to 1200 mL of blood per minute, or 20% to 25% of the cardiac output. Blood reaches these organs through the renal arteries. At the hilus of the kidney, the renal artery divides into several lobar arteries and then subdivides again into interlobar arteries, which run between the pyramids. When these vessels reach the corticomedullary zone, they make well-defined arches over the bases of the pyramids. These vessels, known as arcuate arteries, divide into a series of arteries known as interlobular arteries (see Figure 29-2). An interlobular artery may terminate as an afferent arteriole or as a nutrient artery to the tubule.

The afferent arterioles form the high-pressure capillary bed within the Bowman capsule called the *glomerulus*. Because little or no oxygen is removed in the glomerulus, the blood that is not filtered begins its passage to the venous system via the efferent

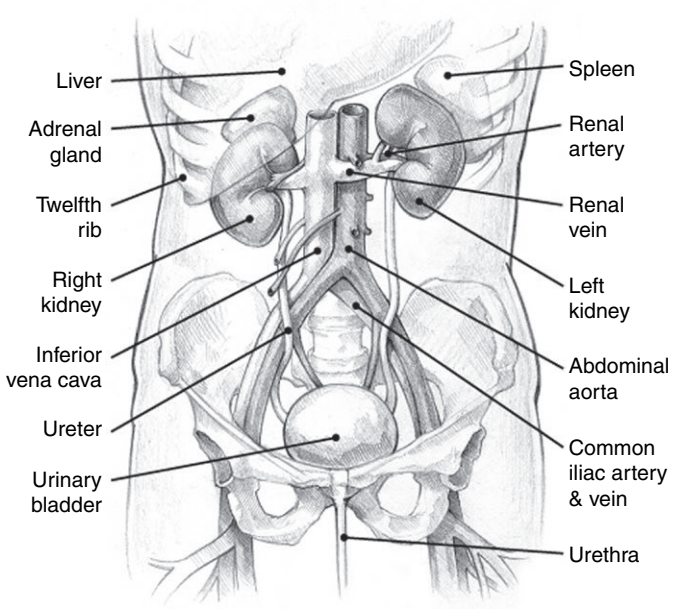

FIGURE **29-1** Kidney position.

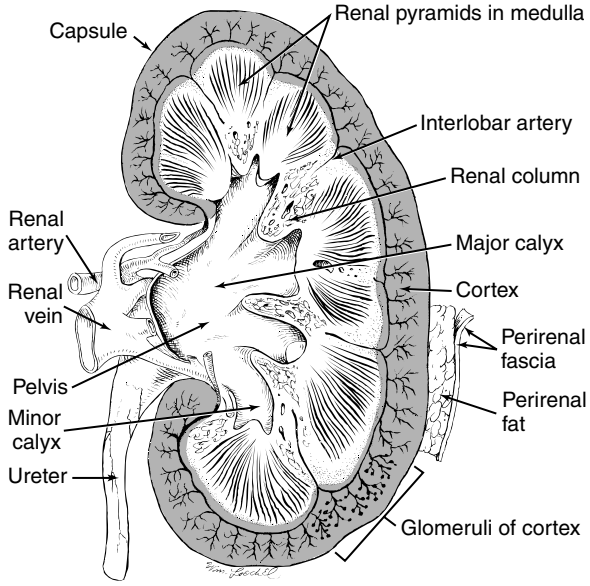

FIGURE **29-2** Longitudinal section of the kidney.

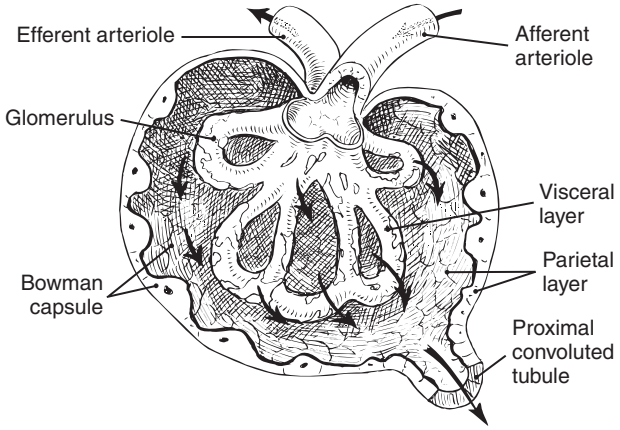

FIGURE **29-3** The nephron.

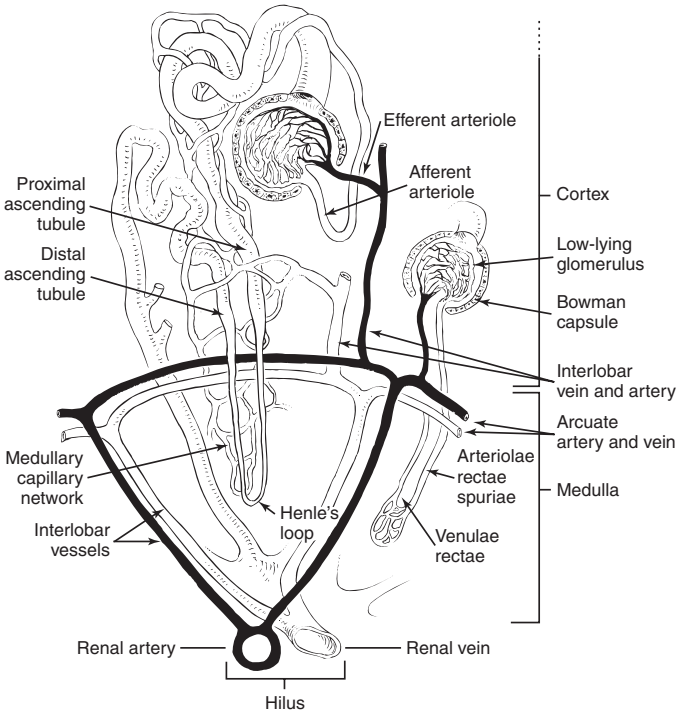

FIGURE **29-4** Renal filtration.

arteriole. The efferent arteriole is smaller than the afferent arteriole, thereby affording some resistance to blood flow. The efferent vessel soon becomes a plexus of capillaries again, and this low-pressure bed is known as the *peritubular capillary*. The peritubular capillary bed winds and twists around the proximal and distal tubule. A few hairpin loops, called vasa recta, dip down among the loops of Henle. Anatomic arrangements of these capillary beds and the renal tubules set the stage for filtration, reabsorption, and concentration of urine.

After leaving the peritubular capillary, blood returns to the central circulation via the veins. Renal veins are named in reverse order of the arteries, and therefore are the interlobular, arcuate, interlobar, lobar, and renal veins. The renal vein leaves the kidney at the hilus and empties into the inferior vena cava.

The portion of the cardiac output that passes through the kidney is called the *renal fraction*. Because cardiac output in a 70-kg man is approximately 5600 mL/min, and blood flow through both kidneys is 1200 mL/min, the normal renal fraction is 21%. This flow may vary from 12% to 30%. Distribution of renal blood flow is to the renal cortex and the medulla, with the cortex receiving the larger amount. Values obtained from dogs indicate that 3 to 5 mL/g/min are distributed to the cortex, 1 to 2 mL/g/min to the outer medulla, and 0.3 to 0.6 mL/g/min to the inner medulla. Only a small portion of blood (1% to 2%) flows through the vasa recta in the medulla. [1]

Regulation of Renal Blood Flow

Blood flow to any organ is determined by the arteriovenous pressure difference across the vascular bed and is given by the following relationship:

$$\text{Renal blood flow} = (\text{MAP} - \text{VP}) \times \text{VR}$$

where MAP is the mean arterial pressure, VP is the venous pressure, and VR is the vascular resistance. Renal blood flow is regulated by intrinsic autoregulation and neural regulation.

Autoregulation of renal blood flow implies that blood flow remains normal despite a considerable change in pressure. With

a MAP between 50 and 180 mmHg, renal blood flow to both kidneys remains 1200 mL/min. If mean systemic blood pressure falls below 50 mmHg, filtration ceases. Afferent arteriole vasodilation and myogenic mechanisms are responsible for autoregulation.[1]

When renal blood flow decreases, glomerular filtration is reduced. A reduction in glomerular filtration leads to dilation of the afferent arteriole. An increase in blood flow to the glomerulus returns glomerular filtration to normal.

Myogenic mechanisms also play a role in renal autoregulation. When arterial pressure rises, the arterial wall is stretched, the vessel constricts, and blood flow remains normal. When arterial pressure decreases, the opposite effect occurs. Therefore renal blood flow remains constant over a wide range of pressure changes.

Neural regulation also has a role in renal blood flow. The sympathetic nervous system innervates both the afferent and efferent arterioles. Although autoregulation overrides the adrenergic system with mild stimulation, acute sympathetic stimulation with its associated vasoconstriction can decrease renal blood flow substantially. The parasympathetic nervous system is not physiologically significant.[1]

RENAL PHYSIOLOGY

The kidneys maintain a steady state essential to life. This is accomplished through three major mechanisms: filtration, reabsorption, and tubular secretion. What is filtered or secreted but not reabsorbed is excreted as urine.

Filtration

Filtration, which results from pressures that force fluids and solutes through the glomerulus, is the first step in the formation of urine. The quantity of glomerular filtrate formed each minute in all nephrons is called the *glomerular filtration rate (GFR)*. The filtration fraction is the quantity of renal plasma flow that becomes filtrate and is defined as GFR divided by the flow to one kidney. Because the GFR is approximately 125 mL/min, and the flow to one kidney is 650 mL/min, the filtration fraction is 125/650, or 19% (approximately one fifth) of plasma flow. Of the 125 mL/min (or 180 L/day) of this protein-free filtrate made, 99% is reabsorbed from the renal tubules, and the remaining small portion is excreted as urine.[1]

Regulation of Glomerular Filtration Rate

Glomerular filtration is also dependent on several physiologic factors:

- The pressure inside the glomerular capillaries
- The pressure in the Bowman capsule
- The colloid osmotic pressure of the plasma proteins

The pressure inside the high-pressure glomerulus (60 mmHg) is an outward force, whereas the colloid osmotic pressure created by proteins in the glomerulus (28 mmHg) is an inward force that tends to hold fluid within the glomerulus. Pressure in the Bowman capsule (18 mmHg) opposes filtration. As illustrated in Figure 29-4, filtration pressure is the pressure that forces fluid through the glomerular membrane. It is equal to the glomerular pressure minus the sum of the glomerular colloid osmotic pressure and the capsular pressure. With the values given, the normal filtration pressure is 10 mmHg. Several factors can alter GFR. Increased renal blood flow, dilation of the afferent arteriole, and increased resistance in the efferent arteriole increase GFR. Afferent arteriole constriction and efferent arteriole dilation tend to decrease GFR.

A special structure called the *juxtaglomerular complex* regulates GFR. At the juxtaglomerular complex, the distal convoluted tubule lies between the afferent and efferent arterioles. Cells of the distal tubule coming into contact with the arterioles are dense and therefore are referred to as the macula densa. Smooth muscle cells of both the afferent and efferent arterioles consist of juxtaglomerular cells, which contain renin. Anatomically this structure is arranged to allow fluid in the distal tubule to alter afferent or efferent arteriolar tone and thus regulate GFR.

Decreased glomerular filtration causes overabsorption of sodium ions (Na^+) and chloride ions (Cl^-) in the ascending limb of the loop of Henle and therefore a reduction in the delivery of these ions to the macula densa. Decreases in the concentrations of sodium and chloride cause afferent arterioles to dilate and thus increase renal blood flow and GFR. Sympathetic stimulation and decreased delivery of both sodium and chloride to the macula densa also cause the juxtaglomerular cells to release renin. Renin clears angiotensinogen from the liver to form angiotensin I. In the lung, angiotensin I is changed into angiotensin II under the influence of a converting enzyme. In addition to having a generalized vasoconstricting effect, angiotensin II causes constriction of the efferent arteriole. This causes the pressure in the glomerulus to increase and the GFR to return to normal.[1]

Filtrate Composition

Although permeability at the glomerulus is 100- to 500-fold greater than that of most capillaries, filtration at the glomerulus is a selective process. The process by which some substances are filtered and others are not is only partially understood. It is thought that the glomerular capillary contains pores that are negatively charged. These pores, which are 70 to 100 nm in size, are freely permeable to water and small molecules, as well as to some ions. Molecules with diameters up to 80 nm that do not have a negative charge are easily filtered. The glomerulus is almost impermeable to all plasma proteins but highly permeable to most other dissolved substances. Glomerular filtrate is therefore similar to plasma, except that it lacks significant amounts of proteins.

Tubular Reabsorption and Secretion

Conversion of glomerular filtrate to urine is the result of filtration at the glomerulus, tubular reabsorption or transport from the tubular lumen to the renal cell, and secretion or transport from the renal cell to the filtrate. Of all that is filtered or secreted, 99% is reabsorbed as the filtrate moves along the nephron.

Tubular reabsorption permits conservation of essential substances such as water, glucose, amino acids, and electrolytes. Some substances, such as water and sodium, are reabsorbed throughout the nephron, whereas others, such as glucose, are completely reabsorbed when plasma concentrations are low. Certain substances have a reabsorption maximum value, and after that value is reached, excess filtered material is excreted, regardless of plasma concentration. This maximum value is termed *maximum transport*. Maximum transport occurs because of saturation of a carrier for a particular substance.

By the time the blood has reached the peritubular capillary, one fifth of the plasma has been filtered into the Bowman capsule. The hydrostatic pressure in this low-pressure capillary bed has dropped to 13 mmHg, whereas the osmotic pressure has increased to 30 to 32 mmHg. The peritubular capillaries are extremely porous compared with those in other body tissues, and their proximity to the proximal and distal tubule sets the stage for movement of water and solutes from the tubule to the peritubular capillary bed. Anatomic location and the colloid osmotic pressure of plasma proteins account for the rapid absorption required in this area.[1]

Transport Mechanisms

Basic mechanisms of transport through the tubular membrane can be divided into active transport and passive transport. Active transport is the net movement of particles across a membrane against an electrochemical gradient, generally at the cost of metabolic energy. Passive transport involves the movement of substances across membranes and relies on either concentration gradients or chemical gradients. Active transport can be further divided into primary active transport, which requires energy, and secondary active transport, which does not require energy. Most primary active transport is for sodium. Secondary active transport is a result of the movement of sodium from the tubular lumen to the interior of the cell. For example, the active transport of sodium pulls glucose and amino acids with it. Because a carrier protein in the membrane combines with sodium and glucose, the process is termed *cotransport*. In addition to glucose and amino acids, chloride, phosphate, calcium, magnesium, and hydrogen ions are co-transported.

Some substances are actively secreted into the renal tubule in exchange for other molecules. Hydrogen, potassium, and urate ions are secreted in this manner. Hydrogen and potassium are generally secreted in exchange for sodium in a process termed *countertransport*.

When substances are actively transported from the tubule to the peritubular capillary bed, a concentration gradient that causes passive absorption of water by osmosis is established. When positive ions are actively transported, negative ions follow to maintain electrical neutrality. Chloride ions and urea are examples of substances that are passively absorbed.[1]

Proximal Tubule

Each portion of the renal nephron is selective with regard to what is reabsorbed or secreted. Active transport of sodium is the primary function of the proximal tubule. Water, most electrolytes, and organic substances are cotransported with sodium. The osmotic force generated by active sodium transport promotes passive diffusion of water out of the tubules into the peritubular capillaries. Passive transport of water is further enhanced by the elevated osmotic pressure of the blood in the peritubular capillaries. Reabsorption of water leaves an increased concentration of urea within the tubular lumen, thereby creating a gradient for its passive diffusion into the peritubular plasma. As positively charged sodium ions leave the tubular lumen, negatively charged chloride ions passively follow to maintain electroneutrality. Hydrogen ions are actively secreted in exchange for sodium. Secretory transport of sodium also occurs in the proximal tubule.

As the filtrate passes along the proximal tubule, 60% to 70% of filtered sodium and water, 50% of urea, and potassium, calcium, phosphate, uric acid, and the bicarbonate (HCO_3) form of carbon dioxide (CO_2) have been reabsorbed. Glucose, proteins, amino acids, acetoacetate ions, and vitamins are completely or almost completely reabsorbed by active processes. Because protein molecules are too large to be reabsorbed by normal mechanisms, a special mechanism called *pinocytosis* is used to save proteins. In this process, the tubular membrane engulfs the protein and internalizes it. Once inside the cell, the protein is digested into amino acids that can then be absorbed into the interstitial fluid.

Loop of Henle

The primary function of the loop of Henle is to establish a hyperosmotic state within the medullary area of the kidney, a function vital to conservation of salt and water. Water conservation and the production of a concentrated urine involve a countercurrent exchange system in which a concentration gradient causes fluid to be exchanged across parallel pathways. The fluid moves up and down the parallel sides of the hairpin loop of Henle in the medulla. The longer the loop, the greater the concentration gradient, because the gradient increases from the cortex to the medulla. Sluggish blood flow in the vasa recta helps maintain the gradient.

Countercurrent exchange begins in the thick, ascending limb of the loop of Henle with the active transport of sodium and chloride out of the tubular lumen and into the medullary interstitium. Because the lumen in this area is impermeable to water, water cannot follow. The tubular fluid becomes hypoosmotic, and the medullary interstitium hyperosmotic. The descending limb of the loop is highly permeable to water but does not actively transport sodium and chloride. Sodium and chloride diffuse into the interstitium, the hypertonic interstitium causes water to move out, and the remaining fluid in the descending loop becomes concentrated at the tip of the medulla. As the tubular fluid rounds the loop and enters the ascending limb, water is retained, and sodium and chloride are removed. The filtrate therefore is very dilute as it reaches the distal tubule. The thick segment of the loop of Henle has a powerful role in renal mechanisms for diluting or concentrating the urine.[1]

Late Distal Tubule

In the late distal tubule, sodium, under the influence of aldosterone, is reabsorbed. In this area, potassium is secreted into the lumen in exchange for sodium. It is mainly by this means that the potassium concentration is controlled in the extracellular fluids of the body.

The late distal tubule also secretes hydrogen against a concentration gradient. This function has a role in acid-base balance and the final degree of urine acidification. The late distal tubule reabsorbs 10% of filtered water. This area is permeable to water only in the presence of antidiuretic hormone (ADH).

Collecting Duct

The permeability of the collecting duct to water also is controlled by ADH. When this neurohypophyseal hormone is present, water is reabsorbed into the medullary interstitium, and the urine volume is reduced and concentrated. The collecting duct also can secrete hydrogen and therefore has a role in acid-base balance. Figure 29-5 illustrates renal blood flow, filtration, reabsorption, and secretion.[1]

Renal Secretion

In addition to renin, hydrogen, and potassium, the kidneys release erythropoietin, a glycoprotein that stimulates red-blood-cell production in the bone marrow. Any condition that causes the quantity of oxygen transported to the tissues to decrease stimulates the release of erythropoietin, production of red blood cells, and correction of hypoxia. A clinical diagnosis of anemia emerges when both kidneys are destroyed by renal disease.

Renal Hormones

Aldosterone

A number of hormones affect renal function. Aldosterone, the chief mineralocorticoid produced by the adrenal cortex, affects the distal segment of the nephron, causing the reabsorption of sodium and water. Several physiologic control systems regulate aldosterone release: potassium concentration in extracellular fluid; the renin-angiotensin system; and sodium concentration in extracellular fluid. Of these, potassium is the strongest trigger, followed by renin and then sodium.

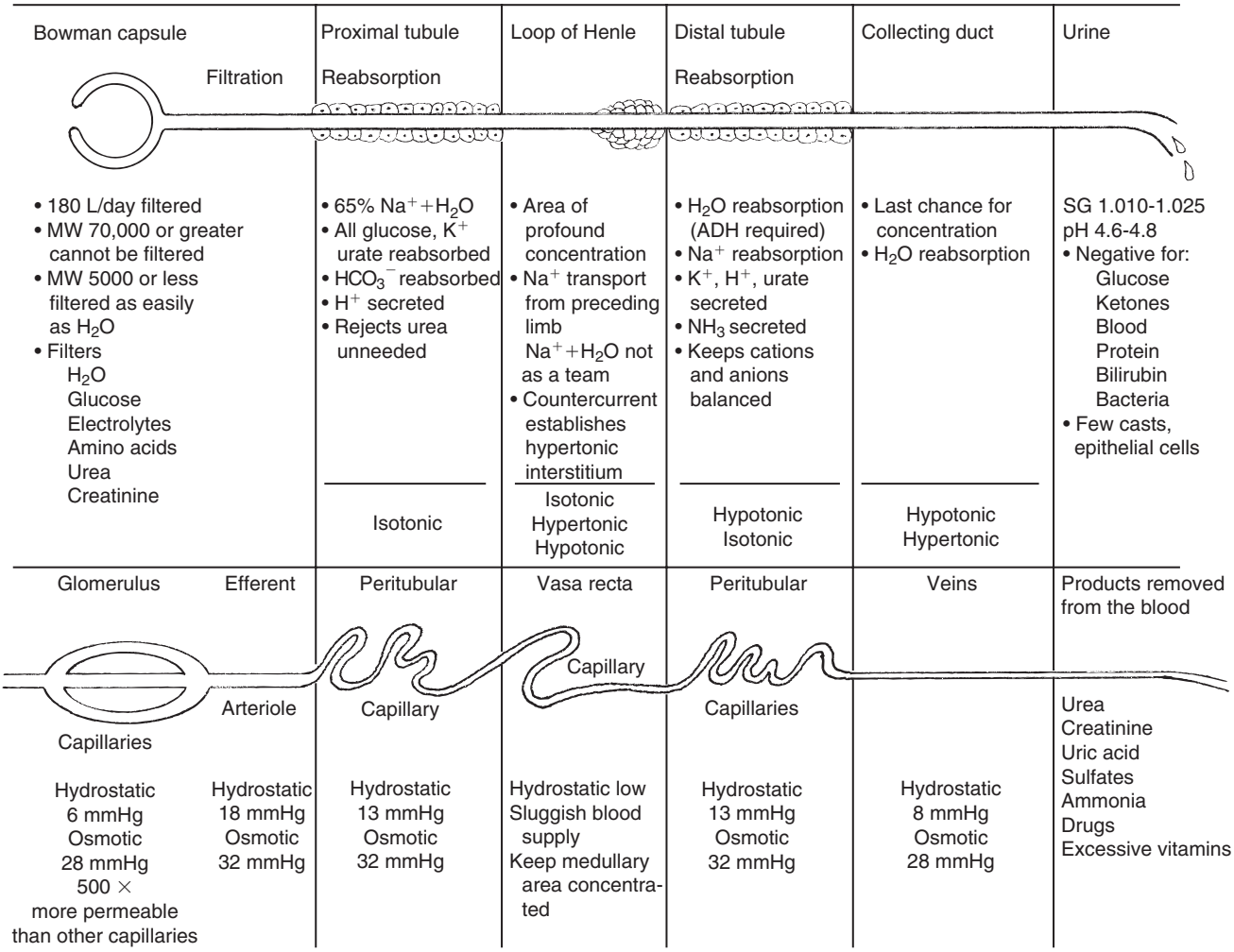

FIGURE **29-5** Renal blood flow, filtration, reabsorption, and secretion. *ADH,* Antidiuretic hormone; *SG,* specific gravity.

Antidiuretic Hormone

ADH, a hormone synthesized in the hypothalamus but released from the neurohypophysis, also has the distal nephron as its target tissue. Because the distal tubule and collecting ducts are almost totally impermeable to water in the absence of ADH, water is not reabsorbed and is lost in the urine. In the presence of ADH, tubular permeability is increased, and water is reabsorbed. The release of ADH is controlled by the osmotic concentration of the extracellular fluids (Figure 29-6). Osmoreceptors located near the hypothalamus sense extracellular fluid concentration and release ADH accordingly. ADH is inhibited by stretch of atrial baroreceptors.

Angiotensin

Angiotensin is a hormone that has a direct renal effect, as well as a general systemic effect. As previously discussed, renin is a small protein enzyme released by the kidneys. Stimuli for the release of renin include β-adrenergic stimulation, decreased perfusion to the afferent arterioles, and reduction in sodium delivery to the distal convoluted tubule. Once released, renin acts on hepatic angiotensinogen to form angiotensin I. Angiotensin I is then converted by the angiotensin-converting enzyme (ACE) in the lung to form angiotensin II. In addition to causing powerful vasoconstriction, angiotensin II stimulates the release of aldosterone from the adrenal cortex. Aldosterone increases salt and water retention by the kidneys. Both of these actions increase arterial pressure.[2]

Atrial Natriuretic Factor

Atrial natriuretic factor (ANF) is a peptide hormone synthesized, stored, and secreted by the cardiac atria.[3] It acts on the kidney to increase urine flow and sodium excretion, and it may enhance renal blood flow and GFR. In addition, ANF antagonizes both the release and end-organ effects of renin, aldosterone, and ADH. The stimulus for ANF release is atrial distention, stretch, or pressure.[4] ANF is one of the most potent diuretics known. Inhibition of plasma renin, angiotensin, and aldosterone can produce a dose-dependent decrease in blood pressure.

Vitamin D

Vitamin D, along with parathyroid hormone and calcitonin, has a vital role in calcium metabolism. Vitamin D or cholecalciferol is obtained in the diet or synthesized by the action of ultraviolet radiation on cholesterol in the skin. To become active, cholecalciferol is first hydroxylated in the kidney to 25-hydroxycholecalciferol, then in the liver to 1,25-dihydroxycholecalciferol. Patients with advanced renal disease often have abnormal serum calcium levels.

Prostaglandins

Prostaglandins (PGs) such as PGE_2 and thromboxane A_2 modulate the renal effects of other hormones. PGE_2 is a vasodilator, and thromboxane A_2 produces contraction of vascular smooth muscle. Renal PGs influence renal excretion.

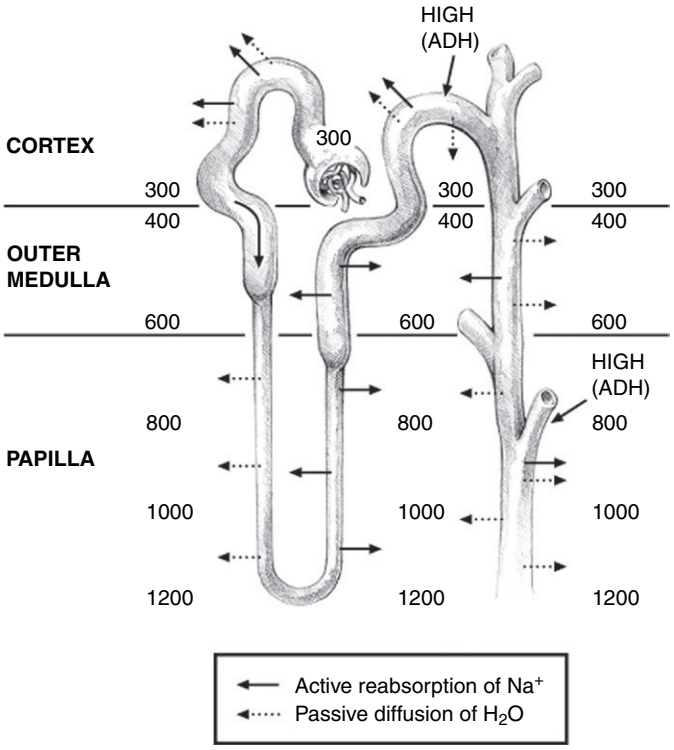

FIGURE **29-6** The countercurrent mechanism. *ADH,* Antidiuretic hormone.

Renal Regulation of Acid-Base Balance

The kidneys, along with the body's fluid buffers and respiratory system, play a major role in regulating acid-base balance. Epithelial cells of the proximal tubules, the thick portion of the loop of Henle, distal tubules, and collecting ducts secrete hydrogen into the tubular fluid. This secretory process actually begins with CO_2 in the epithelial cells, where under the influence of carbonic anhydrase, CO_2 combines with water to form carbonic acid (H_2CO_3). H_2CO_3 dissociates into HCO_3 and hydrogen ions, and hydrogen ions are actively secreted into tubular fluid in exchange for sodium ions. This exchange maintains appropriate electrical balance between anions and cations in the tubular fluid.

An increase in HCO_3 in alkalosis means that the filtered amount of HCO_3 exceeds the amount of hydrogen secreted. Because excess HCO_3 must react with hydrogen ($HCO_3^- + H^+ \rightarrow H_2CO_3 \rightarrow CO_2^- + H_2O$) and be absorbed as CO_2, excess HCO_3 ions are lost in the urine along with sodium. In this way, sodium and excess HCO_3 are removed from the extracellular fluid.

In acidosis the concentration of hydrogen ions increases to a level far greater than that of HCO_3 in the tubules. Excess hydrogen ions are lost in the urine through the phosphate or ammonia (NH_3) buffer system.

The phosphate buffer is composed of hydrogen phosphate (HPO_2^-) and dihydrogen phosphate (H_2PO_4). Both of these ions become concentrated in the tubular fluid because of poor reabsorption. The quantity of HPO_2^- is normally fourfold that of H_2PO_4. Excess hydrogen ions entering the tubules combine with monohydrogen phosphate to form H_2PO_4, which is lost in the urine. A sodium ion is absorbed into the extracellular fluid in exchange for hydrogen. It combines with HCO_3, which was formed in the process of secretion of the hydrogen, and sodium bicarbonate is added to the extracellular fluid.

NH_3, which is synthesized by all epithelial cells except those in the thin segment of the loop of Henle, is also secreted into the tubules. NH_3 reacts with hydrogen to form the ammonium ion (NH_4). Ammonium ions are lost in the urine with chloride and other tubular anions.

The kidneys control extracellular fluid hydrogen concentration by excreting an acidic or basic urine. Excretion of acidic urine removes excess acid from the extracellular fluid, whereas loss of basic urine removes base from the extracellular fluid.

Concentration and Dilution of Urine

The kidneys have the ability to respond to the changing tonicity of body fluids by excreting dilute or concentrated urine. This function involves a countercurrent exchange system in which a concentration gradient causes fluid to be exchanged across parallel pathways (see Figure 29-6). In a countercurrent exchanger, reversal of flow in one stream results in the formation of a gradient that allows water and solutes to be exchanged along the length of the tube. The countercurrent exchanger in the kidney is the descending and ascending loop of Henle. The concentration gradient increases from the cortex to the tip of the medulla. The anatomic arrangement of this part of the nephron and sluggish blood flow in the vasa recta help maintain the gradient.

Plasma water filtered at the glomerulus is isotonic with plasma. The daily urinary output is approximately 1.5 L/day, and its osmolarity may vary from 40 to 1400 mOsm/L, depending on water intake or loss. This is possible because of the countercurrent mechanism.

Approximately two thirds of the tubular fluid is reabsorbed between the glomerulus and the end of the proximal tubule. The tonicity of the filtrate in this area is the same as that of the surrounding tissue, or 300 mOsm. As the filtrate leaves the proximal tubule, it passes through an increasingly more concentrated medulla. Changes in the thick ascending limb of the loop of Henle are responsible for the hypertonicity.

The thick ascending limb of the loop of Henle is responsible for the active transport of sodium and chloride into the medullary interstitium. In contrast to the descending limb of the loop of Henle, the tonicity of which is in equilibrium with that of the interstitium, the ascending loop has a low permeability to water. The active transport of sodium and chloride produces a gradient between the ascending loop of Henle on one side and the descending loop and interstitium of the renal medulla on the other. The descending limb is highly permeable to water but does not actively transport sodium and chloride. The hyperosmotic interstitium causes water to move out of the descending limb, and the filtrate in the descending tubule is concentrated to 1200 mOsm at the tip of the medulla. As the tubular fluid rounds the loop and enters the ascending limb, active transport of sodium and chloride and retention of water create a hypoosmotic fluid of 100 mOsm at the distal tubule.

The hypoosmotic fluid of the distal tubule is delivered to the collecting duct, where the final adjustments of urine volume and concentration take place. In the absence of ADH, water permeability is low, and water is not reabsorbed. Because sodium and chloride can be reabsorbed, the osmolality decreases to below that of the distal tubule, and the urine is dilute. When the need for water conservation arises, ADH is secreted, permeability of the collecting duct increases, and water diffuses out of the duct into the hyperosmolar environment of the medullary extracellular fluid. In this way urine is concentrated and its volume is reduced.

The sluggish blood supply of the vasa recta in the medulla allows blood to flow through the medullary tissue without disturbing the osmotic gradient. If blood flow were rapid, the medullary concentration gradient and the ability to concentrate the urine would be lost.[1,5]

EFFECTS OF ANESTHESIA ON NORMAL RENAL FUNCTION

Before considering anesthetic implications for patients with renal disease, it is important to review the effects of anesthesia and surgery on normal renal function. Numerous studies have attempted to identify the effects of anesthesia on renal function, and although some have contributed to a better understanding of this area, differences among the studies in premedication, depth of anesthesia, fluid regimens, and other aspects of the experimental protocol allow only the broadest comparisons.

Anesthetic Effects

General anesthesia is associated with a temporary depression of renal blood flow, GFR, urinary flow, and electrolyte excretion. Although similar changes occur after spinal and epidural anesthesia, the magnitude of change tends to parallel the degree of sympathetic block and blood pressure depression. This consistent and generalized depression of renal function has been attributed to a number of factors, including type and duration of surgical procedure, physical status of the patient, volume and electrolyte status, depth of anesthesia, and choice of agent.[5]

Anesthesia may alter renal function by direct or indirect effects. Indirect effects are mediated through changes in the circulatory, endocrine, or sympathetic nervous system. Anesthetic drugs alter the circulatory system by decreasing renal perfusion, increasing renal vascular resistance, or a combination of both. Drugs associated with catecholamine lead to vasoconstriction, an increase in renal vascular resistance, a decrease in renal blood flow, and a decrease in renal function. Volatile agents such as isoflurane cause a mild to moderate increase in renal vascular resistance as a compensatory response to decreased perfusion pressure secondary to alterations in cardiac output or systemic vascular resistance.[6-10] Desflurane has been shown to produce hemodynamic effects comparable to those produced by isoflurane.[11] It increases heart rate and decreases both mean arterial pressure and systemic vascular resistance while maintaining cardiac output. In some studies, but not all, desflurane maintains arterial pressure and systemic vascular resistance to a greater degree than equianesthetic concentrations of isoflurane. Otherwise, desflurane and isoflurane have similar effects on most vascular beds, including the renal circulation.

Although earlier studies suggested that renal blood flow was reduced with sevoflurane, no renal functional or morphologic defects were noted after administration of this agent. Issues regarding the renal effects of the release of free fluoride ion associated with sevoflurane metabolism have been debated. Historically, high fluoride ion concentrations in the range of 60 to 90 μmol/L after methoxyflurane metabolism have led to nephrotoxicity characterized by polyuria. This methoxyflurane polyuria was commonly referred to as high-output renal failure. Sevoflurane has not produced the expected toxicity in the same way as methoxyflurane even though significant levels of fluoride ion may result from prolonged administration. A few reasons have been theorized for the lack of nephrotoxicity of sevoflurane, even though levels of metabolically released fluoride ion can approach those of methoxyflurane. They include the fact that sevoflurane metabolism is largely hepatic rather than renal. Intrarenal production of inorganic fluoride may be a more important factor than hepatic metabolism for the nephrotoxicity produced by increased serum fluoride concentration. Sevoflurane also has a much lower blood solubility so that it undergoes rapid elimination Sevoflurane has not been associated with nephrotoxicity.[12-15]

Changes in renal function during barbiturate, opiate, and nitrous oxide anesthesia are similar to those observed during the administration of low-dose volatile anesthesia.[16] Preoperative hydration, lower concentrations of volatile anesthetics, and maintenance of normal blood pressure attenuate reductions in renal blood flow and GFR.[17]

High levels of spinal or epidural anesthesia can impair venous return, diminish cardiac output, and reduce renal perfusion.[18] Epidural blocks at thoracic levels with epinephrine-containing local anesthetics cause moderate reductions in renal blood flow and GFR that parallel the decrease in mean blood pressure.[19] Epidural blocks performed with epinephrine-free solutions generate little change in systemic hemodynamics; however, absorption of local anesthetics is enhanced in uremic patients.[20]

In summary, virtually all anesthetics have the potential to alter the cardiovascular system and affect renal blood flow, GFR, and urinary output. Although systolic arterial blood pressure may not fall below 80 to 90 mmHg, renal blood flow may be decreased by 30% to 40% after the administration of various anesthetics. This suggests impairment of autoregulation. In most cases, changes in renal function are transient and reversible. If they persist into the postoperative period, the cause is often a combination of factors such as preexisting renal or cardiovascular disease, severe fluid imbalance, or mismatched blood, and the importance of the anesthetic effects is decreased.

Physiologic Responses

The renal vasculature is richly innervated by the sympathetic nervous system. Drugs or perioperative events that stimulate this system cause an increase in renal vascular resistance and a decrease in renal blood flow and glomerular filtration. Surgical stress also may alter autonomic and neuroendocrine responses. Norepinephrine from sympathetic postganglionic nerve fibers and epinephrine and norepinephrine from the adrenal medulla shift blood away from the cortical nephrons; this results in decreases in renal blood flow, GFR, electrolyte excretion, and urinary output. Catecholamines also stimulate the release of renin, which ultimately leads to the production of angiotensin II, a potent vasoconstrictor.

Endocrine changes associated with anesthesia and surgical stress involve ADH, aldosterone, and the renin-angiotensin-aldosterone system. Although the perioperative period is associated with high circulating levels of ADH and aldosterone, it is not clear whether anesthetics stimulate the release or the release is secondary to the surgical stress response. General anesthetics and narcotics are thought to be minor stimuli of the release of ADH, but laparoscopic surgical procedures have been shown to increase ADH levels.[21] Clinical studies have specifically identified that pneumoperitoneum during laparoscopic surgery increases the level of ADH.[22] Other studies indicate that patients undergoing anesthetics lasting long durations had significant increases in ADH, with the greatest increase occurring at emergence.[23] Additional investigations have shown that ADH levels increase after the induction of anesthesia and is higher in subjects receiving lower concentrations of remifentanil-propofol anesthesia.[24]

It is clear that ADH release is modulated by blood volume changes that are sensed by stretch receptors in the atrial wall. Hemorrhage, positive pressure ventilation, and the upright position increase ADH release.[25,26] A decrease in arterial pressure stimulates ADH release. Distention of a balloon in the atrium, negative pressure ventilation, and immersion in water up to the neck decrease ADH release.

Renin-angiotensin levels may be elevated during the perioperative period, but the role of anesthetics and stress is not clear. Some studies have reported large increases in plasma renin levels associated with the use of anesthetics, whereas others report

variances dependent on type of anesthesia delivered as well as surgical procedure. Balanced anesthesia has been found to result in higher levels of epinephrine, norepinephrine, and adrenocorticotropic hormones than total intravenous anesthesia.[27] The influence of renin-angiotensin on the renal effects of anesthetic agents needs further clarification. Renin levels have been shown to increase during laparoscopic surgery, as well as vasopressin, epinephrine, norepinephrine, and cortisol.[28] Preoperative hydration is thought to be important in the intraoperative release of renin.

Aldosterone, a hormone released from the adrenal gland, is responsible for the precise control of sodium excretion. It is not known whether anesthetic agents act directly on the adrenal gland to cause aldosterone release. They probably act indirectly through the neuroendocrine system and the renin-angiotensin-aldosterone system. Stimulation of the sympathetic nervous system causes renal vasoconstriction, which is a trigger for the renin-angiotensin-aldosterone system. Aldosterone leads to sodium and water reabsorption and can be associated with decreased urinary output.

Nephrotoxicity of Anesthetic Agents

The kidneys are extremely vulnerable to toxicity because of their rich blood supply and the increase in the concentration of excreted compounds that occurs in the renal tubules during the process of reabsorption. Medullary hyperosmolality encourages concentration of all substances, including toxins. The amount of renal damage associated with nephrotoxic agents depends on the concentration of the toxins, the degree of toxin binding to plasma proteins and nonrenal versus renal tissue, and the length of exposure of the kidneys to the toxin. The nephrotoxicity of anesthetic agents became fully appreciated in 1966, when vasopressin resistant–polyuria renal insufficiency was reported in patients receiving prolonged methoxyflurane anesthesia for abdominal surgery.[29] Evidence gathered indicated that the release of the inorganic fluoride ions (F^-) in the metabolism of this fluorinated anesthetic was the causative agent in nephrotoxicity. Fortunately none of the modern inhalation anesthetics are nephrotoxic.

Fluoride Ion Toxicity

Fluoride alters renal concentration mechanisms by interfering with active transport of sodium and chloride in the medullary portions of the loop of Henle. It also acts as a potent vasodilator, resulting in increased blood flow in the vasa recta and washout of medullary solute. Fluoride is a potent inhibitor of many enzyme systems, including those involving ADH, which is necessary for distal nephron reabsorption of water. Proximal tubular swelling and necrosis associated with fluoride ions also contribute to nephrotoxicity. Signs and symptoms of fluoride nephrotoxicity include polyuria, hypernatremia, serum hyperosmolality, elevations in blood urea nitrogen (BUN) and serum creatinine levels, and decreased creatinine clearance. The extent of nephrotoxicity in general surgical patients has been correlated with dosage or maximum allowable concentration hours (MAC-hours), duration, and peak fluoride concentrations.[29]

Methoxyflurane

Methoxyflurane, an anesthetic no longer used, was the first anesthetic associated with serious nephrotoxicity. The serum fluoride concentration after methoxyflurane anesthesia showed positive correlation with the degree of renal dysfunction.[30] Vasopressin-resistant polyuria similar to that seen after methoxyflurane anesthesia was later produced in Fischer 344 rats injected with sodium fluoride.[31] After 2.5 to 3 MAC-hours of methoxyflurane anesthesia, fluoride concentration was 50 to 80 µmol, and subclinical toxicity evidenced by a delayed return to maximum preoperative urine osmolarity and decreased urate clearance were noted.

Isoflurane

Isoflurane is metabolized only slightly and defluorinated much less than other halogenated agents. In one report of nine surgical patients, mean peak serum fluoride concentration measured 6 hours after anesthesia was only 4.4 µmol.[32] Clinical experience has indicated that renal toxicity does not occur after the administration of isoflurane.[33]

Desflurane

The metabolism of desflurane has been assessed in both animals and humans with the appearance of fluoride metabolites (fluoride ion, nonvolatile organic fluoride, trifluoroacetic acid) in blood and urine. Administration of desflurane to rats that were either pretreated or not pretreated with phenobarbital or ethanol for 3.2 MAC-hours, as well as to swine for 5.5 MAC-hours, produced fluoride levels in blood that were almost indistinguishable from values measured in control animals.[34] In human studies, desflurane administered to patients for 3.1 MAC-hours and volunteers for 7.3 MAC-hours resulted in postanesthesia serum fluoride concentrations that did not differ from background fluoride concentrations. Similarly, postanesthesia urinary excretion rates of fluoride and organic fluoride in volunteers were comparable with preanesthetic excretion rates.[35-37] Small but statistically significant increases in the levels of trifluoroacetic acid were found in both the serum and urine of volunteers after exposure to desflurane. Although these increases in trifluoroacetic acid were statistically significant, they were approximately one tenth the levels seen after exposure to isoflurane. Desflurane strongly resists biodegradation, and only a small amount is metabolized in animals and humans.[38] Desflurane does not produce nephrotoxicity.

Sevoflurane

Sevoflurane undergoes approximately 5% to 8% metabolism, and the primary metabolites are fluoride and hexofluro-2-propranolol (HFIP). The oxidative defluorination of sevoflurane in the liver with the liberation of free fluoride ions raised concerns that sevoflurane, like methoxyflurane, might impair the ability of the kidneys to concentrate urine. Earlier research indicated that with methoxyflurane, renal dysfunction was likely to occur when plasma fluoride levels exceeded 50 µmol. The same does not appear to be true with sevoflurane.

Preliminary investigations with sevoflurane found that some adult patients receiving the drug had plasma fluoride levels that exceeded 50 µmol. However, renal function, assessed by BUN, creatinine, and decrease in urine osmolality, was not different from that in patients receiving similar amounts of other fluorinated anesthetics. In one study, serum fluoride levels averaged 29 µmol after 1 to 7 MAC-hours of anesthesia. The fluoride levels peaked 2 hours after the end of anesthesia and decreased by 50% within 8 hours.[39] The fast decline in plasma fluoride levels was attributed to insolubility of the agent and rapid pulmonary elimination of sevoflurane.

Numerous published reports indicate the absence of renal toxicity after sevoflurane anesthesia.[40-43] As mentioned previously, an explanation for the absence of fluoride-induced nephrotoxicity may be that intrarenal production of fluoride ion is important in the pathogenesis of this complication. The intrarenal metabolism of methoxyflurane is four times greater than that of sevoflurane.[42]

Studies of surgical patients receiving intermediate-duration sevoflurane with high and low fresh gas flow and long-duration

sevoflurane with high fresh gas flow included sensitive measures of renal function or injury. These studies also indicate the absence of renal toxicity after sevoflurane anesthesia.[43-48]

In addition to release of inorganic fluoride ion resulting from biotransformation, CO_2 absorbents degrade sevoflurane, causing the production of a vinyl ether called *compound A*. This reaction occurs in the anesthesia machine, and the resulting toxin, compound A, is then delivered to the patient via the machine breathing system. Factors associated with the generation of higher levels of compound A during administration of sevoflurane to patients include: (1) a high concentration of the agent, (2) increased temperature in the CO_2 absorbent, (3) low fresh gas flow rates, and (4) increased states of CO_2 production. The potential for compound A nephrotoxicity theoretically exists although no reports of problems in clinical practice have been reported.

Because the potential for renal injury exists with sevoflurane, studies in volunteers have raised the question of whether it is important to apply more sensitive measures of renal function in evaluation of this drug. Such tests have included urine concentrations or excretion of enzymes, albumin, protein, and glucose and creatinine clearance.[49] Two studies of volunteers receiving prolonged sevoflurane anesthesia with fresh gas flow no greater than 2 L/min concluded that the potential for adverse renal effects of sevoflurane may exist.[50,51] However, other studies of volunteers did not find the same results.[52-55]

A number of reports describe instances in which sevoflurane has been given to patients with renal dysfunction and other conditions that might enhance renal injury. Such conditions include patients who are hypotensive, hypertensive, elderly, or obese or who have renal insufficiency or hepatic failure.[56-65] The only proven direct toxic effect of any anesthetic agent is the fluoride-related toxicity of methoxyflurane.[65]

Because the amount of compound A produced increases with lower gas flows, the package insert at one time recommended flows of 2 L/min or more. Several studies indicate no effect of low-flow sevoflurane on renal function, even those with moderate renal insufficiency.[66,67] Today, the U.S. Food and Drug Administration recommends the use of sevoflurane for a minimum of 1 L/min of fresh gas flow and advises that 2 MAC-hours at this flow rate should not be exceeded.[68] The use of newer carbon dioxide absorbents such as Litholyme® and others, which do not react with sevoflurane, to replace soda lime–type absorbents in modern anesthesia practice are eliminating any concern regarding compound A toxicity.

ACUTE KIDNEY INJURY

Acute kidney injury (AKI) describes the clinical syndrome formerly called acute renal failure (ARF). AKI is defined as a functional or structural abnormality of the kidney that manifests within 48 hours as determined by blood, urine, or tissue tests or by imaging studies. Diagnostically, the reduction in kidney function is associated with either an absolute increase in serum creatinine of 0.3 mg/dL or a percentage increase in serum creatinine of 50%. In addition, a reduction in urine output with oliguria (<0.5 mL/kg/hour) for more than 6 hours also fulfills the diagnostic criteria. Patients are frequently classified based on urine flow rates as nonoliguric (urine output >400 mL/day), oliguric (urine output <400 mL/day), or anuric (urine output <100 mL/day)

Most episodes of AKI occur in the hospital, with an incidence ranging from 5% to 7% among all hospitalized patients and 15% to 40% among patients in intensive care units (ICUs). By contrast, the incidence of community-acquired AKI is less than 1%.

BOX 29-1

Causes of Prerenal Acute Kidney Injury

Intravascular Volume Depletion
- Hemorrhage—trauma, surgery, postpartum, gastrointestinal
- Gastrointestinal losses—diarrhea, vomiting, nasogastric tube loss
- Renal losses—diuretic use, osmotic diuresis, diabetes insipidus
- Skin and mucous membrane losses—burns, hyperthermia
- Nephrotic syndrome
- Cirrhosis
- Capillary leak

Reduced Cardiac Output
- Cardiogenic shock
- Pericardial diseases—restrictive, constrictive, tamponade
- Congestive heart failure
- Valvular diseases
- Pulmonary diseases—pulmonary hypertension, pulmonary embolism
- Sepsis

Systemic Vasodilation
- Sepsis
- Cirrhosis
- Anaphylaxis
- Drugs

Renal Vasoconstriction
- Early sepsis
- Hepatorenal syndrome
- Acute hypercalcemia
- Drugs—norepinephrine, vasopressin, nonsteroidal antiinflammatory drugs, angiotensin-converting enzyme inhibitors, calcineurin inhibitors
- Iodinated contrast agents

Increased Intraabdominal Pressure
- Abdominal compartment syndrome

From Sharfuddin AA, et al. Acute kidney injury. In Taal MW, et al, eds. *Brenner & Rector's The Kidney*. 9th ed. Philadelphia: Saunders; 2012:1045.

AKI is usually divided into three broad pathophysiologic categories based on cause:

1. *Prerenal AKI*—diseases characterized by effective hypoperfusion of the kidneys in which there is no parenchymal damage to the kidney
2. *Intrinsic AKI*—diseases involving the renal parenchyma
3. *Postrenal (obstructive) AKI*—diseases associated with acute obstruction of the urinary tract

Each of the categories represents a unique pathophysiologic process with distinctive diagnostic parameters and prognosis. Causes of prerenal (Box 29-1), intrinsic (Table 29-1), and postrenal (Box 29-2) AKI are summarized in the boxes noted.[69-70]

Classification

Historically, acute kidney injury was classified according to urine output: oliguric, nonoliguric, or polyuric, or by its predominant cause: prerenal, renal, or postrenal. Oliguria is defined as a urinary flow rate less than 0.5 mL/kg/hr. Polyuric failure is associated with elevations of BUN and serum creatinine levels and is characterized by urine flow rates that exceed 2.5 L/day.[71] Prerenal AKI results from hemodynamic or endocrine factors impairing renal perfusion, intrinsic AKI results from tissue damage, and postrenal AKI results from urinary tract obstruction.

TABLE 29-1 Major Causes of Intrinsic Acute Kidney Injury

Tubular Injury	
Ischemia due to hypoperfusion	Hypovolemia, sepsis, hemorrhage, cirrhosis, congestive heart failure
Endogenous toxins	Myoglobin, hemoglobin, paraproteinemia, uric acid
Exogenous toxins	Antibiotics, chemotherapy agents, radiocontrast agents, phosphate preparations
Tubulointerstitial Injury	
Acute allergic interstitial nephritis	Nonsteroidal antiinflammatory drugs, antibiotics
Infections	Viral, bacterial, and fungal infections
Infiltration Allograft rejection	Lymphoma, leukemia, sarcoid
Glomerular Injury	
Inflammation	Anti–glomerular basement membrane disease, antineutrophil cytoplasmic autoantibody disease, infection, cryoglobulinemia, membranoproliferative glomerulonephritis, Immunoglobulin A nephropathy, systemic lupus erythematosus, Henoch-Schönlein purpura, polyarteritis nodosa
Hematologic disorders	Hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, drugs
Renal Microvasculature	
	Malignant hypertension, toxemia of pregnancy, hypercalcemia, radiocontrast agents, scleroderma, drugs
Large Vessels	
Arteries	Thrombosis, vasculitis, dissection, thromboembolism, atheroembolism, trauma
Veins	Thrombosis, compression, trauma

From Sharfuddin AA. et al. Acute kidney injury In Taal MW et al. eds. *Brenner & Rector's The Kidney* 9th ed. 2012 Philadelphia Saunders: 1046.

BOX 29-2

Causes of Postrenal Acute Kidney Injury

Upper Urinary Tract Extrinsic Causes
- Retroperitoneal space—lymph nodes, tumors
- Pelvic or intraabdominal tumors—cervix, uterus, ovary, prostate
- Fibrosis—radiation, drugs, inflammatory conditions
- Ureteral ligation or surgical trauma
- Granulomatosis diseases
- Hematoma

Lower Urinary Tract Causes
- Prostate—benign prostatic hypertrophy, carcinoma, infection
- Bladder—neck obstruction, calculi, carcinoma, infection (schistosomiasis)
- Functional—neurogenic bladder secondary to spinal cord injury, diabetes, multiple sclerosis, stroke, pharmacologic side effects of drugs (anticholinergics, antidepressants)
- Urethral—posterior urethral valves, strictures, trauma, infections, tuberculosis, tumors

Upper Urinary Tract Intrinsic Causes
- Nephrolithiasis
- Strictures
- Edema
- Debris, blood clots, sloughed papillae, fungal ball
- Malignancy

From Sharfuddin AA, et al. Acute kidney injury. In Taal MW, et al, eds. *Brenner & Rector's The Kidney*. 9th ed. Philadelphia: Saunders; 2012:1046.

Current classification focuses on serum creatinine clearance and urinary output as markers for severity of injury: the Acute Dialysis Quality Initiative's RIFLE (*R*isk of renal dysfunction, *I*njury to the kidney, *F*ailure of kidney function, *L*oss of kidney function, and *E*SKD [end-stage kidney disease]) or the Acute Kidney Injury Network's (AKIN) stages 1 through 3. Both classifications tout serum creatinine clearance as a more sensitive marker for AKI, versus urine output. The classifications delineate the progression of kidney injury from an at-risk standpoint to complete end-stage kidney disease (ESKD).[72,73] Table 29-2 shows the RIFLE and AKIN classification systems.

Conditions that lead to reductions in urine output include acute reductions in GFR, excessive reabsorption of salt or water, or both. Increases in circulating levels of catecholamines, ADH, or aldosterone are physiologic factors that can decrease urinary output.[72] If not reversed, initial stages of AKI may progress to injury, tissue loss, or end-stage kidney disease with progressively increasing mortality rates.[67]

Acute tubular necrosis (ATN) may be produced by a variety of factors that interfere with glomerular filtration or tubular reabsorption. Reabsorption of urea, sodium, and water are all impaired, in contrast to AKI, in which these functions are maintained.[73]

Renal hypoperfusion or a nephrotoxic insult may initiate renal failure. Surgical patients with external and internal fluid losses or sepsis may have renal hypoperfusion. The renal medulla, with its sluggish blood supply and active transport mechanisms, is especially susceptible to even moderate renal ischemia.

The initiating insult culminates in the development of one or more maintenance factors, such as decreased tubular function, tubular obstruction, sustained reductions in renal blood flow, and glomerular filtration. Urine flow and solute excretion are reduced. Once the maintenance period has begun, pharmacologic interventions to improve renal blood flow do not reverse the failure.

Hemodynamic optimization is crucial in preventing postoperative AKI. Decreasing the need for renal replacement therapy (RRT) decreases AKIN classification as well as the incidence of progression. Administering fluids and inotropes, to maintain adequate perfusion, in the pre-, intra-, and postoperative periods, is associated with significantly decreased mortality and less risk of AKI.[74]

Patients with parenchymal disease have trouble concentrating the urine. Urine sodium levels are high, and osmolality is low. Renal damage is also associated with a progressive rise in serum urea, creatinine, uric acid, and polypeptide levels. Serum potassium levels increase, and a decrease, or dilution, occurs in the serum levels of sodium, calcium, and proteins such as albumin. Exogenous factors may alter BUN level, and subtle changes in serum creatinine concentration are easily ignored.[73,75]

Risk Factors

A number of conditions may place patients at high risk for acute renal injury. Renal reserve decreases progressively with age. Older

TABLE 29-2 RIFLE and Acute Kidney Injury Network (AKIN) Definition and Staging of Acute Kidney Injury

DEFINITION	
RIFLE	**AKIN**
An increase in serum creatinine of ≥50% developing over <7 days *or* A urine output of <0.5 mL/kg/hr for >6 hr	An increase in serum creatinine of ≥0.3 mg/dL or ≥50% developing over <48 hr *or* A urine output of <0.5 mL/kg/hr for >6 hr

STAGING CRITERIA				
RIFLE Stage	**Increase in Serum Creatinine**	**Urine Output Criteria**	**Increase in Serum Creatinine**	**AKIN Stage**
*R*isk	≥50%	<0.5 mL/kg/hr for >6 hr	≥0.3 mg/dL or ≥50%	Stage 1
*I*njury	≥100%	<0.5 mL/kg/hr for >12 hr	≥100%	Stage 2
*F*ailure	≥200%	<0.5 mL/kg/hr for >24 hr or anuria for >12 hr	≥200%	Stage 3
*L*oss	Need for renal replacement therapy for >4 wk			
*E*nd stage	Need for renal replacement therapy for >3 mo			

RIFLE (*R*isk of renal dysfunction, *I*njury to the kidney, *F*ailure of kidney function, *L*oss of kidney function, and *E*SKD [end-stage kidney disease])
From Sharfuddin AA, et al. Acute kidney injury. In Taal MW, et al, eds. *Brenner & Rector's The Kidney*. 9th ed. Philadelphia: Saunders; 2012:1046.

patients are less able to cope with fluid and electrolyte imbalance and are more prone to renal damage. Overall mortality rates associated with AKI increase.[76]

Patients with preexisting renal dysfunction are also at high risk. Cardiac and hepatic failure is associated with abnormal renal hemodynamics. Reduced GFR is associated with cortical redistribution of blood flow and salt and water retention. All of these aberrations are increased by anesthetics, stress, and hypovolemia. Further, these alterations correlate with greater incidences of postoperative AKI and an increase in mortality up to four-fold.[77] Elevated bilirubin is related to acute hepatitis and is an independent risk factor of AKI.[78]

Certain surgical procedures are associated with a higher risk of AKI. The risk increases in patients with preoperative ventricular dysfunction or bacterial endocarditis, those undergoing emergency or high-risk procedures, those who are anemic or receive perioperative blood products, and those who have procedures requiring cardiopulmonary bypass longer than 2 hours. Postoperative bleeding with reexploration and low cardiac output requiring use of the intraaortic balloon pump also carry a higher incidence of injury.[79-81]

A ruptured abdominal aortic aneurysm commonly results in hypovolemia, shock, and the need for high aortic cross-clamping. Of these patients, 40% have renal damage, and 11% develop AKI with an associated mortality rate of 80%. Renal dysfunction after elective surgery is less profound if attention is given to adequate hydration and if a brisk diuresis is established before, and maintained during, aortic cross-clamping. The proximity of the aortic clamp to the renal arteries is critical. Aortic arteriography performed just before surgery also increases risk. Predisposing factors include preexisting renal disease with serum creatinine levels greater than 3 mg/dL; proteinuria; diabetes; and hypovolemia. Risk is reduced by minimizing the amount of dye given, maintaining hydration, and using diuretics such as mannitol to promote diuresis. Postoperative AKI is a common complication of thoracic aorta, thoracoabdominal aorta, and aortic arch surgeries. It is observed in 6% to 18% of such surgical procedures. Predisposing factors for this complication include age older than 50, preoperative renal dysfunction, duration of renal ischemia, and amount of blood transfused.[82]

Mechanical obstruction by calculi or prostatic disease is the most common cause of obstructive uropathy.[73] Risk is increased by the frequent presence of hypovolemia and electrolyte imbalance and by preoperative diagnostic studies that involve the use of dye.

Hypovolemia, decreased pulmonary function, and acidosis are key factors in the development of AKI in septic patients. The use of vasoconstrictive adrenergic agonists and antibiotics with nephrotoxic potential compounds the problem.[83,84]

Complications of pregnancy such as hemorrhage, amniotic fluid embolus, and toxemia carry a high risk of renal failure, but because patients are usually young and healthy, mortality in this group is reduced. Proteinuria, related to or independent of pregnancy, also serves as a major risk factor for the development of AKI.[85]

In the first trimester of pregnancy, hyperemesis gravidum or septic abortion pose a risk for renal injury. Risks in the third trimester include preeclampsia, HELLP (*h*emolysis, *e*levated *l*iver *e*nzymes, and *l*ow *p*latelet count) syndrome, acute fatty liver of pregnancy, or thrombosis. Diagnosis is by serum creatinine because GFR calculations are complicated due to the altered volume status of pregnant women.[85]

Prevention and Management

Prevention of acute kidney injury is far more successful than management. Prevention can be based on the following generalizations:

- The most common cause of AKI is prolonged renal hypoperfusion.
- Prophylaxis reduces mortality more effectively than dialytic therapy.
- The duration and magnitude of the initiating renal insult are critical in determining the severity of AKI.

A key strategy in reducing the incidence of AKI is limiting the magnitude and duration of renal ischemia. Prevention begins in the preoperative period.[74,84]

Preoperative Strategies

High-risk patients and procedures should be identified. Reversible renal dysfunction should be addressed, and fluid losses and hypovolemia should be corrected by intravenous fluids and inotropes.

Perioperative ADH and renin-angiotensin-aldosterone secretion can be minimized with adequate hydration before anesthetic induction. Administration of saline, rather than solutions low in sodium, is helpful in prevention of aldosterone secretion, hyponatremia, and oliguria.[74]

Oliguria often signals inadequate systemic perfusion, and prevention of AKI requires its rapid recognition through adequate monitoring. In addition to standard monitors and a urinary catheter, monitors for patients with questionable cardiac and pulmonary function should include: (1) a direct arterial line for blood pressure monitoring and (2) a central venous pressure (CVP), pulmonary artery catheter, or transesophageal echocardiography as appropriate, for assessment of cardiac function and volume status. The hemodynamic end-point should be adequate cardiac output and renal perfusion.[74]

Perioperative Strategies

Use of a urinary catheter is the standard means of monitoring renal function in the operating room. A fluid challenge may be necessary if hourly urinary output decreases to below acceptable levels.

The use of diuretics in the face of inadequate urinary output is common; however, controversial. Data suggest that diuretic use to prevent AKI is not useful. Diuretic use in established AKI offers little benefit in changing outcome of mortality or need for renal replacement therapy, particularly in the presence of oliguria. Given the current literature, use of diuretics for volume management when necessary in patients with AKI can be considered. However, diuretic use to prevent oliguria in the AKI setting is not indicated.[86,87]

High-dose diuretics have been effective in decreasing 60-day mortality rates associated with AKI. Diuretic therapy must be balanced with fluid administration to prevent hypotension and hypoperfusion. The best outcomes have been with furosemide and fluid balance to avoid a fluid excess or deficit. Mechanisms for protection include the inhibition of sodium reabsorption and the prevention of tubular obstruction through the maintenance of high flow and pressure within the tubules and the reversal of intrinsic renal vasoconstriction. Prophylactic use of diuretics may be of benefit in the case of jaundice in surgical patients, excessive exposure to contrast media, hyperuricemia, or the presence of pigment in the urine.[86,87]

Fenoldopam (Corlopam) is a selective dopamine-1 (DA_1) receptor agonist. It causes both systemic and renal arteriolar vasodilation and has no effect on dopamine-2 (DA_2), α-adrenergic, or β-adrenergic receptors. Unlike dopamine, which causes renal vasoconstriction and systemic cardiovascular changes at higher doses, fenoldopam at high doses produces renal vasodilation with little systemic effects. Despite theoretically promising pharmacology, clinical benefit with fenoldopam has been limited. It is not currently recommended for use in AKI. No benefit in survival or the need for RRT has been noted as compared with placebo. A recent study found that fenoldopam had no greater renal protection in patients undergoing infrarenal aortic cross-clamping for abdominal reconstruction than sodium nitroprusside and dopamine.[88,89] Newer therapies under evaluation include atrial natriuretic peptide, urodilatin, and nesiritide.

Treatment of Acute Kidney Injury

Therapy for AKI involves rapid recognition and correction of reversible causes, avoidance of any further renal injury, and correction and maintenance of a normal electrolyte and fluid volumes. Preventive therapy or medical interventions performed early provide the greatest chance for minimizing injury.

Key approaches include administering volume (e.g., normal saline) to achieve euvolemia, improving cardiac output by afterload reduction, and normalizing systemic vascular resistance. Postrenal AKI secondary to prostatic hypertrophy can frequently be corrected by placement of a bladder catheter or nephrostomy tube. Intrarenal AKI can be the most complex and difficult to treat. AKI caused by glomerulonephritis or vasculitis frequently requires immunosuppressive therapy. For suspected acute interstitial nephritis, the offending medication must be determined and discontinued; a 2-week tapering course of glucocorticoids, beginning with 1 mg/kg of prednisone for 3 days, is commonly recommended despite the absence of definitive data. Serum electrolytes, creatinine, and BUN should be monitored at least daily, more frequently if the patient's renal function appears to be tenuous. Patients with AKI should also receive a low sodium, potassium, and protein diet. Early nephrology consultation will ensure that the patient receives optimal care. Some patients will require urgent hemodialysis because of marked metabolic acidosis unresponsive to sodium bicarbonate infusions; electrolyte abnormalities, such as hyperkalemia that is unresponsive to medical management; pulmonary edema not responding to diuretic therapy; and uremic symptoms of encephalopathy, seizures, and pericarditis. Intermittent hemodialysis and continuous renal replacement therapy may be necessary.[71,74]

Prognosis. Typically, AKI secondary to prerenal causes, if diagnosed and treated early, has the best prognosis for renal recovery. Patients with prerenal AKI commonly return to their baseline level of renal function and have a mortality rate of less than 10%. Similarly, patients with postrenal AKI also have a good prognosis for renal recovery if the outlet obstruction is promptly diagnosed and definitively treated.

In contrast, patients with intrarenal AKI have a less predictable renal outcome, and mortality in this group varies between 30% and 80%, depending on the severity of injury. Patients who have a severe episode of AKI requiring hemodialysis may not recover their renal function and may need hemodialysis indefinitely. AKI hastens progression of chronic kidney disease to end-stage kidney disease and is often the major factor that causes such progression.[71,74] Clinical management of oliguria is found in Box 29-3.

CHRONIC KIDNEY DISEASE

Chronic kidney disease, or chronic renal failure, is a slow, progressive, irreversible condition characterized by diminished functioning of nephrons and a decrease in renal blood flow, GFR, tubular function, and reabsorptive capacity. By definition, chronic kidney disease exists when GFR is less than 60 mL/min/1.73 m^2 for 3 months or more.[90,91] Although many conditions may lead to renal failure, primary causes include glomerulonephritis, pyelonephritis, diabetes mellitus, hyperlipidemia, autoimmune disease, obesity, vascular or hypertensive insults, and congenital defects. Table 29-3 outlines the systemic effects of chronic renal failure.

The general course of progressive chronic kidney disease may be divided into five stages[92,93]:

- Stage 1: Kidney damage with normal or increased GFR
- Stage 2: GFR 60 to 89 mL/min/1.73m^2 with evidence of kidney damage
- Stage 3: GFR 30 to 59 mL/min/1.73m^2
- Stage 4: GFR 15 to 29 mL/min/1.73m^2
- Stage 5: End-stage renal failure with GFR less than 15 mL/min/1.73 m^2

Initial nephron injury causes adaptation in remaining nephrons, including increased glomerular size and pressure, which

BOX 29-3

Clinical Management of Perioperative Oliguria

- Oliguria is a urine output less than 0.5 mL/kg but may be 1 to 2 mL/kg in a patient who has received mannitol.
- Assume oliguria is prerenal until proven otherwise. Signs of prerenal include the following:
  - Oliguria
  - High urine osmolality
  - Low urine sodium
- Begin treatment with serial fluid boluses if assessment does not indicate overload.
- Do *not* give a diuretic to "make urine" in the face of intravascular hypovolemia or hypotension because this may result in exacerbation of renal injury.
- Do give diuretics if there are signs of fluid overload or if oliguria persists despite fluid challenges and stabilized hemodynamics.
- If improvement is not noted with fluid challenge or diuretics, institute invasive hemodynamic monitoring (central venous pressure and arterial pressure monitoring when large fluid shifts are expected).
- Maximize renal blood flow by enhancing cardiac function: normalize preload, heart rate, and rhythm; institute afterload reduction with vasodilators or inodilator agents.
- Maintain renal perfusion pressure.
- Prophylactic pharmacologic agents may be used when renal risk is high, but there is little evidence to suggest they are better at maintaining glomerular filtration rate than volume.
- Diuretic resistance may be related to the following:
  - Acute tolerance induced by hypovolemia
  - Chronic tolerance
  - Refractory states

TABLE 29-3 Systemic Effects of Chronic Renal Disease

System	Effects
Cardiovascular	Hypertension Congestive heart failure Peripheral and pulmonary edema Pericarditis Coronary artery disease
Hematologic	Normochromic, normocystic anemia Platelet dysfunction Leukocyte, immunologic dysfunction
Neurologic	Encephalopathy Peripheral and autonomic neuropathy
Endocrine	Hyperparathyroidism Adrenal insufficiency
Respiratory	Pneumonitis Pulmonary edema
Gastrointestinal	Bleeding Nausea, vomiting Delayed gastric emptying
Metabolic	Acidosis Electrolyte imbalance

BOX 29-4

Indications for Renal Replacement Therapy

Absolute indications
- Volume overload unresponsive to diuretic therapy
- Hyperkalemia despite medical treatment
- Persistent metabolic acidosis
- Overt uremic symptoms
  - Encephalopathy
  - Pericarditis
  - Uremic bleeding diathesis

Relative indications
- Progressive azotemia without uremic manifestations
- Persistent oliguria

From Sharfuddin AA, et al. Acute kidney injury. In Taal MW, et al, eds. *Brenner & Rector's The Kidney*. 9th ed. Philadelphia: Saunders; 2012:1083.

results in progression of renal disease. As the number of functioning nephrons declines, the signs, symptoms, and biochemical abnormalities become more severe.

Clinical signs or laboratory evidence of renal disease are absent until less than 40% of normal-functioning nephrons remain. Loss of nephron function without symptoms is known as a decrease in renal reserve. Renal insufficiency occurs when only 10% to 40% of nephrons are functioning adequately. Nocturia occurs secondary to a decrease in concentrating ability. Elimination of a large protein load or excretion of certain drugs is impaired. Preservation of remaining nephron function is a major goal in renal insufficiency.

Toxic substances such as aminoglycosides, nonsteroidal antiinflammatory drugs, and piperacillin have been implicated in causing interstitial nephritis and renal insufficiency.[92,93] The administration of radiographic contrast media in at-risk patients results in renal insufficiency at the same rate as in 1979. Patients at greatest risk for developing contrast-induced renal insufficiency include those with preexisting renal insufficiency (creatinine greater than 1.2 mg/dL) and diabetes. Strategies including the administration of *N*-acetylcysteine (NAC), sodium bicarbonate, and ascorbic acid have been studied.[94]

As renal function deteriorates further, end-stage renal disease develops. In this stage, concentrating and diluting properties of the kidney are severely compromised, and electrolyte, hematologic, and acid-base disturbances are common. The loss of 95% of functioning nephrons culminates in uremia, which is associated with volume overload and congestive heart failure. Uremia, which can be viewed as urine in the blood, adversely affects almost every organ system. Mortality is inevitable unless dialysis is performed for end-stage renal disease.[95]

Renal Failure and Dialysis

Approximately 350,000 people in the United States today require chronic dialysis, and the end-stage renal failure population is projected to grow about 8% per year. Three hundred thirty-nine patients per 1 million receive renal replacement therapy for end-stage renal disease per year, and almost half of these patients require treatment early in the postoperative period.[96,97] Indications for renal replacement therapy are shown in Box 29-4.

Dialysis Techniques

Dialysis is a general term used to describe therapy in which solute moves from blood through a semipermeable membrane into a chemically prescribed solution. The movement of solute, which

is called *diffusive transport*, depends on differences in molecular concentration between the blood compartment and the dialysate. Ultrafiltration is a technique in which a hydraulic pressure difference across a semipermeable membrane causes the bulk removal of fluid and solute by convective transport.

Major types of dialysis include hemodialysis and peritoneal dialysis. In hemodialysis, blood moves through a device that exposes it to an individually prescribed dialysate solution across a semipermeable membrane. Hemodialysis requires systemic or regional anticoagulation. Concerns about hemodynamic stability during hemodialysis, nephron injury, and the inability to adequately remove excess water and solutes have led to the development of a slower, less aggressive renal replacement therapy: continuous renal replacement therapy (CRRT).

CRRT is an extracorporeal process in which blood is removed from the arterial lumen of a catheter by a peristaltic blood pump and pushed through a semipermeable membrane before being pumped back into patients via the venous lumen of the catheter. CRRT includes a number of treatment modalities. Pump-driven, venovenous CRRT is currently the most common technique. The modalities of venovenous CRRT vary primarily in their mechanism of solute removal: in continuous venovenous hemofiltration (CVVH), solute transport occurs by convection; in continuous venovenous hemodialysis (CVVHD), it occurs by diffusion; and continuous venovenous hemodiafiltration (CVVHDF) is a combination of the two. The hybrid modalities of RRT with conventional hemodialysis equipment that is modified to provide extended-duration dialysis provides enhanced hemodynamic tolerability.[96]

Peritoneal Dialysis. The use of peritoneal dialysis in the management of AKI has diminished as the use of continuous and hybrid therapies have increased. Peritoneal dialysis has the advantage of requiring minimal technology. Access for short-term peritoneal dialysis can be obtained either by percutaneous placement of an uncuffed temporary peritoneal catheter or through surgical placement of a tunneled cuffed catheter. Peritoneal dialysis has the advantage of avoiding the need for vascular access or anticoagulation. Solute clearance and control of metabolic parameters may be inferior to that achieved with other modalities of RRT. Although systemic hypotension is less of an issue than with other modalities of RRT, ultrafiltration cannot be as tightly controlled. Other limitations include the relative contraindication in patients with acute abdominal processes or recent abdominal surgery, the risk of visceral organ injury during catheter placement, the risk of peritoneal dialysis–associated peritonitis, and an increased tendency toward hyperglycemia, which is associated with adverse outcomes in acute illness, due to the high glucose concentrations in peritoneal dialysate.[97]

Physiologic Effects

Dialysis and ultrafiltration are associated with a number of physiologic effects and complications. Major systems involved include the nervous system, cardiovascular system, and respiratory system. The disequilibrium syndrome is the most severe central nervous system (CNS) effect of dialysis. This syndrome is associated with a rapid increase in brain intracellular volume because serum sodium and BUN levels are reduced. Predisposing factors include a BUN concentration greater than 150 mg/dL, hypernatremia, severe acidemia, and preexisting brain disease. The syndrome may be mild or may progress to seizures, stupor, and coma. The incidence is reduced by the avoidance of high rates of hemodialysis therapy in high-risk patients.

Hemodialysis is associated with a 30% incidence of hypotension. Contributing factors include reduced plasma volume and blunted sympathetic nervous system response associated with uremia. Acetate from the dialysate moves into the blood and contributes to the hypotension by causing vasodilation and cardiac depression.

The incidence of hypotension with dialysis is less in patients who have fasted than in those who have not. Fasting prevents the contribution to hypovolemia of increased gastrointestinal blood flow and the secretion of isotonic intestinal juices. Anemia should be corrected if the hematocrit is less than 20% to increase vascular resistance. Leg elevation, a decrease in dialyzer transmembrane pressure, or the use of volume expanders or vasoconstrictors usually corrects hypotension. Substitution of HCO_3 for acetate in the dialysate also decreases the incidence of hypotension.[96-99]

Hypoxemia is a common side effect of hemodialysis and may be seen during peritoneal dialysis.[97] During hemodialysis, arterial oxygen tension often decreases by 5 to 20 mmHg. Pulmonary leukostasis and extracorporeal loss of CO_2 with a reduction in minute ventilation have been implicated. Hypoxemia is managed by increasing the inspired oxygen concentration during dialysis. The use of HCO_3 in place of acetate limits extracorporeal losses of CO_2 and reduces the incidence of hypoxemia.

Muscle cramping is the most common neuromuscular complication of dialysis. It is seen almost exclusively with hemodialysis and results from the rapid reduction of intravascular volume and serum sodium level. Intravenous administration of hypertonic saline relieves muscle cramping.

The nutritional depletion common in dialysis-dependent patients may be caused by the primary disease, dietary restrictions, or the loss of protein associated with peritoneal dialysis. Protein depletion may produce hypoalbuminemia and immunocompromise. The large quantities of hypertonic glucose solutions absorbed with peritoneal dialysis contribute to obesity, hyperglycemia, and hyperlipidemia. Administration of insulin controls hyperglycemia, and diet and exercise limit hyperlipidemia.

PREOPERATIVE RENAL ASSESSMENT

Preoperative assessment of the patient with suspected or known renal dysfunction must include a thorough history and physical examination, as well as appropriate laboratory evaluation (Box 29-5). The medical history is the single most important source of information in establishing the presence or absence of renal disease. Poorly controlled hypertension, trauma to the urinary system, prior renal surgery, or systemic disease (e.g., diabetes) may be associated with renal impairment. A history that arouses suspicion should lead to a more thorough evaluation of renal function.

Although abnormalities are commonly identified by urinalysis, the quality of urinalysis results obtained by dipstick technique varies.[100] Because abnormal results on urinalysis usually fail to lead to a change in management, the test is generally omitted. If the test is available, attention should be directed to the following:

1. *Specific gravity.* Specific gravity, a measurement of solutes in the urine, indicates the ability of the kidney to excrete concentrated or dilute urine. It is a reflection of tubular function and normally varies from 1.003 to 1.030, depending on fluid intake and the presence or absence of high-molecular-weight substances such as glucose or mannitol. In the absence of such substances, a specific gravity of 1.018 or greater after overnight dehydration indicates reasonable function. A low specific gravity is meaningless if the condition under which the sample was collected is not known.
2. *Urine osmolality.* Osmolality, or the number of moles of solute (measured in osmoles) per kilogram of solvent, is more specific than specific gravity. Excretion of concentrated

BOX **29-5**

Preoperative Assessment and Preparation of the Patient with End-Stage Renal Disease

I. Clinical History
   A. Evaluate renal function.
   B. Document central nervous system deficits.
   C. Review cardiovascular history; look for significant hypertension, accelerated atherosclerosis, pericarditis, tamponade; assess extent, stability, and management of coronary artery disease.
   D. Look for history of excessive bleeding; if present consider use of desmopressin.
   E. Assess intravascular volume; correlate body weight changes with changes in blood pressure and heart rate before and after dialysis.
   F. Review pulmonary history.
   G. Dialyze 24 hours or less before surgery; ideal weight preoperatively is 1 to 2 kg above "dry" weight.
II. Physical Examination
   A. Locate and check patency of arteriovenous fistula or shunt.
   B. Evaluate vessels for venous or arterial access.
   C. Look for signs of congestive heart failure, pericarditis, or cardiac tamponade.
   D. Look for evidence of noncardiogenic pulmonary edema or aspiration.
III. Laboratory Tests
   A. Electrocardiography, chest radiography
   B. Glomerular filtration rate or creatinine clearance
   C. Blood urea nitrogen, creatinine
   D. Complete blood count with platelet count
   E. Bleeding time; prothrombin time; partial thromboplastin time
   F. Hematocrit; red-blood-cell index
   G. Electrolytes (especially potassium)
   H. Acid-base status
   I. Hepatitis antigen status

urine (specific gravity 1.030; 1400 mOsm/kg) indicates excellent tubular function, whereas urinary osmolality fixed to that of plasma (serum gravity 1.010; 290 mOsm/kg) suggests tubular concentrating defects. Urinary diluting mechanisms are present after concentrating ability is lost.

3. *Proteinuria.* Proteinuria exists when more than 150 mg of protein is excreted per day. Massive proteinuria or the renal loss of more than 750 mg/day is always abnormal and usually indicative of severe glomerular damage. In addition to its association with glomerular damage, proteinuria also may be present with abnormal plasma proteins or increased concentrations of normal proteins or when the renal tubules fail to reabsorb the small amount of protein that may be filtered. Patients can have proteinuria without renal disease under conditions of stress, fever, dehydration, exercise, or congestive heart failure. Patients who have significant proteinuria are more likely to develop AKI postoperatively than those who do not. The incidence of hypoalbuminemia and its consequences is increased in patients with severe proteinuria. In a concentrated urine sample, trace or 1+ proteinuria is a nonspecific finding, whereas 3+ or 4+ proteinuria suggests glomerular disease.

The kidneys share regulation of acid-base balance with the lungs. Because they provide the sole pathway for the excretion of the 60 mEq of hydrogen ions produced per day, urinary pH is a reflection of the ability of the kidneys to acidify urine. The inability to excrete acid urine in the presence of systemic acidosis is indicative of renal insufficiency.

Laboratory Tests for Renal Function

Patients with suspected or known renal disease should be tested preoperatively to evaluate GFR and renal tubular function. Although urine specific gravity (1.003 to 1.030), urine osmolality (65 to 1400 mOsm/L), and urine sodium concentration (130 to 260 mEq/day) reflect renal tubular function, BUN concentration (10 to 20 mg/dL), plasma creatinine level (0.7 to 1.5 mg/dL), and creatinine clearance (110 to 150 mL/min) are necessary for the evaluation of GFR.

Blood Urea Nitrogen

Urea, the chief end product of protein metabolism, is formed in the liver. It is excreted by glomerular filtration, but significant amounts of urea are reabsorbed along the renal tubule. Although the normal range for BUN level is 10 to 20 mg/dL, it is altered by a variety of factors, including ingestion of protein, anabolic and catabolic states, GFR, state of hydration, and reabsorption of urea by the nephrons. Because of the numerous extrarenal factors that can influence BUN, it is a better indicator of uremic symptoms than of GFR. Levels below 8 mg/dL suggest overhydration or underproduction of urea, whereas those between 20 and 40 mg/dL suggest dehydration, high nitrogen levels, or decreased GFR. Levels higher than 50 mg/dL almost always indicate decreased glomerular filtration. Elevations of BUN level in the presence of normal serum creatinine concentration suggest a nonrenal cause of the elevation. In general, BUN level is a late indicator of renal disease because it does not increase in most patients until the GFR is reduced by more than 50%.[101]

Serum Creatinine

Creatinine is a metabolite of creatine, a major muscle constituent. The daily rate of production of creatinine is constant and determined by skeletal muscle mass. Because body creatinine is eliminated almost entirely by glomerular filtration, its steady-state concentration in the serum has been used as a marker of glomerular function. Normal values range from 0.7 to 1.5 mg/dL, but the serum concentration can be lower in the elderly or in women who have reduced muscle mass. Patients with muscle wasting have lower levels, whereas those who are heavily muscled or those in acute catabolic states have higher values because of more rapid muscle breakdown. Because the production and release of creatinine are relatively stable throughout the day and from day to day, serum levels are inversely related to GFR if a steady state exists. In other words, for every 50% reduction in GFR, creatinine level doubles. Excretion of drugs dependent on glomerular filtration may be significantly decreased despite only a slight elevation in serum creatinine level.

An elevation of both BUN and serum creatinine levels provides more information than an elevation of either level alone. The usual ratio of urea nitrogen to creatinine in the serum is 10:1. Increased ratios are seen with increased urea input, decreased circulatory blood volume, and obstructive uropathy. Decreased ratios are seen with decreased urea input, increased creatinine production, and volume expansion.

Creatinine Clearance

Creatinine clearance is a specific test of GFR and the most reliable assessment tool for renal function. This test measures the ability

of the glomeruli to excrete creatinine into the urine for a given plasma creatinine concentration. Although not dependent on corrections for age or the presence of a steady state, a disadvantage of this test is the need for accurate 24-hour urine specimens. Creatinine clearance is calculated according to the following formula:

$$\text{GFR} = (\text{Urine creatinine} \times \text{Urine volume}) \times \text{Serum creatinine}$$

A 2-hour urine sample collected through a urinary catheter permits acceptable accuracy. In the absence of urine volume, creatinine clearance can be approximated with use of the following Cockcroft-Gault formula:

$$\text{GFR} = \frac{([140 - \text{Age}] \times \text{Lean body weight [kg]})}{(72 \times \text{Serum creatinine [mg/dL]})}$$

where weight is expressed in kilograms. To compensate for their smaller muscle mass, when values for women are calculated, the weight should be multiplied by 0.85.[102,103]

The normal range for creatinine clearance is 95 to 150 mL/min. Mild renal dysfunction is present when creatinine clearance is 50 to 80 mL/min, and moderate dysfunction is present at values below 25 mL/min. In patients with dysfunction, the administration of drugs that depend on renal excretion should be reduced, and fluid and electrolyte balance should be carefully monitored. Patients with creatinine clearance less than 10 mL/min are anephric and require dialysis for fluid and water hemostasis.

Other Tests

Advanced renal disease affects most organ systems. Additional tests that may be useful in patients with advanced renal disease include chest radiography, electrocardiography, complete blood count, serum electrolytes, and acid-base studies.

Systemic Abnormalities and Advanced Renal Disease

Renal failure is characterized by a wide variety of biochemical disturbances. Although most organ systems are involved (see Table 29-3), only those most relevant to anesthetic management are discussed in this section.

Cardiovascular Alterations

Cardiovascular disease accounts for approximately 50% of all deaths in patients on hemodialysis.[96,97] Hypertension and congestive heart failure often accompany end-stage renal disease. Ninety percent of the hypertension is volume dependent and related to sodium and water retention. The remainder can be attributed to high circulatory levels of renin. The combination of hypertension, anemia, hypoalbuminemia, and circulatory overload secondary to salt and water retention contributes to peripheral and pulmonary edema and to an increased risk of congestive heart failure.

In nonsurgical settings, ischemic heart disease is the most common cause of death in patients with chronic renal failure. Multiple risk factors such as hypertension, hyperlipidemia, and abnormal carbohydrate metabolism contribute to this high incidence of ischemic heart disease.[102,103] The anesthetist should assume that clinically significant coronary artery disease exists and should evaluate the extent and stability of the disease. Several uncontrolled studies suggest that correction of coronary lesions with coronary artery bypass grafting is associated with better outcomes than coronary angioplasty in patients on hemodialysis.[104,105] Improvement of symptoms is common after coronary artery bypass grafting. The advent of drug-eluding stents has led to numerous studies to determine the incidence of restenosis in hemodialysis patients. The results of these studies remain inconclusive.[104,105]

A fibrous pericarditis is clinically evident in approximately 50% of patients with severe uremia. Signs and symptoms may include pain on deep inspiration or when lying down, and a friction rub over the pericardium noted during auscultation. An enlarged cardiac silhouette on chest radiography indicates pericardial effusion. Patients with uremic pericarditis occasionally develop a massive hemorrhagic effusion and cardiac tamponade, especially when anticoagulants are used for hemodialysis.

Uremic patients exhibit a wide range of hemodynamic abnormalities when studied during hemodialysis.[96] The striking feature of these studies is that the peripheral vasculature responds abnormally to hypovolemia induced by dialysis. Hypovolemia decreases arterial pressure without increasing heart rate. Peripheral vascular resistance is unchanged or decreased, and cardiac output is increased.

Because the potential for significant cardiovascular complications exists, patients with advanced renal disease should undergo chest radiography and electrocardiography preoperatively. Administration of antihypertensive drugs should be continued, blood pressure should be monitored, and signs and symptoms of cerebrovascular disease should be recorded. The blood pressure should be normal or slightly elevated before induction. Because adequate intravascular volume is necessary for hemodynamic stability, the patient's weight should ideally be 1 to 2 kg more than dry weight at the end of the last dialysis before anesthetic induction.

Hematologic Changes

Normochromic, normocytic anemia is an inevitable finding in advanced renal disease. Hematocrit levels often decrease to the 20% to 30% range and generally parallel the degree of azotemia. The primary reason for anemia is a decrease in erythrocyte formation secondary to a decrease in production by the failing kidney.[106] Also, some evidence suggests that uremic toxins may inactivate erythropoietin or suppress the response of the bone marrow to its action. A second factor that contributes to the anemia in uremic patients is reduction of the life span of the erythrocyte because of an increase in hemolysis secondary to the presence of an abnormal chemical environment. Additionally, blood loss from frequent sampling for laboratory tests, loss in hemodialysis tubing, and a tendency for gastrointestinal bleeding further aggravate anemia.

Hematocrit and red-blood-cell indexes should be measured preoperatively, and their values should be checked against dialysis records to ensure that no acute changes have occurred. Preoperative hematocrit levels that are similar to those of a patient maintained on dialysis suggest that the patient can withstand the chronic anemia. Routine transfusion of blood preoperatively is not recommended for these patients. If transfusion is necessary because of acutely decreased or poorly tolerated hematocrit values, no need exists to withhold red-blood-cell transfusions for fear of sensitization to histocompatibility antigens.[107]

Exogenous administration of human recombinant erythropoietin corrects the anemia associated with chronic renal failure. The risks of treatment with erythropoietin include hypertension, vascular access clotting, and death. Adequate iron stores and good dialysis are essential if the response to recombinant erythropoietin or epoetin is to be maximized.[108,109] Endogenous erythropoietin levels and hematocrit values increase to normal within 8 to 10 weeks after successful renal transplantation.[110] There are three erythropoiesis-stimulating agents (ESAs) currently available to treat anemia in patients with chronic renal disease who are on dialysis. They are peginesatide (Omontys), epoiten (Procrit, Epogen), and darbepoetin (Aranesp). [111]

Patients with chronic uremia have a tendency to bleed excessively. Although platelet counts are only mildly reduced, a defect

in platelet function appears to be responsible for prolonged bleeding time and a tendency for excessive bleeding. Dialysis partially corrects platelet dysfunction, and dialysis 24 hours or less before surgical intervention is recommended.[112-113]

Desmopressin is known to shorten bleeding time and increase circulating levels of factor VIII, the von Willebrand antigen, in uremic patients. Desmopressin is the agent of choice because of its rapid onset and minimal side effects.[114] Repeated doses over time may increase bleeding time between treatments. Cryoprecipitate and conjugated estrogens also shorten bleeding time and may reduce blood loss.[115]

Gastrointestinal Effects

Patients on dialysis have a high incidence of gastrointestinal mucosal inflammatory changes and are at high risk of gastrointestinal bleeding perioperatively. The use of histamine-2 (H_2) blocking drugs or antacids is recommended throughout the perioperative period for decreasing the incidence of stress ulcers.[116]

Infections

Infectious complications are common in patients with renal failure and represent a leading cause of death in dialysis-dependent patients. Protein malnutrition and abnormalities in neutrophil, monocyte, and macrophage function contribute to this problem.[117] Mechanisms that lead to leukocyte dysfunction and increased susceptibility to infection are not known but may be related to uremia, immunosuppressive therapy, and increased exposure to invasive therapy. Frequent exposure to blood and blood products increases the risk of infection with hepatitis B and C and the human immunodeficiency viruses. Universal precautions are mandatory for the protection of both patients and health care providers.[96,97,118]

Neurologic Effects

Neurologic symptoms associated with end-stage renal disease roughly parallel the degree of azotemia. Early symptoms include apathy, decreased mental acuity, and lethargy. Fatigue and weakness are early complaints, and untreated patients eventually become confused and comatose. Seizures may be associated with hypertensive encephalopathy. Peripheral and autonomic nervous system neuropathy is common. Autonomic neuropathy is associated with delayed gastric emptying and places the patient at risk for aspiration pneumonitis.

Endocrine Abnormalities

Endocrine abnormalities in patients with end-stage renal disease include hyperparathyroidism and adrenal insufficiency. Hypocalcemia is common in patients with advanced renal disease, and hyperparathyroidism represents an appropriate compensatory increase in parathormone in response to a reduction in serum calcium levels. Adrenal insufficiency often is secondary to exogenous steroid administration.

Respiratory Effects

Respiratory complications associated with renal failure include pneumonitis and the "uremic lung." Chest radiographs of the uremic lung reveal bilateral butterfly-shaped infiltrates indicative of pulmonary edema. Pulmonary congestion and edema usually are related to volume overload.[119]

Electrolyte Abnormalities

Abnormalities of water, electrolyte, and acid-base balance become more common as the degree of renal failure increases. With a normal diet, the kidneys typically excrete 40 to 60 mEq of hydrogen ions per day to prevent acidosis. Impaired ability of the kidney to excrete hydrogen ions with renal failure results in metabolic acidosis characterized by decreases in plasma pH and HCO_3 concentration. Acidosis is usually moderate, but symptoms of anorexia, nausea, vomiting, and lethargy, which are common in uremic patients, may be partly related to acidosis.

Sodium ion excretion by the kidney normally varies according to intake. Patients with chronic renal failure lose this flexibility and have sodium wasting or retention. In early renal insufficiency with polyuria, an increased solute load for each intact nephron results in sodium wasting. In renal failure, the patient is more likely to retain sodium. Salt and water retention leads to circulatory overload, hypertension, edema, and congestive heart failure.

Although the ability to excrete magnesium is reduced in uremic patients, hypermagnesemia is generally not a serious problem. Magnesium intake is usually reduced because of anorexia, reduced protein intake, and decreased absorption from the gastrointestinal tract.

Calcium balance is controlled by parathyroid hormone, calcitonin, and vitamin D. Vitamin D, or cholecalciferol, is inactive until it has been hydroxylated in the liver and kidney. Inability of the diseased kidney to hydroxylate 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol (active vitamin D) results in hypocalcemia. Patients with chronic renal failure have skeletal disorders or osteodystrophy, and defective mineralization of bone predisposes patients to fractures. Special precautions should be taken when these patients are moved and positioned.

Potassium imbalance is one of the most serious disturbances that occurs in patients with renal failure. Although hypokalemia may be associated with the polyuria of renal insufficiency, end-stage renal disease invariably leads to hyperkalemia. Although the major mechanism for hyperkalemia is the inability of distal nephrons to secrete potassium in exchange for calcium, systemic acidosis also contributes to potassium imbalance. Acidosis causes potassium ions to shift from intracellular to extracellular fluid.

Fatal dysrhythmias or cardiac standstill can occur when serum potassium levels reach 7 to 8 mEq/L. Dialysis is the most effective means of managing perioperative hyperkalemia, and hemodialysis is indicated when serum potassium exceeds 6 mEq/L. Other techniques for treating hyperkalemia include insulin in glucose infusions (25 to 50 g of glucose with 10 to 20 units of regular insulin) and administration of bicarbonate (50 to 100 mEq intravenously slowly). These measures promote rapid translocation of extracellular potassium to the intracellular space during hyperkalemic emergencies. Hyperventilation of the lungs with respiratory alkalosis lowers serum potassium concentration by approximately 0.5 mEq/L for every 10-mmHg change in arterial CO_2 tension. Life-threatening cardiac dysrhythmias are treated with intravenous administration of calcium chloride. A typical dose may be 1 g in adults. Although calcium does not change the serum concentration of potassium, it antagonizes the cardiotoxic effects of hyperkalemia.

Unexpected hyperkalemia can develop rapidly, so it is important to measure potassium even when dialysis has been performed within 6 to 8 hours of surgery. Hyperkalemia occurs early postoperatively and is the primary reason patients with renal failure require dialysis within the first 24 hours after surgery.[120]

Surgical procedures are becoming increasingly more common in anephric patients. The perioperative course of these patients may be complicated by a high incidence of untoward events that increase morbidity and mortality. These complications are related to the abnormal physiology of the anephric state. They are predictable and can be minimized by preoperative evaluation and preparation.[121] Pertinent points in the preoperative assessment

and preparation of patients with end-stage renal disease are listed in Box 29-5.

ANESTHETIC MANAGEMENT OF PATIENTS WITH ADVANCED RENAL DISEASE

Preoperative preparation of patients with advanced renal disease should include an evaluation of recent laboratory measurements, coexisting diseases, and current medications. Patients with end-stage renal disease should undergo preoperative determination of BUN and serum creatinine levels, complete blood count, bleeding-time measurement, and electrolyte studies. Special attention should be given to serum potassium, the type of and schedule for dialysis, and volume status.

Premedications

Discussions regarding premedication should take into consideration unexpected sensitivity to CNS depressants and delayed gastric emptying. Benzodiazepines are useful as premedicants. Midazolam is preferred because it has virtually no active metabolites, and its half-life is only slightly prolonged in renal failure. Although this drug is useful when it is carefully titrated, patients with renal disease may be more susceptible to the sedative-hypnotic effects of benzodiazepines than those without renal dysfunction.[122]

Reduced protein binding may be responsible for increased sensitivity to these drugs in patients with advanced renal disease. Protein binding of morphine decreases by 10% in the presence of chronic renal failure.[123] This alters the free fraction only slightly because morphine generally is protein bound to such a small extent. Morphine is almost completely metabolized in the liver, resulting in two metabolites (morphine-3-glucuronide and morphine-6-glucuronide). Both metabolites are excreted by the kidney. Patients with kidney disease can develop high levels of morphine-6-glucuronide and resultant respiratory failure.[124] Morphine is not removed by dialysis.

Meperidine is more lipophilic than morphine. It is 60% protein bound and is metabolized to a normeperidine, which has analgesic properties and stimulates the CNS system. Meperidine metabolites can cause convulsions when used in high concentrations, and cannot be removed by dialysis.[125] Meperidine should be avoided in patients with renal failure.

Hydromorphone does not directly cause adverse effects in renal failure; however, its metabolite, hydromorphone-3-gluconuride does accumulate. For this reason, hydromorphone should be used with caution, although it can readily be removed by dialysis.[126]

A review of recent publications on opioid use in patients with renal failure reveals that transdermal buprenorphine, methadone, fentanyl, and sufentanil appear to be safe in these patients.[127] Anticholinergic drugs, such as atropine and glycopyrrolate, are partially dependent on renal elimination, although no reports of toxicity exist.

Gastric hyperacidity and gastrointestinal bleeding are common in patients with renal failure. H_2 blockers and magnesium-free antacids should be considered. Cimetidine has been used, but renal elimination accounts for 80% of total elimination, and elimination is impaired with reduced renal function. Although newer H_2 antagonists are now available, all H_2-receptor blockers are very dependent on renal excretion. Metoclopramide is partly excreted unchanged in the urine and will accumulate in patients with renal failure.

Intraoperative Monitoring

The selection of monitors for a patient with diminished or absent renal function is based on the physiologic status of the patient and the proposed surgical procedure. Frequent measurements of blood pressure and continuous recording of temperature and heart rate and rhythm are essential. Electrocardiography may allow early detection of hyperkalemia, including observation of peaked T waves, prolongation of the PR interval, and absent P waves with widened QRS complex.[128]

Because these patients are often chronically anemic, a further reduction in oxygen delivery secondary to hypoxia can be extremely hazardous. Pulse oximetry is essential for the early detection of arterial desaturations. Pulse oximetry and capnography are required in all patients. Minor surgical procedures in stable patients can be monitored noninvasively.

The decision to use invasive monitors depends on the patient's functional cardiac reserve and the severity and control of hypertension. Significant hypotension on induction of anesthesia is common in recently dialyzed patients. Continuous monitoring of arterial blood pressure is helpful when major surgical procedures are performed. A femoral or dorsalis pedis artery is sometimes used for cannulation, because vessels in the upper extremities may be needed later for vascular shunts. Vascular volume and fluid replacement can be guided by central venous pressure monitoring. A pulmonary artery catheter is rarely indicated, because sophisticated evaluation of fluid status and ventricular function can be accomplished with echocardiography.[129]

Vascular shunts and fistulas must be protected. Patency is easily monitored with Doppler imaging. Because of the immunocompromised state of these patients, strict aseptic technique is required during the placement of vascular catheters.

Regional Anesthesia

Regional anesthesia is tolerated by patients with advanced renal disease, provided no significant coagulation disorder is present and mean arterial pressure is maintained. Regional techniques avoid most of the pharmacokinetic and pharmacodynamic problems associated with general anesthetics and sedative drugs. Major concerns regarding this type of anesthesia include psychologic intolerance, coagulation abnormalities, the presence of peripheral neuropathies, difficulty in making intravascular volume adjustments, and risk of infection.

Arteriovenous shunts or fistulas may be surgically created with the use of local infiltration or brachial plexus block. In addition to providing analgesia, brachial plexus blocks improve surgical conditions by providing maximum vascular vasodilation and abolishing vasospasm. Studies have shown that brachial plexus block is associated with greater brachial artery blood flow than local anesthesia, greater fistula blood flow, and decreased maturation time.[130] Both brachial plexus block and local infiltration are good alternatives to general anesthesia for creation of arteriovenous fistula. Age, American Society of Anesthesiologists (ASA) class, and cardiac status are the determining factors for choice of anesthetic technique.[131]

Data suggest a similar duration of anesthesia with brachial plexus blocks in patients with renal failure and normal renal function.[132] High-dose mepivacaine has been used for brachial plexus block in patients with end-stage chronic renal failure. Brachial plexus anesthesia with 650 mg of plain mepivacaine did not result in serious systematic toxicity in these patients despite high mepivacaine plasma concentrations.[133] Ropivacaine has been shown have a longer duration of action with higher plasma concentrations in renal dysfunction.[134,135] The use of clonidine (150 mcg) as an adjuvant for lidocaine in axillary blocks for arteriovenous fistula construction prolongs blockade, decreases heart rate and blood pressure, and provides sedative effects.[136]

With regard to spinal or epidural anesthesia, patients with long-standing renal disease often have undergone multiple procedures and prefer general anesthetic techniques. In addition to the history, the uremic patient's bleeding time, platelet count, prothrombin time, partial thromboplastin time, and fibrinogen level should be evaluated before subarachnoid or epidural catheters are placed. Paraplegia secondary to hematoma formation with spinal anesthesia has been reported in patients with chronic renal failure and clotting abnormalities.[137]A case of epidural hematoma in a surgical patient with chronic renal failure and epidural postoperative analgesia has been reported. The only risk factor for development of epidural hematoma was a history of chronic renal failure. High-risk patients should be monitored closely for early signs of cord compression such as severe back pain and motor or sensory deficits. An opioid or opioid and local epidural solution rather than local solution alone allows continuous monitoring of neurologic function. If spinal hematoma is suspected, the patient should undergo immediate magnetic resonance imaging (MRI) or computed tomography (CT) scan, and decompressive laminectomy should be performed without delay.[138]

Peripheral neuropathies should be discussed with the patient and documented before regional anesthesia is undertaken. The incidence of hypotension with subarachnoid or epidural blockade may be increased because of effects of chronic hypertension or hypovolemia related to recent dialysis. Correction of hypovolemia postoperatively is hazardous. Recession of the sympathetic block in patients who cannot undergo diuresis may lead to pulmonary edema. One must weigh the advantages of fluid infusion against the effects of pressor drugs with these factors in mind.

Patients with end-stage renal disease are often acidotic, and local anesthetic toxicity may be increased with acidosis. The onset and duration of blocks have also been shown to vary in these patients. Subarachnoid blockade induced with 3 mL of 0.75% bupivacaine developed more rapidly, attained a greater level, and was of shorter duration in patients with renal failure than in control patients.[139,140] The slower onset of epidural anesthesia is an advantage in these patients.

General Anesthesia

Intravenous Drugs

Intravenous anesthetics can be used in patients with advanced renal disease, but the response of these patients may be more variable than normal. Variability arises from a complex interplay among changes in volume of distribution (which is often increased), protein binding (which may be low), low pH, and dependence on renal excretion for the parent drug or metabolites.

The action of many drugs is potentiated by metabolic abnormalities associated with renal failure. Highly protein-bound drugs may have more target-organ effect in the presence of hypoalbuminemia. The acidemic state associated with renal failure increases the proportion of the agent that is unionized and unbound and therefore more available to target tissue. Anemia associated with renal failure increases cardiac output and enhances delivery to the brain. Uremia alters the blood-brain barrier; this also increases the sensitivity to intravenous drugs.

Ketamine and benzodiazepines are less heavily protein bound. The sympathomimetic effects of ketamine are frequently associated with an increase in blood pressure and cardiac output, which may be deleterious in hypertensive patients who are at risk for coronary artery disease or decreased left ventricular function. In addition, metabolites of ketamine depend on renal excretion and can accumulate in patients with renal failure.[141]

The pharmacokinetic profile of narcotics can be altered in the presence of renal disease. Fentanyl is metabolized in the liver, and 85% of it appears in the urine and feces as inactive metabolites. Its slow elimination half-life is the result of a large volume of distribution. The effect is exaggerated in renal failure. Chronic renal failure is associated with a decrease in alfentanil plasma protein binding, but it does not change plasma clearance of the drug. The volume of distribution at steady state is greater in patients with renal failure. Altered protein binding of alfentanil must be considered in patients with renal failure.[142] Although the pharmacokinetics of sufentanil do not appear to be altered in patients with advanced renal disease, clearance and half-life are more variable in this group. Sufentanil should be carefully administered to these patients.[143] Although remifentanil is metabolized by nonspecific plasma esterases, it has been shown to have a significant reduction in clearance in patients with end-stage renal disease.[144]

Propofol has gained wide acceptance for both induction and maintenance of anesthesia and appears to be safe. Studies suggest, however, that patients with end-stage renal disease require a higher dose to achieve hypnosis. A hyperdynamic circulation in these anemic patients may be responsible.[145] Propofol pharmacokinetics are unaltered by established renal failure. The time interval between cessation of a propofol infusion and eye opening is significantly shorter in renal failure patients compared with controls, although blood propofol concentrations are not significantly different on emergence.[146]

Dexmedetomidine, an α_2-adrenergic agonist with sedative and analgesic properties, is predominantly cleared by the liver. Studies reveal minimal pharmacokinetic differences between healthy volunteers and patients with renal failure. There were no reported differences in hemodynamics during administration of dexmedetomidine, but patients with renal failure exhibited prolonged duration of sedation.[147]

Volatile Anesthetic Agents

Inhalation agents offer some advantage in patients with renal failure. Although biotransformation of some agents may produce metabolites excreted by the kidneys, elimination of volatile agents does not rely on renal function. Volatile agents potentiate neuromuscular blocking drugs, allowing administration of reduced doses. Although the potency of these agents allows them to be administered without nitrous oxide, excessive depth of anesthesia may lead to a depression of cardiac output. Reductions in cardiac output and tissue blood flow must be avoided in these anemic patients if tissue oxygen delivery is to be maintained.

A theoretic disadvantage of inhalation agents relates to their biotransformation and nephrotoxic potential. None of the modern inhalation anesthetics has this problem. Fluoride levels after isoflurane anesthesia increased by only 1 to 2 μmol, and desflurane is metabolized approximately one tenth as much as isoflurane. It is the least metabolized of the currently available volatile agents. In studies of patients and volunteers administered desflurane for prolonged periods, no evidence of renal, hepatic, or hematologic toxicity was observed.[148]

Some practitioners may avoid use of sevoflurane in patients with severe renal dysfunction because of the potential for nephrotoxicity. Studies do not support this concern. One study compared renal function after long-duration, low-flow (less than 1 L/min) sevoflurane and isoflurane anesthesia in surgical patients with normal renal function. Postoperative renal function was no different as assessed by serum creatinine and BUN levels and urinary excretion of protein and glucose, suggesting that low-flow sevoflurane is as safe as low-flow isoflurane.[149] Another study concluded that

TABLE 29-4 Regional Versus General Anesthesia

Technique	Advantages	Disadvantages
Regional	Patient responsiveness Minimal changes in renal hemodynamics	Presence of peripheral neuropathy Tendency for bleeding Patient anxiety Prolonged procedures Hypotension with sympathetic block; may cause reluctance to expand volume
Volatile anesthetics	Good airway control Blood pressure control Duration not dependent on urinary excretion Less neuromuscular blocking with drugs required Fio_2 can be increased because N_2O not necessary	Alterations in renal hemodynamics Decreased cardiac output Hypotension Biodegradation and potential nephrotoxicity; halothane 15%-20%; sevoflurane 5%; isoflurane 0.2%; desflurane 0.02%
Intravenous anesthetics	Hemodynamic stability	Unpredictable response Hypertension Greater need for N_2O and neuromuscular blockers

Fio_2, Fraction of inspired oxygen; N_2O, nitrous oxide.

prolonged low-flow sevoflurane anesthesia had the same effect on renal and hepatic function as high-flow sevoflurane and low-flow isoflurane anesthesia.[150]

In summary, both regional and general anesthesia has been used successfully in patients with advanced renal disease. Advantages and disadvantages of both techniques are listed in Table 29-4.

Neuromuscular Blocking Drugs

The appropriate use of neuromuscular blocking drugs in patients with advanced renal disease has received much attention over the years. At one time, caution was advised in all cases of the use of a muscle relaxant in patients with renal disease. Because these drugs are ionized, water-soluble compounds freely filtered at the glomerulus, it was believed that their action would be prolonged. It was further theorized that as the anticholinesterase or relaxant antagonist level decreased, the patient would be at risk of postoperative residual neuromuscular blockade. It is now known that renal excretion is of major importance for cholinesterase inhibitors as well. Approximately 50% of neostigmine and 70% of edrophonium are excreted in the urine. Excretion of all cholinesterase inhibitors is delayed to the same or to a greater extent than muscle relaxants in patients with renal impairment.[151]

Succinylcholine. Several problems have been associated with the use of succinylcholine in patients with renal failure. Succinylcholine is metabolized by hepatic-derived pseudocholinesterase to succinic acid and choline. A metabolic precursor of these two compounds is succinylmonocholine, which has some nondepolarizing blocking activity and is eliminated by the kidneys. Prolongation of succinylcholine also has been associated with depressed levels of pseudocholinesterase in uremic patients who require hemodialysis.

Serum potassium increases by approximately 0.5 mEq/L in both normal patients and those with renal failure. This elevation in extracellular potassium is not reliably prevented by pretreatment with a nondepolarizing muscle relaxant. The rise in serum potassium level is particularly dangerous in uremic patients who are hyperkalemic. The use of succinylcholine is inadvisable unless a patient has undergone dialysis within 24 hours before surgery and the potassium concentration is less than 5.5 mEq/L. Succinylcholine is safe in normokalemic patients who have recently undergone dialysis.[152,153]

Pancuronium. Up to 80% of pancuronium is excreted in the urine. Biliary excretion accounts for much of the nonrenal elimination.[154] A significant portion of the renal excretion of pancuronium occurs after its biotransformation to a less active metabolite.[155] Pancuronium has a prolonged terminal elimination half-life in patients with reduced renal function. Because of its high dependence on renal excretion and long-acting classification, it should be avoided in patients with renal dysfunction.

Atracurium and Cisatracurium. Initial reports indicated that the action of neither atracurium nor vecuronium was prolonged in patients with decreased renal function; however, it now appears that this is true only for atracurium.[156] Atracurium and cisatracurium are broken down by Hoffman elimination and non–esterase-dependent hydrolysis to inactive products. Neither process is dependent on renal excretion for termination of action. Atracurium is less potent and has a shorter duration of action than cisatracurium. It produces histamine release, which limits its desirability.[146,156] Chronic kidney disease does not alter the pharmacokinetics or pharmacodynamics of atracurium. Cisatracurium pharmacodynamics are not changed; however, there is a slight slowing of onset. Many clinicians consider these the drugs of choice in patients with renal failure.

Vecuronium. Approximately 30% of administered vecuronium is excreted renally, and the duration of neuromuscular blockade is longer in patients with renal failure than in those without renal failure.[157] This accumulation is the result of reduced clearance and a prolonged half-life.[146] If vecuronium is used, a low dose is recommended, and repeated administration should be avoided. Vecuronium neuromuscular blockade is rapidly reversible with dialytic treatment.[158]

Rocuronium. Rocuronium is the most commonly used nondepolarizing neuromuscular blocking drug. It has a rapid onset of action, and in humans it produces good to excellent conditions for tracheal intubation in 60 to 90 seconds.[159] It has no clinically significant cardiovascular effects and an intermediate duration of action.[160] Studies indicate that the onset of action of twice the effective dose (ED_{95}) of rocuronium is not altered in patients with renal failure who are undergoing renal transplantation. A rapid onset is particularly attractive in these patients because they are subject to autonomic neuropathy and delayed gastric emptying. Rocuronium is excreted primarily in the bile, although up to 33% may be excreted renally. Renal failure reduces the clearance of rocuronium by 39%. The duration of action and recovery time are significantly prolonged in patients with renal failure (49 vs. 32 min). Interpatient variability is also increased.[146,161]

INTRAVENOUS FLUID MANAGEMENT

Perioperative management of fluids and electrolytes in patients with renal disease is critical. The state of hydration affects renin, aldosterone, and antidiuretic levels. Dehydration and hypovolemia lead to elevations in these hormones and to a decline in urinary output.

Perioperative Renal Function

Surgical patients at high risk for AKI , or those with advanced disease who do not require hemodialysis, present unique challenges. Preservation of renal function intraoperatively is dependent on the maintenance of intravascular volume and cardiovascular stability and on the avoidance of events that cause renal vasoconstriction. Intraoperatively, urinary output is the most immediate monitor for renal function. A urinary output of 0.5 to 1 mL/kg/hr perioperatively is recommended, because urinary output less than 0.5 mL/kg/hr is a risk factor for renal injury (see RIFLE and AKIN classifications in Table 29-2. Serum creatinine is a more specific assessment of renal function than urinary output.[162]

Patients with normal or mildly compromised renal function should receive balanced salt solutions at 3 to 5 mL/kg/hr. A bolus of 500 mL ought to improve output related to hypovolemia. Use of mannitol or furosemide to increase output may further exacerbate volume depletion. No potassium-containing solutions (lactated Ringer's) should be administered to anuric patients.

Dialysis patients present a unique challenge to the anesthetist. This population requires a narrow window of control between hypovolemic and fluid overloaded states. Insensible losses are replaced with 5 to 10 mL/kg of 5% glucose in water (D_5W). If any urine is produced, it may be replaced with 0.45% saline.

The greater expected fluid losses of thoracic and abdominal surgery cases may require significant volume replacement. Either a balanced salt solution, 5% albumin, or a combination thereof is recommended for replacing these larger volumes in patients with, or at risk for, kidney disease or injury. The administration of blood products should be reserved for patients who need increased oxygen-carrying capacity.[163] The safety of synthetic colloids in patients with preexisting renal dysfunction still remains unclear.[164]

Renal Insufficiency

In patients with renal insufficiency, volume deficits should be replaced preoperatively, as in normal patients. Basal fluids must be carefully regulated because these patients cannot tolerate much deviation. Overall basal fluid requirements must be related to metabolic rate and designed to provide an overall fluid balance that allows an isotonic urine to carry excreted electrolytes and waste products. Intraoperative losses greater than 10% to 15% of the blood volume should be replaced with colloid solution on a 1:1 basis after red-blood-cell losses are corrected. Smaller losses can be replaced with the usual 3:1 ratio of crystalloid infusion to blood loss. Third-space losses are ideally replaced initially with crystalloid solution without potassium or excess chloride. Initial third-space losses should be replaced with crystalloid solution at a rate of 2 to 3 mL/kg/hr. The critical goal in patients with renal insufficiency is sustaining blood volume. Monitoring of colloid osmotic pressure and hemoglobin can guide the choice between crystalloid and colloid infusions. If hemoglobin and colloid osmotic pressure are increasing, crystalloid solution is clearly indicated. If they are decreasing, crystalloid solution should be withheld in favor of colloid solution. Close monitoring of blood pressure, heart rate, CVP, pulmonary artery occlusion pressure, and cardiac output also guides fluid titration. This is especially true in patients with cardiac or respiratory compromise.

End-Stage Renal Disease

With regard to perioperative fluid management, patients with end-stage renal disease who are hemodialysis dependent require special attention. Although these patients are similar to normal patients in terms of fluid deficit, basal, and third-space requirements, they have a narrow margin of safety. The patient's ability to compensate for either fluid excess or fluid deficiency progressively declines as renal function is lost.

Fluid deficits must be replaced preoperatively in patients with end-stage renal disease. If deficits exceed 10% to 15% of the blood volume, invasive monitoring is justified. Dialysis is recommended on the day before anesthesia to allow time for equilibration of fluid and electrolyte shifts that are common with dialysis. Electrolyte levels must be checked before anesthesia.

Basal fluids in patients with end-stage renal disease should be replaced in a manner similar to that for patients with renal insufficiency. Volume restriction is recommended for intraoperative losses. Third-space losses should be replaced with a balanced salt solution that contains no potassium and small amounts of chloride. Close monitoring of hemoglobin and cardiac filling pressures is indicated for all major procedures. Patients with end-stage renal disease generally require dialysis within 24 to 36 hours after major surgery.

Uremia

Deficit replacement in patients with uremia must be guided by hemodynamic monitoring. Basal fluids should be replaced with red blood cells, fresh frozen plasma, or colloid solutions. Third-space losses are best replaced with crystalloid solutions in association with frequent monitoring of hemoglobin. Cardiac filling pressures should be monitored when warranted by the surgical procedure. A moderate degree of volume overload is not a grave problem. Many uremic patients require dialysis within 24 to 36 hours for the removal of mobilized fluid and the control of hypertension.

Although volume overload is most often emphasized in patients with end-stage renal disease, complications of hypovolemia are also serious. Hypotension associated with hypovolemia increases the risk of thrombosis of the arteriovenous fistula and predisposes to cardiac and cerebral ischemia. Hemodynamic goals include the avoidance of hypotension and gross fluid overload. This can be accomplished only through careful titration with the patient well monitored.

ANESTHESIA FOR RENAL TRANSPLANTATION

Patients with end-stage renal failure have a complex medical history with many comorbid diseases. Diabetes and hypertension are the most common causes of end-stage renal disease (ESRD). Multiple cardiovascular disorders also may be present, including ischemic heart disease and congestive cardiac failure. Other frequent problems include anemia, hyperparathyroidism with elevated calcium and phosphate, dyslipidemia, infections, and hepatitis B and C.[165,166]

These patients also are typically on multiple medications. Optimization of the patient's condition results in a smoother operative course.

Transplantation Procedure

Renal transplantation has been performed for nearly a century and is an accepted means of replacing kidney function in patients with end-stage renal disease who are on maintenance dialysis. Kidney transplants are the most commonly performed transplantations in the United States.[165] In this procedure, the donor kidney is placed extraperitoneally in the recipient's iliac fossa. The renal artery is anastomosed to the internal iliac artery, the renal vein to either the external or the common iliac vein, and the ureter to the bladder. The anesthesia provider plays a vital role in management of the viability

of the transplanted kidney. Three interrelated variables affect surgical outcomes: management of the donor, preservation of the harvested organ, and perioperative care of the transplant recipient. Additionally, improved surgical and immunosuppressive techniques have contributed to better outcomes in terms of graft survival.[166]

Harvested Organ Preservation

Ischemic time, beginning with the clamping of the donor's renal vessels and ending with the vascular anastomosis in the recipient, is a crucial factor in graft preservation. Warm ischemia is more deleterious. When renal ischemic time is less than 30 minutes, diuresis begins quickly, but if it is 2 hours or longer, a variable period of oliguria or anuria may occur according to the following ischemic times:

Warm	Cold
Begins: Clamping of donor vessels; initial placement in recipient	Perfusion of harvested organ with cold preservation solution; storage at 4° C
Ends: Vascular anastomosis in recipient; interrupted with perfusion of cold preservation solution	Perfusion by recipient

Donor Preparation

Choice of anesthesia for the living, related donor is not critical. Adequate amounts of balanced salt solution and colloid bolus just before pneumoperitoneum has been demonstrated to ensure a brisk diuresis from the donor kidney and to offset reduced venous return resulting from use of laparoscopy.[166,167] The greatest risk to the donor is hemorrhage. Adequate intravenous access and blood must be available in the event that transfusion becomes necessary.

If the donor kidney is obtained from a brain-dead patient, preservation of graft function is the highest priority. The loss of sympathetic tone after brain death may produce mild hypotension, despite adequate volume replacement. Many patients with irreversible cerebral dysfunction are hypovolemic and require vigorous fluid resuscitation. Anesthetic goals in the donor include maintenance of a Pa_{O_2} over 100 mmHg; normocapnia; hematocrit 30% or greater; and systolic blood pressure 100 mmHg or greater. If pharmacologic support of the cardiovascular system is necessary, a dopamine infusion at a rate of 1 to 3 mcg/kg/min is recommended. Other acceptable pharmacologic support includes dobutamine and low-dose epinephrine. Renal vasoconstrictive properties of high-dose vasopressors reduce immediate allograft function and increase the risk of kidney damage.[168] Maintenance of urinary output is paramount and may warrant the use of adjuncts such as furosemide, mannitol, and a low-dose dopamine infusion.[169]

Recipient Preparation

Because cadaveric kidneys can be preserved for 36 to 48 hours with cold perfusion, time is sufficient for optimal preparation of the transplant recipient (Box 29-6). The recipient should be free of acute illness and infections because of the likelihood of their spread during immunosuppressive therapy. Acute alterations in fluid and electrolyte balance should be corrected with dialysis carried out 24 hours before transplantation. Postdialysis laboratory values should be checked, and serum potassium (K^+) level should be

BOX 29-6

Anesthesia for Renal Transplantation

I. Preoperative Assessment and Preparation
  A. Clinical evaluation
    1. Evaluate status of coexisting diseases
      a. Diabetes mellitus
      b. Hypertension
      c. Cardiac disease
      d. Hyperparathyroidism
      e. Pericardial tamponade
    2. Perform dialysis within 24 hr of transplantation; check weight
    3. Evaluate tolerance to chronic anemia
  B. Laboratory evaluation
    1. Complete blood count with platelet count
    2. Prothrombin time, partial thromboplastin time, bleeding time
    3. Blood urea nitrogen, creatinine, calcium, fluid balance
    4. Electrocardiography; chest radiography
  C. Type and cross-match 2 units of washed, packed red blood cells
  D. Determine current drug regimen
  E. Premedication
    1. Benzodiazepines, narcotics
    2. Antacids, histamine-2 antagonist, metoclopramide

II. Monitors
  A. Electrocardiography
  B. Indirect or direct blood pressure measurement
  C. Precordial, esophageal stethoscope
  D. Neuromuscular blockade evaluation
  E. Foley catheter
  F. Central venous, transesophageal echocardiography, pulmonary capillary wedge pressure measurement, if required

III. Anesthetic Management
  A. Regional techniques
    1. Continuous spinal or epidural
    2. Advantages
      a. No need for muscle relaxants
      b. Potential respiratory tract infection from intubation is avoided
      c. Amount of local anesthetic required is small
      d. Patients awake and comfortable postoperatively
    3. Disadvantages
      a. Patient anxiety
      b. Uncomfortable surgical positions, especially for donor
      c. Coagulation abnormalities present
      d. Fluid management with sympathetic blockade a challenge
      e. Unprotected airway in patients with delayed gastric emptying
  B. General anesthesia
    1. Induction with propofol or etomidate
    2. Maintenance with volatile anesthetic (isoflurane, or desflurane) or narcotic-based technique
    3. Neuromuscular blockers
      a. Succinylcholine
      b. Cisatracurium
      c. Rocuronium

IV. Miscellaneous Drugs
  A. Mannitol or furosemide
  B. Dopamine
  C. Calcium channel blockers
  D. Prednisone or methylprednisolone
  E. Patient-specific immunosuppressants

below 5.5 mEq/L. Coagulation studies and acid-base status should be normal. Serum creatinine concentration should be below 10 mg/dL, and BUN level should be below 60 mg/dL after dialysis.

Chronic anemia is common, and transfusion is not required if oxygen delivery is adequate. Because of the danger of volume overload, anemia should be corrected during dialysis with transfusion of packed red blood cells. It was formerly thought that multiple blood transfusions increased the risk of kidney rejection secondary to sensitization of the human leukocyte antigen system, but this belief has been disproved. Studies have shown a lower survival rate for transplanted kidneys in nontransfused patients and in those receiving leukocyte-poor blood.[170]

Abnormal platelet function, as well as ineffective production of factor VIII and von Willebrand factor, accounts for the syndrome of uremic coagulopathy seen in patients with renal failure. Correction of coagulation abnormalities can be accomplished through dialysis and administration of conjugated estrogen and desmopressin as seen in the following chart[171-173]:

Treatment	Effect
Dialysis	Improves platelet formation
Conjugated estrogen	Decreases transfusion need
Desmopressin	Increases factor VIII and von Willebrand factor

Acceptance of kidney transplantation in patients with type 1 diabetes mellitus is widespread. Patients with type 2 diabetes may have relative contraindications due to significant comorbidities, particularly a recent history of myocardial infarction, stroke, or peripheral gangrene. However, recent evidence suggests some patients with type 2 diabetes may benefit from transplantation.[174]

Patients should fast for 6 to 8 hours if possible. Premedication may include narcotics or benzodiazepines in usual to reduced doses, depending on the status of the patient. The use of antacids, H_2 antagonists, and metoclopramide should be considered if gastric emptying is delayed; however, reduced doses should be considered because these drugs depend on the kidney for excretion, and metoclopramide is partially excreted unchanged in the urine.[175]

In addition to routine monitors, a Foley catheter is inserted for the assessment of graft function. A central venous line is essential for the assessment of volume status. Intraarterial blood pressure monitoring is useful for patients with significant cardiovascular disease. Central venous pressure monitoring may improve graft function by aiding in the assessment of hydration status with the goal of maintaining a CVP of 10- to 5 mmHg.[176] Evaluation of pulmonary artery catheter pressures has been shown to correlate with graft function, although it is usually reversed for select patients with symptomatic coronary artery disease (CAD) or congestive heart failure (CHF). If monitoring pulmonary artery pressures, maintenance of a mean pulmonary artery pressure of greater than 20 has been shown to reduce the risk of acute tubular necrosis.[177] Transesophageal echocardiography may be used for evaluation of fluid status and myocardial function. Protection of vascular access and fistula patency is of prime importance with the use of blood pressure cuffs or if arterial cannulation is necessary. Sterile precautions during insertion of invasive lines are extremely important because transplant patients are immunocompromised. Strict adherence to aseptic technique is mandatory in the management of these lines, catheters, and endotracheal tubes. Commitment to aseptic technique on the part of the entire team may make the difference between safe transplantation and death for the patient.

Fluid management may be generous or conservative, dependent on patient condition. Fluid replacement should be accomplished with a balanced salt solution and albumin as required to maintain a plasma volume of at least 45 to 70 mL/kg. Immediate function of the transplanted kidney cannot be guaranteed, and excessive intraoperative fluid replacement can lead to pulmonary edema and swelling of the grafted kidney.

The early onset of urine output is essential and correlates with improved outcomes and can be improved with aggressive volume expansion with crystalloids and albumin, mannitol, loop diuretics, calcium channel blockers, and dopamine.[178]

Anesthesia

Regional Anesthesia

Both regional and general anesthesia have been used successfully for open surgical renal transplantation. A randomized prospective study compared the incidence of hypotension, bradycardia, and acidemia between regional and general anesthesia for renal transplant. No differences were noted, although combined spinal epidural was preferred to epidural alone for the improved muscle relaxation effects.[179] Advantages of regional anesthesia include avoidance of the use of muscle relaxants and other drugs excreted by the kidney, and the fact that endotracheal intubation is not required. Intubation may increase the risk of nosocomial pneumonia. Pulmonary infection may occur in renal transplant patients after endotracheal intubation, which results in a 40% to 50% mortality rate.[180] An additional advantage of regional anesthesia is postoperative analgesia.

Disadvantages of regional anesthesia techniques in these patients include hypotension associated with sympathetic blockade, the length of the procedure, and heparinization of the kidney. Sympathetic blockade can make control of blood pressure difficult in patients who may be hypovolemic. Given that transplantation procedures may last several hours, large amounts of sedation may be needed to supplement regional techniques. General anesthesia is now the preferred approach for these reasons. Additionally, general anesthesia is indicated for donor nephrectomies, because many of these procedures are now performed laparoscopically.[181]

General Anesthesia

Volatile Agents. When general anesthesia is used, nitrous oxide combined with volatile agents and short-acting opiates is well tolerated. The skeletal muscle relaxant properties, minimal metabolism, and preservation of renal blood flow make isoflurane an attractive choice. Desflurane also has been successfully used and may have beneficial preservation effects. Postconditioning involves the administration of anesthetics during early reperfusion and has been found to have a protective effect on several organs.[166]

Reductions in cardiac output secondary to the negative inotropic effects of volatile drugs must be minimized if suboptimal tissue oxygenation is to be avoided in these anemic patients.

Although the use of sevoflurane during kidney transplantation has not been widely studied, researchers have reported on its effects on the kidney with impaired function. Evidence of increased plasma fluoride concentrations has been the predominant finding, noting peak fluoride concentrations of greater than 30 uM after sevoflurane administration.[182,183] A decrease in fresh gas flow has demonstrated increased Compound A production, which has been shown to be nephrotoxic.[184] Despite these findings, studies of sevoflurane administration in patients with uremia have not yielded a positive correlation between renal toxicity and sevoflurane. Sevoflurane anesthesia appears safe and does not alter kidney function in patients with preexisting renal disease. Sevoflurane anesthesia can be safely used in renal transplant recipients.[166,185]

Muscle Relaxants. The choice of muscle relaxant must take into consideration the unpredictable nature of renal function after transplantation. Relaxants that are independent of renal function for plasma clearance, such as cisatracurium, are excellent for this patient population.[186] The process of Hoffman elimination

and nonesterase hydrolysis are the primary modes of breakdown for cisatracurium. Clearance of cisatracurium has been found to be slightly reduced by approximately 13% in patients with renal failure.[187] Succinylcholine can be used to facilitate intubation if serum K^+ level is normal. Long-acting drugs such as pancuronium are highly dependent on renal elimination and should be avoided.

Opioids. The effect of morphine is prolonged in end-stage renal failure and accumulates the active metabolite morphine-6-glucuronide. Meperidine also should be avoided due to the accumulation of the toxic metabolite normeperidine and potential for seizures.[188] Fentanyl and sufentanil pharmacokinetics are not altered in end-stage renal failure. Remifentanil undergoes rapid metabolism by plasma esterases and results in low concentrations of an active metabolite, which does not appear to be clinically significant. Clearance of remifentanil is delayed and causes accumulation of its metabolite, which can be removed by dialysis. Alfentanil metabolism is not altered by renal failure.[189]

Other Drugs. Mannitol is included in many transplant protocols. It does not depend on renal tubular–concentrating mechanisms to promote urinary formation, and it facilitates urinary output and a reduction in tissue and intravascular volume. The effect of low-dose dopamine administration on cadaver and living graft function also has been evaluated. Dopamine has been shown to have nephroprotective effects.[190,191] Generally inotropic drugs with alpha receptor–stimulation properties are avoided. Early graft function is dependent on ischemic changes, and late graft function is dependent on the management of rejection.

Loop diuretics exert their effect at the Na^+/K^+ pump in the ascending loop of Henle, preventing reabsorption of electrolytes in this segment. The increased osmolarity of fluid in the tubule prevents reabsorption of water and increases urine output.

Cardiac arrest has been reported after completion of the renal artery anastomosis to the transplanted kidney.[192] Arrest occurred at the time the occlusion clamp was released and was attributed to hyperkalemia from washout of the K^+-containing solutions used to preserve the kidney. If clamping of the external iliac artery is necessary during the procedure, K^+ can be released from the ischemic limb. Unclamping also may result in hypotension from the release of vasodilating substances from ischemic limbs and the subsequent increase in vascular capacity.

Immunosuppressants

Patients undergoing renal transplantation require immunosuppression. The goal of immunosuppression therapy is to prevent graft rejection but still allow the immune system to fight infection and malignancy. A multiple-agent strategy allows for a synergistic effect, and reduction of specific drug toxicity T cells is the main target of immunosuppression strategies because of their central role in the alloimmune response. Immunosuppressive medications can be classified in three broad categories relating to their mechanism of action: (1) depleting agents, (2) calcineurin inhibitors (CNIs), and (3) antiproliferating agents, for example, antimetabolites. Immunosuppressive strategies can also be divided into two main categories referred to as induction and maintenance of immunosuppression. Induction of immunosuppression is defined as the rapid achievement of profound immunosuppression, usually at the time of transplant, with the use of depleting agents. Maintenance immunosuppression is achieved by the combination of oral agents that takes advantage of additive or synergistic immunosuppressive effects of different drug categories to minimize their nonimmunosuppressive side effects. Doses are usually greater during the first 3 months after transplantation and decrease afterwards. The combination of a CNI, antiproliferating agent, and steroids is usually used, although steroid sparing or withdrawal strategies are now popular to minimize side effects. Monoclonal and polyclonal antibody induction therapy is frequently given as well.[193,194] Some commonly used immunosuppression drugs are listed in Table 29-5.[194]

Kidney transplant recipients may require surgery for nontransplant-related procedures. Management involves maintenance of adequate volume status, avoiding nephrotoxic medicines such as nonsteroidal antiinflammatory drugs (NSAIDs) or contrast dyes, and proper dosing of immunosuppressive drugs. Whenever possible, immunosuppressive drugs should be given by the enteral route. If this is not possible, a regimen of IV steroids and IV CNIs usually suffices. A simple way to dose IV steroids is to prescribe the same milligram-for-milligram dose of IV methylprednisolone as the maintenance prednisone dose; supplemental stress-dose hydrocortisone is then prescribed separately. IV cyclosporine should be prescribed in slow-infusion form at one third of the total daily oral dose, and intravenous tacrolimus should be at one fifth of the total daily dose. Some specific suggestions for managing kidney transplant patients are noted in Box 29-7.[194]

EXTRACORPOREAL SHOCK-WAVE AND LASER LITHOTRIPSY

Nephrolithiasis is a common condition, with a lifetime prevalence of approximately 13% in men and 7% in women in the United States. Although many kidney stones are asymptomatic, patients with symptomatic stones often require treatment. Between 1.0% and 1.7% of emergency department visits (1 to 2 million visits annually) are for a primary diagnosis of renal colic or renal calculus. The economic burden of urolithiasis is immense. Total health care expenditures reach nearly $4.5 billion annually, and this figure increases to $5.3 billion when the indirect costs of lost workdays are included. Approximately 80% of upper urinary tract stones are calcium-based (composed of calcium oxalate, calcium phosphate, or brushite), with the remaining 20% composed of uric acid, struvite, cystine, or, rarely, other components.[195] Extracorporeal shock-wave lithotripsy (ESWL) is the only noninvasive urinary stone treatment. The technique uses hundreds to thousands of high-energy ultrasonic or pneumatic shock waves or lasers to fragment renal calculi into small particles. ESWL is used for stones less than 10 to 20 mm in the proximal or midureter. Stones in the distal ureters, of all sizes, are removed using ureterorenoscopy (URS). Success rates are highly variable, ranging from 30% to 100%. When lithotripsy fails to resolve the stone, more invasive techniques are employed such as percutaneous nephrolithotomy and ureteroscopy.[196] ESWL uses an external source to deliver pulses of energy into a fluid chamber, generating a shock wave. The shock wave is transmitted unimpeded through the fluid and then through the patient's soft tissues (which have approximately the same density as fluid) until it encounters an abrupt change in acoustic density from body tissue to stone. By focusing the shock waves on a single focal point, the lithotripter concentrates energy at the site in which the stone is located. Fragmentation of the stone by shock waves occurs as a consequence of both direct mechanical stress from the incident shock wave and indirect forces as a result of collapse of cavitation bubbles generated by the trailing negative-pressure wave.[195]

Techniques

Shock-wave lithotripsy is an outpatient procedure that can be performed in a hospital, ambulatory surgery center, or a mobile lithotripter. Initially, all ESWL was accomplished in water baths. Modern lithotriptors create a connection with high-acoustic gel or oil or ionized water bags instead of submersion, providing for a more portable and convenient treatment regimen. Connections between the patient and the shock waves may be diminished by air

TABLE 29-5 Summary of Immunosuppressive Drugs

Drug	Description	Mechanism of Action	Nonimmune Toxicity and Comments
Prednisone	Corticosteroid	Binds nuclear receptor and enhances transcription of IκB, which inhibits NF-κB and T-cell activation	Diabetes, weight gain, psychological disturbances, osteoporosis, ulcers, wound healing, adrenal suppression
Cyclosporine	11-amino-acid cyclic peptide from *Tolypocladium inflatum*	Binds to cyclophilin; complex inhibits calcineurin phosphatase and T-cell activation	Nephrotoxicity, hemolytic-uremic syndrome, hypertension, neurotoxicity, gingival hyperplasia, skin changes, hirsutism, posttransplantation diabetes, hyperlipidemia
Tacrolimus (Prograf)	Macrolide antibiotic from *Streptomyces tsukubaensis*	Binds to FKBP12; complex inhibits calcineurin phosphatase and T-cell activation	Effects similar to cyclosporine but with lower incidence of hypertension, hyperlipidemia, skin changes, hirsutism, and gingival hyperplasia but higher incidence of posttransplantation diabetes and neurotoxicity
Sirolimus (rapamycin; Rapamune)	Triene macrolide antibiotic from *Streptomyces hygroscopicus* from Easter Island (Rapa Nui)	Binds to FKBP12; complex inhibits target of rapamycin and IL-2–dependent T-cell proliferation	Hyperlipidemia, increased toxicity of calcineurin inhibitors, thrombocytopenia, delayed wound healing, delayed graft function, mouth ulcers, pneumonitis, interstitial lung disease
Everolimus	Derivative of sirolimus, similar mechanism and toxicities		
Mycophenolate (CellCept)	Mycophenolic acid from *Penicillium stoloniferum*	Inhibits synthesis of guanosine monophosphate nucleotides; blocks purine synthesis, preventing proliferation of T and B cells	Gastrointestinal symptoms (mainly diarrhea), neutropenia, mild anemia
Azathioprine (Imuran)	Prodrug that undergoes hepatic metabolism to form 6-mercaptopurine	Converts 6-mercaptopurine to 6-thioinosine-5′-monophosphate, which is converted to thioguanine nucleotides that interfere with DNA and purine synthesis	Leukopenia, bone marrow depression, liver toxicity (uncommon)
Antithymocyte globulin	Polyclonal IgG from rabbits or horses immunized with human thymocytes	Blocks T-cell membrane proteins (e.g., CD2, CD3, CD45), causing altered function, lysis, and prolonged T-cell depletion	Cytokine release syndrome, thrombocytopenia, leukopenia, serum sickness
Muromonab-CD3 (OKT3)	Anti-CD3 murine monoclonal antibody	Binds CD3 associated with the T-cell receptor, leading to initial activation and cytokine release, followed by blockade of function, lysis, T-cell depletion	Severe cytokine release syndrome, pulmonary edema, acute renal failure, CNS changes
Basiliximab (Simulect)	Anti-CD25 chimeric monoclonal antibody	Binds to high-affinity chain of IL-2R (CD25) on activated T cells, causing depletion and preventing IL-2–mediated activation	Hypersensitivity reaction, uncommon
Daclizumab (Zenapax)	Anti-CD25 humanized monoclonal antibody	Similar to that of basiliximab	Hypersensitivity reaction, uncommon
Rituximab (Rituxan)	Anti-CD20 chimeric monoclonal antibody	Binds to CD20 on B cells and causes depletion	Infusion or hypersensitivity reactions, uncommon
Alemtuzumab (Campath)	Anti-CD52 humanized monoclonal antibody	Binds to CD52 expressed on most T and B cells, monocytes, macrophages, NK cells, causing lysis and prolonged depletion	Mild cytokine release syndrome, neutropenia, anemia, autoimmune thrombocytopenia, thyroid disease
FTY720	Sphingosine-like derivative of myriocin from the fungus *Isaria sinclairii*	Functions as antagonist for sphingosine-1-phosphate receptors on lymphocytes, enhancing homing to lymphoid tissues and preventing egress, causing lymphopenia	Reversible first-dose bradycardia, potentiated by general anesthetics and beta blockers, nausea, vomiting, diarrhea, increased liver enzyme levels
Belatacept (Nulojix; LEA29Y)	High-affinity homologue of CTLA-4 Ig	Binds to CD80-CD86 and prevents costimulation via CD28	Clinical trials—preliminary results suggest equal efficacy to cyclosporin A but improved glomerular filtration rate

Adapted from Abbas AK, Lichtman AH, Pillai S. *Cellular and Molecular Immunology*. 7th ed. Philadelphia: Saunders; 2012.

pockets in the gel or oil requiring an increased number of shocks and therefore greater risk of tissue damage.[196]

Several types of lithotripters are in clinical use, and they differ in the way they generate the shock waves. Electrohydraulic (spark-gap) lithotripters rely on an underwater discharge of a high-voltage spark that rapidly vaporizes the surrounding water, generating spherically expanding shock waves. Electromagnetic lithotripters are composed of an electromagnetic coil and a closely approximated metallic plate (or membrane) inside a water-filled shock tube. Piezoelectric lithotripters produce shock waves with

BOX 29-7

Precautions for Procedures and Surgery in Kidney Transplant Recipients

- Caution with radiocontrast exposure.
- Maintain hydration.
- Avoid nephrotoxic antibiotics and analgesic.
- "Stress-dose" steroids: not always necessary.
- If enteral route of medication is contraindicated, give CNI via IV route (⅓ total oral dose).
- Monitor allograft function, plasma potassium, and acid-base balance daily.
- Consider wound-healing impairment.

From Taal MW, et al. *Brenner & Rector's The Kidney*. 9th ed. Philadelphia: Saunders; 2012:2551.
CNI, Calcineurin inhibitor; *IV*, intravenous.

BOX 29-8

Side Effects Associated with Extracorporeal Shock Wave Lithotripsy

- Hypothermia, hyperthermia
- Cardiac arrhythmias
- Skin bruising hematomas
- Petechiae, soft tissue swelling at site
- Renal edema
- Renal hematoma
- Lung injury
- Flank pain
- Hypertension, hypotension
- Nausea, vomiting

the use of a spherical dish containing an array of small ceramic elements.[195] Ultrasonic waves fragment stones and allow them to pass in urine. Lasers may not be as effective with larger stones (greater than 1.5-2.0 cm).[197,198]

Water Immersion

The original ESWL procedure required patients to be strapped in a chair in a semireclining position, followed by submersion in water up to the clavicle. This technique is not used today, but the principles underlying the surgical procedure are similar. The focused, reflected shock wave passes through the water and enters the body through the flank. Significant effects on several systems may occur (Box 29-8).[199,200] The electrocardiograph must be of good quality because the R wave is used to trigger the shocks. Synchronization of the shock wave to the electrocardiograph has reduced the incidence of cardiac dysrhythmias, most commonly supraventricular or premature ventricular complexes, but has not totally eliminated them. Atropine or glycopyrrolate may be given to increase the heart rate and thus the shock-wave rate.[201,202]

Contraindications and Complications

Contraindications to shock-wave lithotripsy include active urinary tract infection, uncorrected bleeding disorder or coagulopathy, distal obstruction, and pregnancy. Obesity and orthopedic or spinal deformities may make positioning difficult.[195] Dose-dependent hemorrhagic lesions can develop on the kidneys, secondary to vascular damage.[201-203] The colon, hepatic structure, lungs, spleen, pancreas, abdominal aorta, ileac veins, or any structure in the abdominal region may be perforated, ruptured, or otherwise damaged. Moderate to severe hemorrhage may occur, but usually resolves spontaneously; patients with clotting disorders are at an increased risk. Hematuria develops in the majority of patients, secondary to blood vessel rupture. Diabetes, new-onset hypertension, or permanently decreased renal function may result.[201]

Anesthesia

Patients will not tolerate ESWL without some type of anesthesia. Various anesthetic techniques have been used. General anesthesia is advantageous because of its rapid onset and control of patient movement. Other techniques include spinal or epidural anesthesia, patient-controlled analgesia (PCA), monitored anesthesia care, and topical anesthesia with eutectic local anesthetics. Continuous infusions of propofol, ketamine, and alfentanil have been used alone or with midazolam. Regional anesthesia provides effective analgesia with a T4 to T6 level. A short-acting spinal anesthetic using 50 mcg of sufentanil alone is popular. Epidural catheters and dressings may cause absorption of some of the shock wave, decreasing the efficacy of treatment. Akinesis is critical in reducing number and duration of treatments, determining efficacy of ESWL, and preventing potential tissue damage. General anesthesia or deep sedation techniques decrease the risk of patient movement.[201-204] Preoperative preparation includes the discontinuation of aspirin-containing medications, anticoagulants, platelet inhibitors, and nonsteroidal antiinflammatory agents for 7 to 10 days before the procedure and documentation of a negative urine culture to prevent postoperative urinary tract infection or sepsis. In women of childbearing age, a pregnancy test is administered if ionizing radiation is to be used during the procedure. Depending on the size, radiopacity, and location of the stone, patients may be advised to drink clear liquids, take a laxative, or both the day before the procedure to enhance visualization of the stone. Fasting protocols are within standard guidelines for anesthesia.[195]

For lithotripsy to be most effective, the stone must remain at the focal point. Because patient movement and patterns of respiration can change kidney and stone position, movement must be minimized and ventilation carefully controlled. The number and intensity of shock waves can be reduced when stone movement is minimized.[204] An obstructed kidney or a patient exhibiting signs and symptoms of infection qualifies as an emergency case. Adequate hydration is encouraged postoperatively to promote diuresis of fragments and to flush out hematuria. Close proximity to lasers may cause corneal damage; everyone in the room, including the patient, should wear eye protection.[197]

PERCUTANEOUS NEPHROLITHOTOMY

Removal of kidney stones 25 mm or smaller also can be accomplished through percutaneous nephrolithotomy. This procedure requires general anesthesia and postoperative hospitalization. Stones are removed via a rigid operating scope inserted in the lower calyx of the kidney under fluoroscopy. Once located, calculi are pulverized by using laser, electrohydraulic, or ultrasound probes placed directly on the stones.[204] The procedure is performed with the patient in the prone or supine position; therefore associated anesthetic considerations apply. The following is a list of complications of percutaneous nephrolithotomy).

Minor	Major
Pain	Septicemia
Fever	Bleeding
Urinary tract infection	Pelvic or ureteral tears
Renal colic	Pneumothorax
	Hemothorax
	Anaphylaxis secondary to contrast dye

TABLE 29-6 Pathophysiology and Clinical Features of TURP Syndrome

Pathophysiology	Clinical Features
Fluid overload	Hypertension, bradycardia, arrhythmia, angina, pulmonary edema and hypoxemia, ventricular failure and hypotension
Water intoxication or Hypo-osmolality	Confusion and restlessness; twitching or seizures, lethargy or coma, dilated, sluggish pupils, papilledema, low-voltage EEG, hemolysis
Hyponatremia	CNS changes as above, reduced inotropy, widened QRS complex, low-voltage ECG, T-wave inversion on ECG
Glycine toxicity	Nausea and vomiting, headache, transient blindness, loss of light and accommodation reflexes (blink reflex preserved), myocardial depression, ECG changes
Ammonia toxicity	Nausea and vomiting, CNS depression
Hemolysis	Anemia, acute renal failure, chills, clammy skin; chest tightness and bronchospasm; hyperkalemia resulting in malignant arrhythmias or bradyasystole
Coagulopathy	Severe bleeding, primary fibrinolysis, disseminated intravascular coagulation

From Malhotra V, Sudheendra V. Complications of transurethral surgery. In Atlee JL, eds. *Complications in Anesthesia*. 2nd ed. Philadelphia: Saunders; 2007:844.
CNS, Central nervous system, *ECG*, electrocardiogram; *EEK*, electroencephalogram; *TURP*, transurethral resection of the prostate gland.

TRANSURETHRAL RESECTION OF THE PROSTATE

Surgical Technique

Benign prostatic hyperplasia (BPH) is the most common benign adenoma in men. Up to 40% of men will require intervention for urinary difficulty, and the frequency of those seeking medical treatment is increasing, due in part to the increase in life expectancy. Medical management consists of pharmacotherapy, which may be combined with a minimally invasive technique. Drugs such as the α-blocking agents, alfuzosin (Uroxatral) and tamsulosin (Flomax), or the 5-alpha-reductase (5AR) inhibitors, finasteride (Proscar) and dutasteride (Avodart), are used alone or more often in combination. Minimally invasive therapies include Holmium laser resection, plasma kinetic vaporization, GreenLight laser vaporization, and transurethral microwave thermotherapy. Transurethral resection of the prostate (TURP) is one of the most commonly performed surgical procedures in men older than 60 years of age. It is being performed less frequently as medical management improves; however, it remains the gold standard in surgical treatment approaches.[205]

The procedure consists of opening the outlet channel from the bladder using a resectoscope in the urethra to electrically cut away the obstructing median and lateral lobes of prostate tissue. Bleeding is controlled with a coagulation current. For visualization of the area, the bladder is distended and continuous irrigation is used to wash away blood and dissected prostatic tissue. These patients are often at greater anesthetic risk because they are elderly and more likely to have cardiovascular or pulmonary problems. Transurethral resection of the prostate (TURP) syndrome is a rare but potentially fatal surgical complication. The incidence is reported to range from 0.78% to 1.4% of procedures. Severe TURP syndrome is rare, but the mortality rate may be as high as 25%. It may occur as early as 15 minutes after the start of resection up to 24 hours postoperatively.[206] It is a procedure-induced combination of water intoxication, fluid overload, and hyponatremia. The pathophysiology and clinical features of TURP syndrome are summarized in Table 29-6. Other complications of the procedure include excessive bleeding, bladder perforation, and infection. Average surgical parameters associated with a transurethral resection of the prostate are given in Table 29-7. Improved surgical techniques and knowledge of the pathophysiology, prevention, and management of TURP syndrome has minimized the risks of this procedure.[205,206]

TABLE 29-7 Average Parameters with a Transurethral Resection of the Prostate

Parameter	Average
30-day mortality	0.2%-0.8%
Resection time	Less than 80 min
Resected mass	20-50 g
Absorbed volume	10-30 mL of fluid per min of resection time
Blood loss	2-5 mL per min of resection time
Serum sodium nadir	132-135 mmol/L

Adapted from Malhotra V, et al. Anesthesia and the renal and genitourinary systems. In Miller RD, et al, eds. *Miller's Anesthesia*. 7th ed. Philadelphia: Churchill Livingstone; 2009.

Complications

Fluid Absorption

A number of complications are associated with resection of the prostate. Large amounts of irrigating solution can be absorbed through venous sinuses. The amount absorbed and the rate of absorption depend on the size of the gland to be resected, the congestion of the gland, the duration of resection, the pressure of the irrigating solution, the number of sinuses open at any one time, and the experience of the resectionist.[207] An average of 10 to 30 mL of fluid can be absorbed per minute of resection time, and 6 to 8 L can be absorbed in cases that last up to 2 hours.[208,209] The uptake of 1 L of irrigant into the circulation within 1 hour can decrease the serum sodium 5-8 mEq/L. In general, limiting resection time to 1 hour is desirable.[206]

Complications may occur with irrigation solutions, as determined by their osmolality and solute composition. Various types of irrigating fluid have been used. Although distilled water is associated with the least optical impairment, its hypotonic composition results in hemolysis of red blood cells. Normal saline or lactated Ringer's solution is highly ionized and promotes dispersion of high current from the resectoscope. Although many different irrigating solutions have been tried, current irrigating solutions typically consist of Cytal (sorbitol 2.7% and mannitol 0.54%), glycine 1.2% or 1.5%, or physiologic saline.[206]

Complications specifically related to absorption of irrigating fluid include volume overload with pulmonary edema, dilutional hyponatremia, hypo-osmolality, cardiac effects, retinal toxic effects (with glycine), and hyperglycemia. As fluid enters the vascular compartment, intravascular pressure and myocardial work increase. The fluid dilutes plasma proteins and electrolytes, and the change in intravascular pressure favors movement of fluid from the vascular to the interstitial compartment. This is poorly tolerated by patients with a cardiovascular disease. Cardiac dysrhythmias may also develop. Progressive increases in blood pressure, CVP, or pulmonary artery wedge pressure (when monitored) suggest hypervolemia. Mannitol irrigating solutions have been reported to contribute to the development of pulmonary edema and hypotnatremia.[210]

Absorption of irrigating fluid also leads to dilutional hyponatremia and hypo-osmolality. Sodium is a major cation of extracellular fluid, and it is responsible for the depolarization of excitable cells and the production of action potentials. The severity and speed of the drop in sodium are related to the resulting symptoms.

The decrease in sodium produces an osmotic shift of fluid into the brain resulting in brain edema, increases in intracranial pressure, and neurologic symptoms. Hyponatremia usually results from water excess rather than from sodium loss. CNS symptoms associated with hyponatremia range from restlessness, headache, irritability, and confusion to blindness, coma, and seizures.

Serum sodium (Na^+) concentrations of 120 mEq/L appear to be borderline for the development of severe reactions, which are mainly ECG and central nervous system (CNS) changes. Electrocardiographic changes characterized by widening of the QRS complex and ST-segment elevation are seen when the serum level decreases to 115 mEq/L. At levels less than 100 mEq/L, ventricular tachycardia and fibrillation can occur.[211] CNS symptoms associated with hypovonatremia include restlessness, confusion, nausea, vomiting, coma, and convulsions. These symptoms can be detected more easily in patients receiving regional anesthesia. CNS symptoms are hidden under general anesthesia. Transient hyperglycemia and hypokalemia have been reported when glucose irrigation solutions have been used.[207,208,211]

Bladder Perforation

Perforation of the bladder is another potential complication of prostatic surgery; however, recent advances in technology have reduced its incidence. Symptoms vary, depending on whether the rupture is intraperitoneal or extraperitoneal. Pathophysiology and clinical features of bladder perforation and TURP syndrome are noted in Box 29-10.[212-214] These symptoms are better recognized when the patient has regional anesthesia if the regional technique does not produce a high block. With general anesthesia, only the surgeon can appreciate the inability to recover bladder fluid as a sign of perforation. Small amounts of intraperitoneal fluid will be excreted by the kidney. However, if hemodynamic compromise occurs, suprapubic drainage is effective for removal of excess intraperitoneal fluid.

Glycine Absorption

Absorption of glycine has been associated with toxicity. Glycine, an amino acid normally found in the body, is a major inhibitory transmitter. Toxic effects may occur from absorption during the procedure. Signs and symptoms include nausea, vomiting, fixation and dilation of the pupils, weakness, muscle incoordination, and hypotension due to a decrease in the release of catecholamines. Glycine is also an inhibitory neurotransmitter in the retina. Absorption of 1.5% glycine can cause a deterioration of vision. TURP blindness is caused by retinal dysfunction from glycine toxicity.[206,214]

Glycine may also result in encephalopathy and seizure activity due to NMDA receptor stimulation. Other signs and symptoms of glycine toxicity include nausea, vomiting, headache, malaise, and weakness. Glycine may also result in CNS toxicity as a consequence of its biotransformation in the liver to ammonia. Ammonia toxicity may result in encephalopathy, delayed awakening, and even coma in the postoperative period.[206]

Skin Burns

The use of high voltage for cutting and coagulation during TURP may result in skin burns. Newer technology for TURP, including bipolar enucleation of the prostate and laser therapy, have reduced the risk of skin burns when compared with monopolar techniques.[215] Electrocardiography pads may be placed at other sites so that potential burns are avoided. Many patients who undergo TURP have pacemakers. These devices must be converted to a fixed rate unless they are designed to operate in the presence of applied currents.[216]

Blood Loss

Significant bleeding occurs in less than 1% of TURP cases. Blood loss during TURP generally is related to the weight of the resected tissue, operating time, and skill of the surgeon.[217] Increased blood loss occurs with greater than 45 g of resected tissue and procedures lasting longer than 90 minutes Assessment of blood loss may be difficult because of the dilution of blood in irrigating fluid. Hematocrit may be increased, decreased, or unchanged, depending on the amount of fluid in the intravascular space at the time. Blood transfusion should be based on preoperative hematocrit, the

BOX **29-9**

Management of TURP Syndrome and Bladder Perforation

- Asymptomatic or mildly symptomatic patients should be observed and monitored.
- Severe TURP syndrome requires immediate aggressive therapy if the patient is to survive. The following measures are suggested:
  - Terminate the surgery as soon as possible.
  - Administer 20 mg of intravenous (IV) furosemide.
  - Immediately obtain the following laboratory tests; hematocrit; serum electrolyte, creatinine, and glucose concentrations; serum osmolality (if available); arterial blood gas analyses; and 12-lead ECG.
  - Continue or start the administration of normal saline. Hypertonic saline (3% or 5%) may be administered (at a rate<100 mL/hour) if the serum sodium concentration is less than 100 mEq/L, severe central nervous system side effects of hyponatremia and hypo-osmolality are evident, or reduced inotropy results in cardiovascular collapse.
  - Administer IV midazolam in 1-mg incremental doses to treat twitching or seizures; a barbiturate may be added if seizures persist.
  - Auscultate chest and obtain chest radiographs to detect pulmonary edema. Intubate and mechanically ventilate the patient at the earliest evidence of pulmonary edema.
  - Transfuse packed red blood cells as necessary.
  - If bleeding continues, investigate for disseminated intravascular coagulation (DIC) or primary fibrinolysis. DIC is treated with crystalloids and blood products to achieve hemodynamic stability and normal coagulation. Primary fibrinolysis responds well to amino-caproic acid (Amicar) administered as an IV infusion of 3 to 5 g in the first hour, followed by continuous IV infusion at 1 g/hour until the bleeding is controlled.
  - Institute invasive monitoring and provide supportive therapy to maintain circulation and pulmonary function and to prevent renal failure.

Bladder Perforation

As soon as bladder perforation is detected, undertake the following measures:

- Stop surgery and achieve hemostasis.
- Treat hypotension with IV crystalloids, vasopressors, and inotropes.
- Obtain a hematocrit. Start blood transfusion if brisk bleeding continues. Occult blood loss into the intraperitoneal or retroperitoneal space may occur.
- Perform a cystourethrogram to locate the perforation.
- For most perforations, suprapubic cystotomy, an indwelling Foley catheter, and (occasionally) ureteral stents are sufficient. In some instances, immediate exploratory laparotomy may be necessary to control bleeding and repair the perforation.

Adapted from Hawary A, et al. Transurethral resection of the prostate syndrome: almost gone but not forgotten. *J Endourol.* 2009;23(12):2013-2020; Malhotra V, Sudheendra V. Complications of transurethral surgery. In: Atlee JL, ed. *Complications in Anesthesia.* 2nd ed. Philadelphia: Saunders; 2007:843-845; Gravenstein D, Hahn RG. TURP syndrome. In: Lobato EB, et al, eds. *Complications in Anesthesiology.* Philadelphia: Lippincott Williams & Wilkins; 2008:474-491.

duration and difficulty of resection, and a general assessment of the patient. A recent study of 951 robotic-assisted laparoscopic prostatectomies noted that men with larger prostates and median lobes requiring longer operative times experienced higher blood loss. Resected tissue less than 30 g generally required no transfusion. Thirty to eighty grams resected possibly required up to 2 units of red blood cells, and greater than 80 g up to 4 units.[218]

Prevention of TURP Syndrome. Prevention of TURP syndrome is, of course, the most important approach. Early identification of evolving symptoms is vital to avoid serious morbidity. Suggested preventative measures include: avoid the Trendelenburg position as it promotes fluid absorption; limit resection time to less than 1 hour; keep the prostate capsule intact until the end of the resection; place irrigating fluids less than 60 cm above the prostate gland; measure electrolytes during and after the procedure as indicated; and use a regional technique with light sedation so mental changes can be identified.[206,219,220]

Treatment of TURP Syndrome. An asymptomatic patient with mild hyponatremia only requires monitoring and observation. Mild symptoms can be managed with supportive treatment such as antiemetics, atropine, vasopressors, or diuretics and careful observation as indicated.

If TURP syndrome is detected intraoperatively, bleeding points should be coagulated and surgery completed as soon as reasonable. Severe hyponatremia less than 120 mEq/L must be treated. The challenge is to promptly institute treatment while avoiding overtreatment. The most feared complication of rapid correction of acute hyponatremia is central pontine mylenolysis, also referred to as osmotic demyelination syndrome (ODS). The etiology is unclear; however, osmotic stress appears to cause changes in neuronal cells and the release of myelin toxins. Symptoms usually occur approximately one week after the osmotic stress and may include seizures, palsy, dysarthria, paralysis, mental changes, and coma. Hypertonic saline (3% to 5% sodium chloride) should be given at a rate no greater than 100 mL/hr. Sodium correction should not exceed 0.5 mEq/L per hour or 8 mEq/day. Severe symptoms may require initial doses of 1-2 mEq/L per hour. Target levels for correction are 120 mEq/L.[206,219,220] Suggestions for the management of TURP syndrome and bladder perforations are given in Box 29-9.

Anesthesia for TURP Procedures. Spinal and general anesthesia are both used for TURP procedures. Spinal anesthesia is believed to be the anesthetic of choice because the early signs and symptoms of TURP syndrome, hypervolemia, and bladder perforation are more easily detected in a responsive patient. Under general anesthesia, cardiovascular changes must be relied on to diagnose complications. Pain impulses from the bladder neck and prostate are propagated by afferent parasympathetic fibers originating primarily from the second and third sacral roots in concert with the pelvic splanchnic nerves. The sympathetic nerves via the hypogastric plexus, which is derived from T11 to L2 nerve roots, transmit sensation from the bladder.[221] As a result, a T10 sensory level is necessary for adequate anesthesia. Intrathecal opioids are commonly included with the local anesthetic. Cautious fluid loading may be used to minimize spinal anesthesia-induced hypotension. Although general anesthesia may mask early complications, it may be desirable in the patient who requires pulmonary support or who cannot tolerate a fluid load for compensation of a loss of sympathetic tone. All inhalation agents have been used successfully.[206,219,222] Some key points for anesthesia management of TURP are given in Box 29-10.

BOX 29-10

Key Points for Anesthesia Management of Transurethral Resection of Prostate

- TURP syndrome is caused by disturbance of intravascular volume and/or serum osmolality.
- Five questions to ask prior to a TURP:
  1. What is the irrigation fluid? (Glycine, Cytal, or Physiologic saline?)
  2. What is the bag height over the prostate?
  3. What is the size of the prostate?
  4. What is the expected duration of procedure?
  5. What is the surgical operating position (avoid Trendelenburg)?
- Techniques for detection of pending TURP syndrome include measurement of serum sodium, monitoring for fluid overload, assessment of mental status, and ethanol breath analysis.
- Treat symptomatic (mental status changes, seizures, hypotension) patients aggressively; treat asymptomatic aberrant lab values (hyponatremia, hyperglycemia) very slowly, if at all.
- CNS symptoms of headache, irritability, confusion, nausea, and vomiting are early warning signs of TURP syndrome.

Adapted from Hawary A, et al. Transurethral resection of the prostate syndrome: almost gone but not forgotten. *J Endourol.* 2009;23(12):2013-2020; Malhotra V, Sudheendra V. Complications of transurethral surgery. In Atlee JL, ed. *Complications in Anesthesia.* 2nd ed. Philadelphia: Saunders; 2007:843-845; Gravenstein D, Hahn RG. TURP syndrome. In: Lobato EB, et al, eds. *Complications in Anesthesiology.* Philadelphia: Lippincott Williams & Wilkins; 2008:474-491.

LAPAROSCOPIC UROLOGIC SURGERY

Laparoscopy is the process of inspecting the abdominal cavity through an endoscope. Laparoscopy started in the mid-1950s when gynecologists began to use this technique to diagnose pelvic pain while reducing postoperative pain and length of hospital stay. Over the years, laparoscopy for general and urologic surgery has become a common procedure. Advantages and disadvantages of laparoscopic surgery are found in Box 29-11. Some examples of surgical procedures that can be done laparoscopically include varicocelectomy, percutaneous stone retrieval, nephrectomy, transplants, and radical prostatectomy.[223-225]

Carbon dioxide is the most universally used agent for insufflating the abdominal cavity to facilitate view during this procedure. Several pathophysiologic changes can occur after carbon dioxide pneumoperitoneum and the extremes of patient positioning required for the procedure. Preparation for hemorrhage and conversion to an open procedure are critical.[226] Most of the considerations for laparoscopic surgery are beyond the scope of this chapter, but two unique problems specific to urologic surgery are worth discussing.

The urogenital system is a retroperitoneal system. As such, carbon dioxide insufflated in this space communicates freely with the thorax and subcutaneous tissue. Subcutaneous emphysema can occur and may extend to the head and neck. In severe cases, it may lead to submucous swelling and airway compromise in the unprotected airway.[227-229]

Carbon dioxide is absorbed from the peritoneal cavity and acidosis may develop. Because the carbon dioxide insufflation, together with steep Trendelenburg position and long procedures, may increase intraabdominal and intrathoracic pressure, controlled ventilation is mandatory. Intraperitoneal pressure greater than 10 mmHg results in hemodynamic alterations, including decreased cardiac output and increased systemic vascular resistance. The pneumoperitoneum can cause renal cortical vasoconstriction due to activation of the sympathetic nervous system. Decreased renal perfusion activates the renin-angiotensin-aldosterone system, which causes vasoconstriction. These effects are additive to those seen with surgical stress. Renal and hepatic perfusion may

BOX **29-11**

Advantages and Disadvantages of Laparoscopic Renal Surgery

Advantages

- More precise operative procedure due to magnification of operative site
- Reduced postoperative pain
- Improved cosmetic results
- Quicker return to normal activities
- Reduction in hospital length of stay
- Reduction of cost of care
- Less intraoperative bleeding
- Fewer postoperative pulmonary infections
- Fewer postoperative wound infections
- Reduced metabolic derangements
- Better postoperative respiratory function

Disadvantages

- Potential for extravasation of insufflated carbon dioxide to retroperitoneal space and thorax
- Potential for postoperative airway compromise secondary to subcutaneous emphysema and pharyngeal obstruction
- Increased incidence of acidosis due to absorption of carbon dioxide
- Higher incidence of intraoperative oliguria potentially due to perirenal pressure from pneumoperitoneum
- Potentially longer duration than open procedure

be altered. Some suggested techniques to minimize the effect of positive pressure pneumoperitoneum include: (1) employ lower insufflation pressures, (2) operate in a gasless environment, (3) substitute inert gas for carbon dioxide, (4) use drugs to antagonize the neuroendocrine response, (5) expand volume, and (6) use mechanical devices. It has been reported that the use of intermittent sequential pneumatic compression (ISPC), activated over the lower limbs 15 minutes after the pneumoperitoneum, improves splanchnic and renal perfusion. This technique augments cardiac output and lowers systemic vascular resistance.[230] A complete discussion of laparoscopic surgery can be found in Chapter 31.

ROBOTIC UROLOGIC SURGERY

Robotic-assisted surgery is an emerging technique for managing various urologic procedures such as prostatectomy. It is performed using the da Vinci surgical system (Intuitive Surgical Mountain View, Calif, USA). It consists of a surgeon's console for surgical work, a surgical cart that houses the video and lighting equipment, and a robotic tower that supports three or four robotic arms. Figure 29-7 shows the da Vinci Si surgical system.

The surgeon's console provides the surgeon with a three-dimensional, 10-times magnified view through a binocular viewpoint. Interaction is achieved through "masters" into which the surgeon's hands are inserted. Robotic technology provides the surgeon an enhanced and magnified 3D view, a reduction in scattered ambient light, reduced surgeon fatigue, reduced hand tremor, and improved manual dexterity. This technology also provides a predominantly bloodless field.[231-233]

Robotic surgery necessitates a coordinated approach by anesthetist and surgeon because the surgery is performed using a modified laparoscopic technique and can be long in duration. The patient is placed in Trendelenburg position, with the addition of lithotomy positioning in prostatectomy surgery. Major complications of surgery in the Trendelenburg position include:

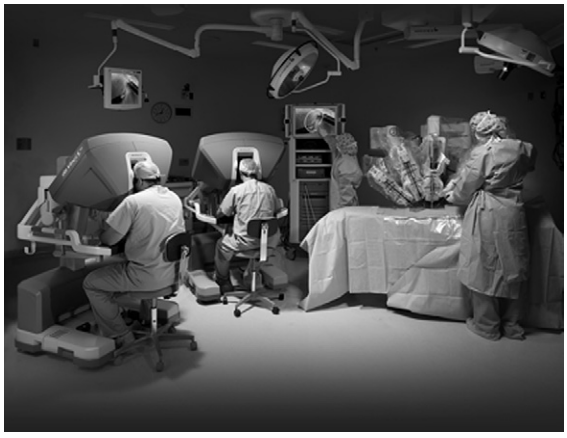

FIGURE **29-7** Da Vinci Si surgical system. (Courtesy Intuitive Surgical Inc., Sunnyvale, California.)

BOX **29-12**

Anesthesia for Robotic-Assisted Surgery

- There is risk of thromboembolism due to lengthy procedures in Trendelenburg position; use thromboembolic stockings to reduce risk.
- Maximize protection over pressure areas to avoid nerve injury and protect face from direct pressure.
- General anesthesia or general and regional combined may be used.
- Difficulties inherent in patients having prolonged surgery in Trendelenburg position are present: increased mean arterial pressure in brain, increased cerebral blood volume, decreased cardiac output and perfusion to lower extremities, and decreased perfusion to vital organs.
- Challenges inherent with lower limbs in lithotomy are present: potential for damage to the common peroneal nerve.
- Difficulties with peritoneal insufflation are present: decreased compliance, increased airway pressure, increased ventilation-perfusion mismatch, and hypercapnia.
- Blood pressure reduction may be necessary secondary to resultant increase in systemic vascular resistance because of the pneumoperitoneum.
- Urine output may be decreased and generally responds to a fluid challenge.

(1) neuropathies, (2) CVP elevation, (3) intraocular/intracranial pressure elevation, (4) increased pulmonary venous pressure, (5) decreased pulmonary compliance, (6) reduced functional residual capacity (FRC), and (7) swelling of the face, eyelids, conjunctivae, and tongue. Facial swelling requires careful airway assessment prior to extubation. Major anesthetic considerations for robotic procedures are summarized in Box 29-12.

SUMMARY

Anesthetic management of the patient during the perioperative period for renal procedures depends upon an understanding of both normal renal function and pathophysiologic changes in the organ system. In addition to normal anatomy and physiology, this chapter highlighted ways to assess renal function and changes in renal function secondary to anesthetics. Various stages of renal pathology were identified and management of patients with acute and chronic renal failure emphasized. Rare and common urologic procedures were identified, and pertinent anesthetic considerations discussed for each procedure.

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Hepatobiliary and Gastrointestinal Disturbances and Anesthesia

CHAPTER 30

◆ *Shawn B. Collins and Mason McDowell*

The hepatobiliary system plays an integral role in anesthetic management. An intimate familiarity with diseases of the hepatobiliary and gastrointestinal systems can help avoid negative anesthetic outcomes. The liver is the largest internal organ and is critical in maintaining the homeostasis of many other physiologic systems, the least of which is drug metabolism. As such, acute or chronic liver dysfunction can impair the intended response to anesthesia.[1]

The purpose of this chapter is to give an overview of pathophysiologic processes specific to the hepatobiliary and gastrointestinal system commonly encountered by the anesthetist. Fundamental relevant anesthetic considerations are described. More specifically, this chapter reviews the anatomy, physiology, and pathophysiology of the liver, to include evaluation of liver function, anesthesia effects on liver function, and perioperative management of patients with liver disease. The chapter continues with diseases of the biliary tract, esophagus, stomach, peritoneum, intestinal tract, and spleen and anesthetic management of patients with conditions affecting these systems. Special consideration is given to carcinoid tumors and transplantation.

LIVER DISEASE

Anatomic, Physiologic, and Pathophysiologic Considerations

Located in the thoracic portion of the abdominal cavity, the liver is the largest organ in the body and generally extends from rib 7 to rib 11 along the right midaxillary line. The liver spans from the right hypochondrium to a portion of the left hypochondrium and is classically divided into four lobes, which may be subdivided into multiple segments as described, for example, by the Couinaud system.[2] These subdivisions are based on the anatomic proximity of hepatic and portal veins, though multiple classifications are used that contain different terminology and no system is recognized as superior.

The functional unit of the liver is the hepatic lobule or acinus. The acinus forms around a portal canal consisting of a portal venule, hepatic arteriole, bile ductule, lymphatic vessel, and nerves. The acinus architecture radiates around a central vein that empties into the hepatic veins and then into the vena cava (Figure 30-1). Hepatic lobules number between 50,000 and 100,000 in the normal liver.

The filtering function of the liver has a prominent physiologic role. Blood from the gut contains large quantities of colonic bacilli; it is cleansed of more than 99% of the bacterial load by Kupffer cells (macrophages) that line the hepatic sinuses.[3] Endothelial cells that line the hepatic sinuses permit diffusion of large plasma proteins and other substances into the extravascular spaces in the liver. This phenomenon results in a large quantity of lymph that is nearly equal in protein concentration to plasma.

The metabolic functions of the liver require a significant quantity of blood, which comes from arterial and venous sources. The portal vein and the hepatic artery provide the primary blood supply to the liver, delivering approximately 1.5 liters per minute of blood flow. The hepatic artery branches off of the abdominal aorta and delivers 400 to 500 mL/minute of oxygenated blood. According to the anatomic peculiarity of the double afferent blood supply of the liver, 75% to 80% of the blood entering the liver is partially deoxygenated venous blood supplied by the portal vein, which collects all the blood that leaves the spleen, stomach, small and large intestine, gallbladder, and pancreas. The blood entering the liver via the hepatic portal vein contains some oxygen and is high in nutrients that have been absorbed from the digestive tract into the mesenteric and portal veins. Hepatic venous blood supply is shown in Figure 30-2. It is responsible for 70% of blood flow to the normal liver (≈1 L/minute), but only 50% of the liver oxygen supply. The dual supply of blood allows the liver to be relatively resistant to hypoxemia. The combined blood from both sources joins in the hepatic sinusoidal channels lying between the layers of cells in the lobule. These channels serve as capillaries. Endothelial cells and Kupffer cells line the sinusoids. Bile canaliculi are located between hepatocytes; these canaliculi empty into terminal bile ducts. A coalescence of central veins from hepatic lobules forms the hepatic veins, which empty into the inferior vena cava. An extensive arcade of lymphatic vessels is also present within the layer of cells.[4]

The mean pressure in the hepatic artery is similar to that in the aorta, whereas portal vein pressure has been reported to range between 6 and 10 mmHg in humans. This relatively low pressure allows the liver to function as a circulatory reservoir. Hepatic blood volume may expand considerably in cardiac failure and, in turn, serves as an important blood reservoir in case of bleeding episodes, and compensates up to 25% of the hemorrhage by immediate expulsion of blood from the capacitance vessels.[5] Both α- and β-receptors are present in the hepatic arterial circulation, but only α-receptors are noted in the portal circulation. There is disagreement as to whether the hepatic arterial vasculature exhibits autoregulation of blood flow. Portal blood flow is dependent on the combined venous outflow from the spleen and gastrointestinal tract. A decrease in either portal or arterial blood flow affects a compensatory increase in blood flow delivered by the other system.[6]

Potent inhaled anesthetics can affect hepatic blood flow, particularly portal blood flow, but present evidence suggests that flow is well maintained relative to oxygen demand. None of the present anesthetics adversely influence hepatic integrity by its effects on blood flow.[7] Effects of *volatile anesthetics* on hepatic blood flow are described in Table 30-1.

Changes in hepatic artery or portal vein blood flow may not result in an overall change in total hepatic flow due to the hepatic artery buffer response (HABR). This response is a semi-reciprocal autoregulatory mechanism whereby changes in portal flow inversely affect hepatic arterial flow.[8] The similarity in total hepatic flow between agents implies an intact HABR.

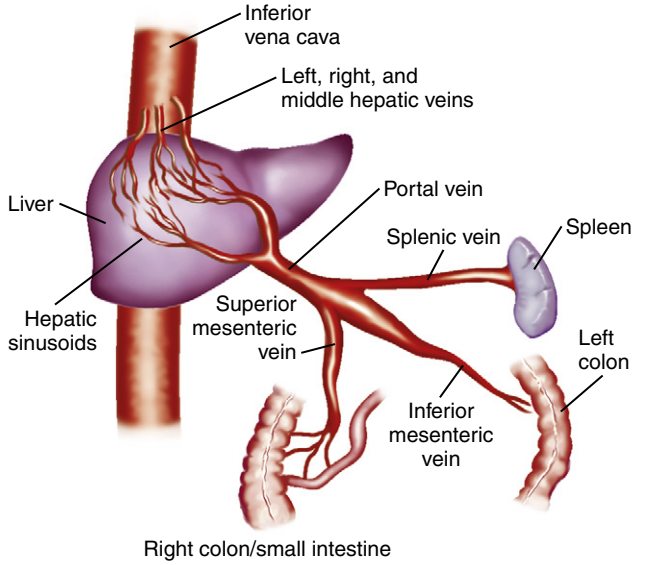

FIGURE **30-1** Anatomy of the portal circulation. Blood vessels that constitute the portal circulation and hepatic outflow tracts are depicted. (From Feldman M, et al, eds. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*. 9th ed. Philadelphia: Saunders, 2010:1490.)

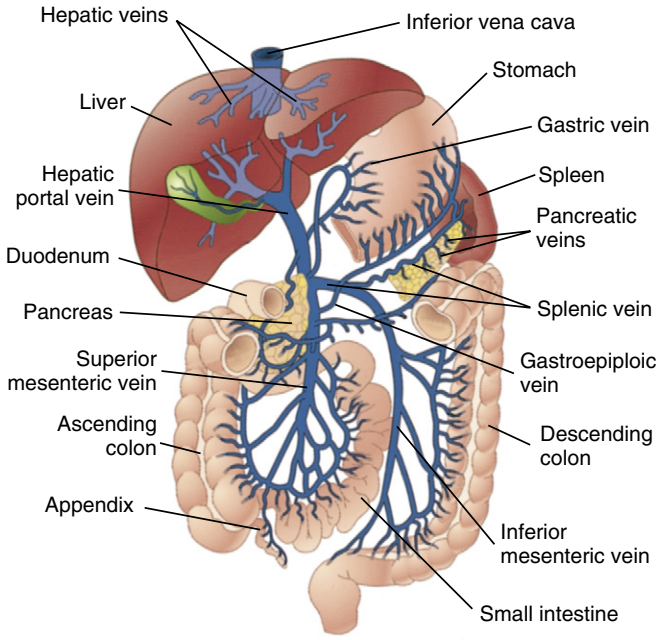

FIGURE **30-2** Hepatic portal circulation. In this unusual circulatory route, a vein is located between two capillary beds. The hepatic portal vein collects blood from capillaries in visceral structures located in the abdomen and empties into the liver for distribution to the hepatic capillaries. Hepatic veins return blood to the inferior vena cava. (From Patton KT, Thibodeau GA. *Anatomy & Physiology*. 8th ed. St Louis: Mosby; 2013:664.)

The liver has many physiologic functions, including synthesis and metabolism of various essential proteins, lipids, and hormones (Box 30-1). There are no artificial devices that can duplicate all of the functions of the liver.

Carbohydrate Metabolism

Because nutritional ingestion and energy demand may not be synchronous, the body relies upon a dynamic system of energy storage and utilization. Glucose is the primary fuel source for many cells of the body (e.g., kidney, red blood cells) and is the preferred energy source for other tissues (e.g., brain). To maintain a steady blood glucose level, the liver moderates gluconeogenesis and glycogenolysis.

Gluconeogenesis is the formation of glucose from noncarbohydrate molecules lactate and pyruvate and amino acids, all of which are products of anaerobic and catabolic metabolism. It is stimulated by reduction of glycogen stores. During periods of fasting, the liver maintains glucose levels at relatively normal levels through glycogenolysis. Initiated by epinephrine and glucagon, glycogenolysis is the process of liberating glucose from glycogen stores found in the liver (and skeletal muscle). Hypoglycemia may therefore be encountered in patients with severe liver disease caused by derangements in insulin clearance, a decrease in glycogen capacities, and impairment in gluconeogenesis. Because these processes deplete stored nutrients, the body's energy needs can only be maintained for a limited time.

Protein Synthesis

Protein synthesis occurs primarily in the liver; this excludes immunoglobulins, which are produced by the humoral immune system. With significant liver disease, a reduction in circulating plasma protein will result in a decrease in plasma oncotic pressure. Additionally, drugs bound to proteins produced by the liver would have a greater unbound fraction if circulating proteins were reduced due to liver disease. In addition, overexpansion of the interstitial space and third-spacing secondary to derangements in plasma oncotic pressure result in a large increase in the volume of distribution of clinically used medications. Clinical concerns should therefore focus on the potential for an exaggerated effect with a given dose of drug, particularly a drug that is highly protein bound. The amount of nondepolarizing muscle relaxant *may* also need to be increased to achieve a given level of blockade. This is secondary to an increased volume of distribution of the drug (secondary to alterations in plasma protein binding and body fluid shifts). Plasma cholinesterase, which is produced in the liver, also

TABLE 30-1 Effect of Selected Volatile Anesthetics on Hepatic Blood Flow

Volatile Anesthetic	Hepatic Artery Blood Flow	Portal Vein Blood Flow
Desflurane	No change	Decrease or no change
Isoflurane	Increase	No change
Sevoflurane	No change or increase	Decrease

BOX 30-1

Selected Essential Physiologic Functions of the Liver

- Carbohydrate metabolism
  - Gluconeogenesis
  - Glycogenolysis
  - Glycogenesis
- Protein synthesis
  - Albumin (osmolarity)
  - Thrombopoietin (platelet production)
- Amino acid synthesis
- Protein metabolism
- Bile production
- Lipid metabolism
  - Lipogenesis
  - Cholesterol synthesis
- Coagulation factor synthesis
  - Factors I, II, V, VII, IX, X, XI
- Insulin clearance
- Drug metabolism/ transformation
- Bilirubin metabolism

may be deficient. This condition may prolong the effects of succinylcholine as well as enhance the potential toxicity of ester local anesthetics.

Protein Metabolism

Other roles in protein metabolism performed by the liver include synthesis of lipoproteins (important for lipid transport in the blood), deamination of amino acids into carbohydrates and fats for production of adenosine triphosphate (ATP) through citric acid cycle oxidation, and production of urea for the removal of ammonia, which is formed by hepatic deamination processes and bacteria in the gut.

Bilirubin Metabolism

Bilirubin is a breakdown product of heme metabolism and is often classified as unconjugated or conjugated. Heme is turned into unconjugated bilirubin in the reticuloendothelial cells of the spleen. This unconjugated bilirubin is not soluble in water and is neurotoxic at sufficiently high levels. It is then bound to albumin and transported to the liver. Once in the liver, the unconjugated bilirubin is conjugated with glucuronic acid. Bilirubin is then incorporated into the bile and is secreted into the intestine, where it is metabolized by bacterial enzymes and predominantly excreted in feces.

Bile Production

The liver aids intestinal digestion by forming bile and secreting it into the common bile duct (CBD). Hepatocytes in each lobule continuously secrete fluid that contains phospholipids, cholesterol, conjugated bilirubin (the end product of hemoglobin metabolism), bile salts, and other substances. Bile is stored and concentrated in the gallbladder. In response to the intestinal hormone cholecystokinin (CCK), bile is released by the gallbladder. The presence of fat and protein in the duodenum initiates contraction of the gallbladder and movement of bile via the common bile duct. This duct merges with the pancreatic duct at the ampulla of Vater, which empties into the duodenum via the sphincter of Oddi (major duodenal ampulla). Obstruction of either of these ducts may result in pathologic illness that may necessitate surgical correction.

Ductal patency may be confirmed by radiologic evaluation. Endoscopic retrograde cholangiopancreatography (ERCP) is performed by passing an endoscope into the lower gastrointestinal (GI) tract and locating the major duodenal ampulla. The ampulla is cannulated and examined using radiographic dye to determine whether the blockage is due to a common bile duct stone. If a stone is present, typically it can be retrieved endoscopically. Sphincterotomy also may be performed to facilitate removal of CBD stones. Correction of ductal stenosis also may require sphincterotomy or insertion of a stent.

Bile secretion assists in the absorption of fat and fat-soluble vitamins (vitamins A, D, E, K). The metabolic end products of many drugs are also removed via the bile. Liver disease may result in impaired bile production or flow, leading to steatorrhea, vitamin K deficiency, and delayed removal of active drug metabolites.

A deficiency in vitamin K results in coagulopathy due to impaired production of clotting factors II (prothrombin), VII, IX, and X.[9] Except for factor VIII, which is produced in endothelial cells, the liver is responsible for producing all clotting factors. Hepatocellular disease therefore results in decreased clotting factor levels and abnormal bile production. Impaired bile production ultimately manifests as altered production of vitamin K–dependent clotting factors.

Intrahepatic obstruction of blood flow (due to disease pathology) ultimately causes portal hypertension. A consequence of the resultant transmission of backward pressure is congestive splenomegaly, leading to platelet sequestration and thrombocytopenia. Therefore, severe liver disease with portal hypertension induces coagulopathy not only as a result of impairment in hepatic coagulation factor production but also as a result of diminution in circulating functional platelets. In the presence of biliary deficiency, parenteral vitamin K administration helps correct coagulopathy. However, significant hepatocellular disease may dictate the need for fresh frozen plasma (FFP) for immediate correction of coagulation-factor deficits.

The use of subarachnoid and epidural blockade should be avoided in the presence of coagulopathy. Derangements in parameters such as prothrombin time (PT), activated partial thromboplastin time (PTT), and platelet count are a relative contraindication to these techniques; most procedures in which bleeding is a possibility are often postponed when international normalized ratio (INR [prothrombin time]) is greater than 1.5. Nasopharyngeal instrumentation and invasive procedures must be performed cautiously and carefully in the presence of increases in PT and activated PTT, a low platelet count, or other laboratory signs that arouse suspicion of coagulopathy.

Insulin Clearance

The liver is the main site for insulin clearance, removing 50% during the first portal passage, but this percentage varies widely under different conditions.[10] During obesity, hyperinsulinemia, insulin-resistant state, dyslipidemia, and type II diabetes mellitus insulin clearance in the liver decreases. A reduction in hepatic insulin extraction would lead, in insulin-resistant states, to a substantial peripheral hyperinsulinemia (due to insulin hypersecretion and reduced hepatic extraction of insulin).[11]

Drug Metabolism/Transformation

The enzyme systems involved in the biotransformation of drugs are located primarily in the liver. Proper hepatic function is necessary to maintain the pharmacokinetic machinery detailed earlier in this textbook. Orally administered drugs may be metabolically inactivated in the liver before reaching the systemic circulation. This first-pass metabolism may limit the oral availability of highly metabolized drugs. Within the liver, phase I and phase II reactions are responsible for metabolism of many exogenous substances and most drugs. The subsequent products are then excreted via excretory transporters on either the canalicular or sinusoidal membranes[12] (Box 30-2). The end products of these processes (except in the case of prodrugs or an active metabolite) are the result of deactivation and transformation of substances into benign by-products capable of being excreted in the bile or urine.

The cytochrome P450 (CYP) class of enzymes are primarily responsible for phase I reactions. More than 50 CYPs have been identified in humans, yet nearly 50% of drugs currently manufactured are metabolized by CYP 3A4/5.[13] Differences in the rate of metabolism of a drug can be due to drug interactions. When two drugs are coadministered and subjected to metabolism by the same enzyme system, the rate of metabolism can be either decreased or increased. Enzyme *induction* hastens metabolism of certain coadministered medications (e.g., ethanol, barbiturates, ketamine, some benzodiazepines) and promotes tolerance to other medications metabolized by the same enzyme class. This relative tolerance can increase the clinical requirement for other drugs (e.g., sedatives, opioids, steroid muscle relaxants). Conversely, coadministration of drugs metabolized by a single CYP (e.g., cimetidine,

BOX **30-2**

Drug Metabolism in the Liver

Phase I Reactions
- Functionalization reactions
- Add or expose a functional group (e.g., oxidation, reduction, hydrolysis)
- Typically result in loss of pharmacologic activity (excluding prodrugs)
- Important for metabolizing many of the anesthetic drugs (e.g., midazolam, diazepam, codeine, phenobarbital)

Phase II Reactions
- Conjugation reactions
- Phase I product (substrate) conjugates with a second molecule
- Lead to formation of a covalent linkage between a functional group and glucuronic acid, sulfate, glutathione, amino acid, or acetate (e.g., morphine, acetaminophen)

chloramphenicol) will compete for binding to the enzyme's active site. This can result in enzyme inhibition of metabolism of one or both of the drugs and lead to elevated plasma levels culminating in increased sensitivity or toxicity.

Tolerance to certain drugs results from overproduction of enzymes within hepatic enzyme systems, including the cytochrome P-450 system. Drugs capable of inducing this process include ethanol, benzodiazepines, ketamine, barbiturates, and phenytoin. The result is an increased clinical requirement for certain drugs like sedatives, opioids, and muscle relaxants, such as vecuronium and rocuronium.

Certain drugs, such as lidocaine, morphine, meperidine, and propranolol, are highly dependent on hepatic extraction from the circulation for sufficient metabolism. Decreased blood flow to the splanchnic circulation, which occurs during hypotensive states and even during uneventful laparotomy, may decrease metabolic clearance of these drugs.

Laboratory Evaluation of Liver Function

No single laboratory test reliably assesses liver function. As stated previously, the huge capacity and functional reserve of the liver allow for the presence of significant disease processes before evidence of liver failure is reflected in abnormal laboratory findings; abnormalities do, however, aid in differentiating parenchymal from obstructive disorders. Parenchymal disorders reflect dysfunction at the hepatocellular level, whereas obstructive disorders reflect disease processes caused by dysfunctional bile excretion.

Ammonia is cleared by the liver and may be used to evaluate hepatic encephalopathy, but ammonia levels do not correlate well with severity of the clinical presentation. As such, its usefulness is limited. Bilirubin levels also reflect hepatic clearance effectiveness, but it is elevated in most significant liver diseases and is not specific in diagnostic value. Albumin synthesis occurs in the liver, and hypoalbuminemia can indicate chronic liver disease once nonhepatic etiologies have been ruled out. Because albumin has a half-life of 14 to 21 days, quantitative laboratory analysis will be slow to decrease in relation to worsening liver function, making it an unreliable indicator of hepatic synthetic function in acute liver injury. The most common reason for a low albumin is chronic liver failure caused by cirrhosis. The serum albumin concentration is usually normal in chronic liver disease until cirrhosis and significant liver damage has occurred. In advanced liver disease, the serum albumin level may be less than 3.5 g/dL. Biochemical markers of liver function are identified in Table 30-2.

Serum transferases (transaminases) are most sensitive in identifying acute hepatic injury. Elevations in transferase levels are common in all forms of liver injury, but the degree of elevation combined with physical examination and patient symptoms can aid in the differential diagnosis of probable types of hepatic disease.

Patients who present soon after passing common bile duct stones can be misdiagnosed with acute hepatitis because aminotransferase levels often rise immediately, but alkaline phosphatase and γ-glutamyl transferase levels do not become elevated for several days. Asymptomatic patients with isolated, mild elevation of either the unconjugated bilirubin or the γ-glutamyl transferase value usually do not have liver disease and generally do not require extensive evaluation.[14]

Overall hepatic function can be assessed by applying the values for albumin, bilirubin, and prothrombin time in the Child-Pugh classification system, which is modified from the earlier Child-Turcotte grading system[15] (Table 30-3).

Effects of Anesthesia on Liver Function

Patients with liver disease who require surgery are at greater risk for surgical- and anesthesia-related complications than those with a healthy liver.[16] The degree of the risk is dependent on the anesthetic technique and associated sequelae, the surgery being performed, and specific type of liver disease and its severity.

Volatile Anesthetic Selection

Given the global nature of general and regional anesthesia, hepatic blood flow may be reduced in a dose-dependent manner. The reduction in mean arterial pressure and cardiac output frequently seen with the use of volatile anesthetics proportionately reduces hepatic blood flow. Another factor that impairs hepatic blood flow is the vasoconstrictive response of the splanchnic circulation; this response occurs as a sympathetic reflex to reduced mean arterial pressure. Isoflurane increases hepatic blood flow through direct vasodilatory properties. This effect is likely offset, however, by a reduction in portal blood flow. Hypotension secondary to regional anesthetic–induced sympathectomy (e.g., epidural or subarachnoid blockade) principally accounts for the reduced splanchnic blood flow associated with the use of these techniques.

All of the volatile anesthetics also have been shown to reduce hepatic blood flow. Halothane causes the greatest reduction, and the use of desflurane has been shown to have hepatic effects similar to those of isoflurane. A rise in serum glutathione-*S*-transferase (GST) level indicates a decrease in splanchnic circulation, which causes a transient reduction in the oxygenation of hepatocytes. Anesthesia with desflurane has demonstrated that liver function is well preserved.[17] Sevoflurane undergoes hepatic biotransformation, producing organic and inorganic fluoride ion. In human subjects, levels of serum inorganic fluoride ion secondary to sevoflurane metabolism are generally below nephrotoxic levels. Prolonged use of higher concentrations, however, may lead to problematic levels. Anesthetic agents may reduce hepatic blood flow by 30% to 50% after induction. Animal data suggest, however, that isoflurane (along with desflurane and sevoflurane, which are believed to be similar) causes less perturbation in hepatic arterial blood flow than other inhaled anesthetic agents and therefore is preferred for patients with liver disease. Studies continue with sevoflurane to determine the influence of biotransformation on renal and hepatic function, but no significant clinical toxicity has yet been reported and they appear to be safe in clinical use.[18,19]

In developed countries, clinical use of halothane as a volatile anesthetic agent is being superseded by the newer low-solubility agents desflurane and sevoflurane. Halothane, however, is still

TABLE 30-2 Clinical Significance of Liver Biochemical Tests

Test (Normal Range*)	Basis of Abnormality	Associated Liver Diseases	Extrahepatic Origin
Aminotransferases			
ALT (10-55 units/L) AST (10-40 units/L)	Leakage from damaged tissue	*Mild to moderate elevations:* Many types of liver disease *Marked elevations:* Hepatitis (viral, toxic, autoimmune, and ischemic) AST/ALT greater than 2 suggests alcoholic liver disease or cirrhosis of any etiology	ALT more specific than AST for hepatic injury AST nonspecific: can originate from skeletal muscle, red blood cell, kidney, pancreas, brain, and myocardium
AP (45-115 units/L)	Overproduction and leakage into serum	*Moderate elevations:* Many types of liver disease *Marked elevations:* Extrahepatic and intrahepatic cholestasis, diffuse infiltrating disease (e.g. tumor, MAC), rarely alcoholic hepatitis	Bone growth or disease (e.g., tumor, fracture, Paget disease) placenta, intestine, and tumors
GGTP (0-30 units/L)	Overproduction and leakage into serum	Same as for AP; induced by ethanol and drugs GGTP/AP greater than 2.5 suggests alcoholic liver disease	Kidney, spleen, pancreas, heart, lung, and brain
5′ Nucleotidase (0-11 units/L)	Overproduction and leakage into serum	Same as for AP	Found in many tissues, but serum elevation is relatively specific for liver disease
Bilirubin (0.0-1.0 mg/dL)	Decreased hepatic clearance	*Moderate elevations:* Many types of liver disease *Marked elevations:* Extrahepatic and intrahepatic bile duct obstruction; viral, alcoholic, or drug-induced hepatitis; inherited hyperbilirubinemia	Increased breakdown of hemoglobin (resulting from hemolysis, disordered erythropoiesis, resorption of hematoma) or myoglobin (resulting from muscle injury)
Prothrombin time (PT) (10.9-12.5 seconds) (international normalized ratio [INR]: 0.9-1.2)	Decreased synthetic capacity	Acute or chronic liver failure (prolonged PT unresponsive to vitamin K) Biliary obstruction (prolonged PT usually responsive to vitamin K administration)	Vitamin K deficiency (secondary to malabsorption, malnutrition, antibiotics, consumptive coagulopathy
Albumin (3.5-5.0 g/dL)	Decreased synthesis; increased catabolism	Chronic liver failure	Decreased in nephritic syndrome, protein-losing enteropathy, vascular leak, malnutrition, malignancy, infections, and inflammatory states

*The normal values tabulated are for adult men and will vary with the methodology used in testing.
ALT, Alanine aminotransferase; *AP*, alkaline phosphatase; *AST*, aspartate aminotransferase; *GGTP*, gamma glutamyl transpeptidase; *MAC*, *mycobacterium avium* complex.

TABLE 30-3 Grading Liver Function Using the Child-Pugh Classification System

	POINTS		
Feature	**1**	**2**	**3**
Albumin	> 3.5 g/dL	2.8-3.5 g/dL	< 2.8 g/dL
Bilirubin	< 2 mg/dL	2-3 mg/dL	> 3 mg/dL
Prolongation Prothrombin time (INR)	< 4 sec (< 1.7)	4-6 sec (1.7-2.3)	> 6 sec (> 2.3)
Ascites Encephalopathy	None None	Controlled Minimal (1 and 2)	Refractory Advanced (3 and 4)

The Child-Pugh class is calculated by adding the points based on the five features: class A = 5 or 6; class B = 7-9; class C = 10 and higher. The classes indicate severity of liver dysfunction: class A is associated with a good prognosis, and class C is associated with limited life expectancy.
INR, International normalized ratio.

in use in some countries and remains on the 2011 World Health Organization Model List of Essential Medicines, which is a list of minimum medical needs for a basic health care system. Continued awareness of the potentially deleterious effect of halothane on hepatic function is therefore justified.

Halothane administration is associated with two types of postoperative liver injury. Minor injury in 10% to 30% of patients may result in elevations in alanine aminotransferase (ALT) levels during postoperative days 1 through 10. Risk of hepatotoxicity is higher after repeat exposure to halothane. Major injury involves halothane-induced hepatotoxicity, which is a severe hepatic reaction with elements of autoimmune allergy. The phenomenon of halothane-induced liver damage has been termed *halothane hepatitis* due to a similar clinical presentation. Clinical features of halothane hepatitis are listed in Box 30-3. Hepatic necrosis may be seen histologically, and the case fatality rate ranged from 14% to 71% (before liver transplant was an option). Evidence for the role of hypersensitivity is found in the increased susceptibility and shortened latency after repeat exposure, the hallmark symptoms and signs of drug allergy. Risk factors for halothane hepatitis are listed in Box 30-4. An estimated 1 in 10,000 patients develops postoperative jaundice after halothane exposure. In this population, a viral source of infection is more likely to be the cause—for instance, as a complication of intraoperative blood transfusion.

Opioid Effects

Spasm of the Oddi sphincter may cause biliary colic, or it may cause a false-positive result on intraoperative cholangiography. All opioids have been implicated in causing spasm of the Oddi sphincter, with a resultant increase in biliary pressure in relation

BOX 30-3

Clinicopathologic Features of Halothane Hepatitis

- Estimated incidence
  - *After first exposure:* 0.3 to 1.5 per 10,000
  - *After multiple exposures:* 10 to 15 per 10,000
- Female-to-male ratio 2:1
- Latent period to first symptom
  - *After first exposure:* 6 days (11 days to jaundice)
  - *After multiple exposures:* 3 days (6 days to jaundice)
- Jaundice as presenting symptom in 25% (range of serum bilirubin: 3-50 mg/L)
- Fever in 75% (precedes jaundice in 75%); chills in 30%
- Rash in 10%
- Myalgias in 20%
- Ascites, renal failure, and/or gastrointestinal hemorrhage in 20%-30%
- Eosinophilia in 20%-60%
- Serum ALT and AST levels: 25-250 x ULN
- Serum alkaline phosphatase level: 1-3 x ULN
- Histologic features:
  - Zone 3 massive hepatic necrosis in 30%; submassive necrosis in 70% (autopsy series)
  - Inflammation usually less marked than in viral hepatitis
  - Eosinophilic infiltrate in 20%
  - Granulomatous hepatitis occasionally
- Course and outcome:
  - Mortality rate (pretransplantation era): 10%-80%
  - Symptoms can resolve within 5-14 days
  - Full recovery can take 12 weeks or longer
  - Chronic hepatitis not well documented
- Adverse prognostic findings:
  - Age >40 years
  - Obesity
  - Short duration to the onset of jaundice
  - Serum bilirubin level >20 mg/dL
  - Coagulopathy

From Lewis JH. Liver disease caused by anesthetics, toxins, and herbal preparations. In: Feldman M, et al, eds. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*. 9th ed. Philadelphia: Saunders; 2010:1448.
ALT, Alanine aminotransferase; *AST,* aspartate aminotransferase; *ULN,* upper limit of normal.

BOX 30-4

Risk Factors for Halothane Hepatitis

- Older age (>40 years)
- Female gender
- Two or more exposures (documented in 80%-90% of cases)
- Obesity
- Familial predisposition
- Induction of CYP2E1 by phenobarbital, alcohol, or isoniazid

From Lewis JH. Liver disease caused by anesthetics, toxins, and herbal preparations. In: Feldman M, et al, eds. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*. 9th ed. Philadelphia: Saunders; 2010:1448.
CYP2E1, Cytochrome P450 2E1.

to potency. The cause of the spasm is unclear, but occurrence may be reduced with judicious titration. Spasm is low even when a fentanyl-based anesthetic is used. The treatment of suspected spasm of the Oddi sphincter involves administration of naloxone or nalbuphine. Atropine or glycopyrrolate, glucagon, and nitroglycerin also have been shown to be effective.

TABLE 30-4 Reported Surgery Risk in Patients with Liver Disease

Liver Disease	Type of Surgery	Mortality	Prognostic Factors
Cirrhosis	Nonlaparoscopic biliary surgery	20%	Ascites, prothrombin time, albumin
	Peptic ulcer surgery	54%	Prothrombin time, systolic blood pressure, hemoglobin
	Umbilical herniorrhaphy	13%	Urgent surgery
	Colectomy	24%	Hepatic encephalopathy, ascites, albumin, hemoglobin
	Abdominal surgery for trauma	47%	
	Emergency abdominal surgery	57%	Child-Pugh class, urgent surgery
	Laparoscopic cholecystectomy	0.9%-6%	
	Emergency cardiac surgery	80%	Child-Pugh class
	Elective cardiac surgery	3%-46%	Child-Pugh class
	Knee replacement	0%	
	TURP	6.7%	
Chronic hepatitis	Various types	0%	
Hepatitis C	Laparoscopic cholecystectomy	0%	
Acute hepatitis	Exploratory laparotomy	100%	
Obstructive jaundice	Abdominal surgery	5%-60%	Hemoglobin, bilirubin, malignancy

TURP, Transurethral resection of the prostate.

Anesthesia-Related Activity: Mechanical Ventilation

The sequelae of mechanical ventilation have been implicated as a contributing factor in a reduction of hepatic blood flow. Positive pressure ventilation can result in airway pressures that adversely affect venous delivery to the right atrium. Increased airway pressures also result in reduced cardiac output,[20] with a consequent reduction in hepatic blood flow. Positive end-expiratory pressure further exacerbates this condition. Impairment in hepatic blood flow under these conditions may result from increased hepatic venous pressure from increased intrathoracic pressure and from increased reflex sympathetic tone caused by reduced cardiac output. Hypercapnia and acidosis have vasodilatory effects on the hepatic circulation that result in increased blood flow, whereas hypocapnia and alkalosis exert vasoconstricting effects that result in decreased flow. The interplay of various intraoperative variables (e.g., surgical site, ventilatory mode, direct and indirect effects of anesthetics used, physiologic responses to intraoperative events) influences the degree of variation in hepatic blood flow.

Site of Surgery

Surgical site, particularly intraabdominal, also has been implicated as a cause of decreased hepatic blood flow (see Table 30-4 for reported surgery risk in patients with liver disease). Traction

TABLE 30-5 Five Types of Acute Viral Hepatitis

Hepatitis Virus	Size (nm)	Genome	Route of Transmission	Incubation Period (Days)	Fatality Rate	Chronic Rate	Antibody
A	27	RNA	Fecal-oral	15-45 (mean = 25)	1%	None	Anti-HAV
B	45	DNA	Parenteral Sexual	30-180 (mean = 75)	1%	2%-7%	Anti-HBs Anti-HBc Anti-HBe
C	60	RNA	Parenteral	15-150 (mean = 50)	<0.1%	70%-85%	Anti-HCV
D (delta)	40	RNA	Parenteral Sexual	30-150	2%-10%	2%-7% 50%	Anti-HDV
E	32	RNA	Fecal-oral	30-60	1%	None	Anti-HEV

From Goldman L, Schafer AI, eds. *Goldman's Cecil Medicine*. 24th ed. Philadelphia: Saunders; 2012.
Anti-HDV, Hepatitis D virus antibody; *Anti-HEV*, hepatitis E virus antibody; *HAV*, hepatitis A virus; *HBc*, hepatitis B core; *HBe*, hepatitis B e-antigen; *HBs*, hepatitis B surface; *HCV*, hepatitis C virus.

on the abdominal viscera may cause reflex dilation of splanchnic capacitance vessels and thereby lower hepatic blood flow.

Additional factors that may contribute to decreased hepatic blood flow intraoperatively include hypotension, hemorrhage, vasoactive drugs, and pneumoperitoneum during laparoscopic surgery.[21]

Diseases of the Liver

Signs and symptoms indicating liver disease vary widely depending on the etiology of the underlying pathologic process. Decline in liver function may be acute, related to drug toxicity or infection, or it may follow a chronic subclinical course. The following discussion focuses on the more commonly encountered diseases of the liver and offers guided clinical anesthetic implications.

Acute Hepatitis

Acute hepatitis presents a variable clinical picture. Manifestations may extend from mild inflammatory increases in serum transaminase levels to fulminant hepatic failure. The cause of this syndrome is usually exposure to an infectious virus. Other causes include exposure to hepatotoxic substances and adverse drug reactions.

Viral Hepatitis

Hepatitis is a generic term that means liver inflammation. Hepatitis may be caused by several factors (e.g., toxins, alcohol, medications, viral or bacterial infections, autoimmune diseases), and viral hepatitis is the leading cause of liver cancer and the most common reason for transplantation.[22]

Although several types of hepatitis viruses are known to cause illness, typically only hepatitis A, B, and C (infections caused by the hepatitis A virus [HAV], hepatitis B virus [HBV], and hepatitis C virus [HCV], respectively) affect persons living in the United States.[22] Hepatitis D requires co-infection with HBV; hepatitis E virus (HEV) diagnosis is made by exclusion after travel to an endemic area (e.g., South/Central America or Southeast Asia). Hepatitis A and E are transmitted by the oral-fecal route, and hepatitis B, C, and D are transmitted by contact with body fluids and physical contact with disrupted cutaneous barriers.

The common clinical course of viral hepatitis begins with a 1- to 2-week prodromal period, the signs and symptoms of which include fever, malaise, and nausea and vomiting. Progression to jaundice typically occurs, with resolution within 2 to 12 weeks. However, serum transaminase levels often remain increased for up to 4 months. If hepatitis B or C is the cause, the clinical course is often more prolonged and complicated. Cholestasis may manifest in certain cases. Fulminant hepatic necrosis in certain individuals is also possible. Table 30-5 lists the major characteristics of hepatitis types A, B, C, D, and E.

Drug-Induced Hepatitis

Drug-related injury to the liver results from an idiosyncratic reaction to a substance or an overdose resulting in toxicity. For idiosyncratic reactions, genetic predisposition is presumed to be the most critical determinant. Important risk factors include age, gender, exposure to other substances, a history or family history of previous drug reaction, other risk factors for liver disease, and concomitant medical conditions.[23] Factors related to the risk of liver injury are summarized in Table 30-6.

Alcoholic hepatitis is probably the most common form of drug-induced hepatitis and results in fatty infiltration of the liver (causing hepatomegaly), with impairment in hepatic oxidation of fatty acids, lipoprotein synthesis and secretion, and fatty acid esterification.[6]

Chronic Hepatitis

Chronic hepatitis occurs in 1% to 10% of acute hepatitis B infections and in 10% to 40% of hepatitis C infections,[6] but does not occur in hepatitis A infections.

Because chronic persistent hepatitis is limited to portal areas and is relatively benign, hepatic cellular integrity is preserved, and progression to cirrhosis is rare. Chronic lobular hepatitis involves recurrent exacerbations of acute inflammation; as in persistent hepatitis, progression to cirrhosis is rare.

Chronic active hepatitis is progressive and results in hepatocyte destruction, cirrhosis, and progressive deterioration of hepatic function. Hepatic failure and death from chronic hepatitis is marked by clinical manifestations such as multiorgan system failure (e.g., hepatorenal syndrome), encephalopathy, and hemorrhage from esophageal varices. Exposure to certain drugs (e.g., methyldopa, isoniazid, and nitrofurantoin) and autoimmune disorders (e.g., systemic lupus erythematosus) are potential causative factors implicated in hepatic failure, though hepatitis B or C are more typical.

Other symptoms present in chronic hepatitis include marked fatigue and jaundice; thrombocytopenia, glomerulonephritis, myocarditis, arthritis, and neuropathy also may be present. Plasma albumin levels are usually decreased related to synthetic dysfunction and PT is prolonged.

Anesthetic Management for Patients with Hepatitis

Evidence from studies indicates that *mild* chronic hepatitis confers no additional risk of surgical morbidity or mortality during laparoscopic cholecystectomy.[24] Surgical outcomes in patients with acute hepatitis are less well studied, and recommendations suggest that elective surgery should be postponed until normalization of biochemical profiles. Existing studies are many

TABLE 30-6 Factors Influencing the Risk of Liver Diseases Caused by Drugs

Factor	Examples of Drugs Affected	Influence
Age	Isoniazid, nitrofurantoin, halothane	Age greater than 60 years: increased frequency, increased severity
	Valproic acid, salicylates	More common in children
Gender	Halothane, minocycline, nitrofurantoin	More common in women, especially with chronic hepatitis
	Amoxicillin/clavulanate acid, azathioprine	More common in men
Dose	Acetaminophen, aspirin; some herbal medicines	Blood levels are directly related to the risk of hepatotoxicity
	Tetracycline, tacrine, oxypenicillins	Idiosyncratic reactions, but partial relationship to dose
	Methotrexate, vitamin A	Total dose, dosing frequency, and duration of exposure are related to the risk of hepatic fibrosis
Genetic factors	Halothane, phenytoin, sulfonamides	Multiple cases in families
	Amoxicillin/clavulanate acid	Strong HLA association
	Valproic acid	Familial cases, association with mitochondrial enzyme deficiencies
History of other drug reactions	Isoflurane, halothane, enflurane	Instances of cross-sensitivity have been reported among members of each drug class but are rare
	Erythromycins	
	Diclofenac, ibuprofen, tiaprofenic acid	
	Sulfonamides, COX-2 inhibitors	
Other drugs	Acetaminophen	Isoniazid, zidovudine, and phenytoin lower dose threshold and increase severity of hepatotoxicity
	Valproic acid	Other antiepileptics increase risk of hepatotoxicity
	Anticancer drugs	Interactive vascular toxicity
Excessive alcohol use	Acetaminophen hepatotoxicity	Lowered dose threshold, poorer outcome
	Isoniazid, methotrexate	Increased risk of liver injury, hepatic fibrosis
Nutritional status:		
Obesity	Halothane, tamoxifen, methotrexate	Increased risk of liver injury, hepatic fibrosis
Fasting	Acetaminophen	Increased risk of hepatotoxicity
Preexisting liver disease	Hycanthone, pemoline	Increased risk of liver injury
	Antituberculosis drugs, ibuprofen	Increased risk of liver injury with chronic hepatitis B and C
Other diseases/conditions:		
Diabetes mellitus	Methotrexate	Increased risk of hepatic fibrosis
HIV infection/AIDS	Sulfonamides	Increased risk of hypersensitivity
Renal failure	Tetracycline, methotrexate	Increased risk of liver injury, hepatic fibrosis
Organ transplantation	Azathioprine, thioguanine, busulfan	Increased risk of vascular toxicity

From Teoh NC, et al. Liver disease caused by drugs. In: Feldman M, et al, eds. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*. 9th ed. Philadelphia: Saunders; 2010:1416.
AIDS, Acquired immunodeficiency syndrome; *COX-2*, cyclooxygenase-2; *HIV*, human immunodeficiency virus; *HLA*, human leukocyte antigen.

decades old and the statistical risks associated may not reflect improvements in either surgical technique or anesthetic management. Anesthetic management recommendations are found in Box 30-5.

Operative procedures performed in patients with alcohol intoxication are likely to be associated with increased perioperative complications, and anesthetic management must be well planned (Box 30-6). Surgery performed in those undergoing alcohol withdrawal is associated with an increased mortality rate. If surgery is of urgent or emergent nature, attention must be paid to managing comorbidities with a focus on risk reduction and symptom management.

Cirrhosis

The term *cirrhosis* derives from the Greek word that means yellowish or tawny and describes the coloration of the diseased liver. Cirrhosis is defined as the histologic development of regenerative nodules surrounded by fibrous bands in response to chronic liver injury, which leads to portal hypertension and end-stage liver disease.[25] Cirrhosis may be caused by a variety of diseases (Box 30-7), but the resultant anatomic alterations secondary to hepatocyte necrosis are the primary cause of deterioration that occurs in liver function. Over time, the liver parenchyma is replaced by fibrous and nodular tissue, which distorts, compresses, and obstructs normal portal venous blood flow. Portal hypertension develops and impairs the ability of the liver to perform various metabolic and synthetic processes.

Cirrhosis characteristics are presented in Table 30-7. Obstructive engorgement of vessels within the portal system ultimately results in transmission of increasing retrograde pressure within the splanchnic circulation. The progressive reversal of portal venous blood flow results in esophageal varices and splenomegaly. As portal hypertension persists, physical changes can be seen systemically (Figure 30-3).

The development of esophageal varices places the patient at risk for spontaneous, severe, upper-gastrointestinal hemorrhage. Development of ascites (related to altered intravascular osmolarity) results in fluid retention and impairment of the renin-angiotensin system. Subsequent reduction in renal perfusion progresses to eventual renal failure concomitant with hepatic failure (hepatorenal syndrome). Hepatorenal syndrome is a severe complication of advanced liver cirrhosis, in patients with ascites and marked

BOX 30-5

Anesthetic Management of the Patient with Acute Hepatitis

Preserve hepatic blood flow:
- Use isoflurane or desflurane and avoid halothane
- Maintain normocapnia
- Avoid PEEP if possible
- Provide adequate/liberal intravenous hydration
- Consider regional anesthesia if coagulation and procedure are acceptable

Avoid medications with potential for hepatotoxicity or inhibition of CYP450:
- Halothane
- Acetaminophen
- Sulfonamides
- Tetracycline
- Penicillin
- Amiodarone

Thoughtful titration of neuromuscular blocking agents may be prolonged in patients with liver disease because of:
- Reduced pseudocholinesterase activity
- Decreased biliary excretion
- Larger volume of distribution

PEEP, Positive end-expiratory pressure.

BOX 30-6

Management Recommendations for the Acutely Intoxicated Patient

- Anesthetic requirement is reduced
  - Acute intoxication reduces MAC
- Aspiration precautions are needed
  - Full stomach, alcohol-related impaired pharyngeal reflexes
- Alcohol increases GABA receptor activity
  - Enhanced effects of benzodiazepines, barbiturates, propofol, other CNS depressants
- Alcohol inhibits NMDA receptors
  - Reduces CNS excitability

CNS, Central nervous system; *GABA*, gamma-aminobutyric acid; *MAC*, maximum allowable concentration; *NMDA*, *N*-methyl-D-aspartate.

BOX 30-7

Causes of Cirrhosis

- Alcohol abuse
- α_1-antitrypsin deficiency
- Biliary obstruction
- Chronic hepatitis
- Hemochromatosis
- Right-sided heart failure
- Wilson disease

TABLE 30-7 Laboratory Tests and Findings in Cirrhosis

Laboratory Finding	Description	Cause
AST/ALT	Normal or modest increase	Leakage from damaged hepatocytes
Bilirubin	Increased (important predictor of mortality)	Cholestasis, systemic inflammation
Albumin	Decreased in advanced cirrhosis	Decreased production; sequestered in ascites
Prothrombin time	Decreased in advanced cirrhosis	Decreased hepatic production of factor V/VII
Sodium imbalance	Hyponatremia	Inability to excrete free water (increased ADH)
Anemia	Low hemoglobin Low red blood cell count	Folate deficiency, hypersplenism, varices
Thrombocytes	Thrombocytopenia	Hypersplenism, decreased hepatic thrombopoietin production

AST/ALT, aspartate aminotransferase/alanine aminotransferase ratio; *ADH*, antidiuretic hormone.

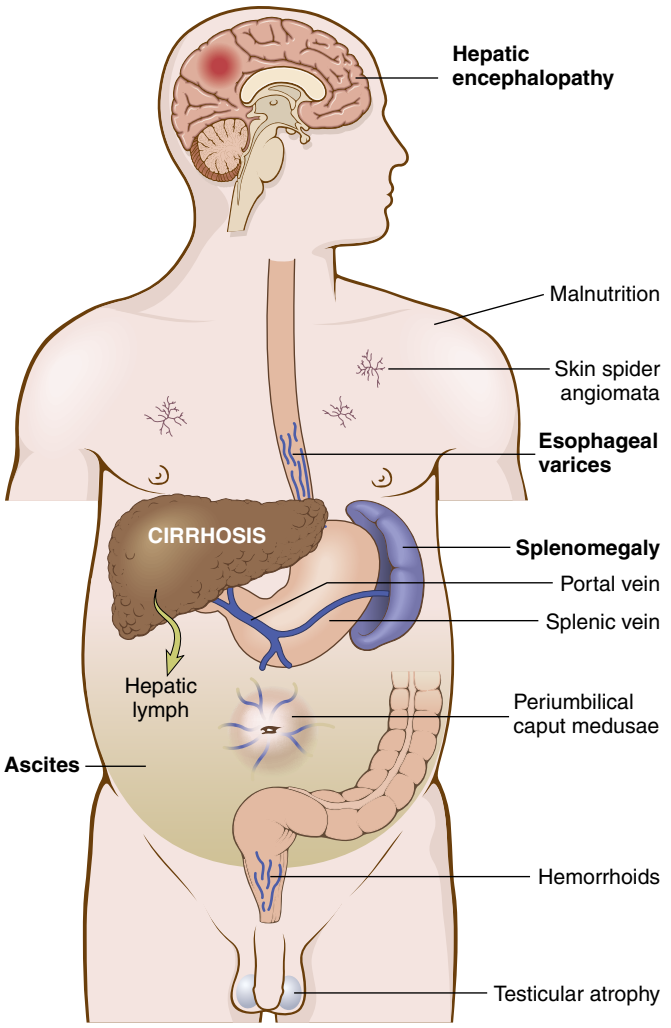

FIGURE 30-3 The major clinical consequences of portal hypertension in the setting of cirrhosis, shown for the male. In women, oligomenorrhea, amenorrhea, and sterility are frequent, as a result of hypogonadism. (From Kumar V, Abbas AK, Aster J. *Robbins Basic Pathology*. 9th ed. Philadelphia: Saunders; 2013:609.)

BOX 30-8

Anesthetic Preparation and Management in Cirrhosis

Preserve hepatic blood flow.
Avoid halothane (isoflurane is the best studied alternative; better preserves flow).
Consider regional anesthesia if procedure and coagulation allow.
- Maintain normocapnia.
- Avoid PEEP if possible.
- Provide generous volume maintenance.

Avoid medications with situational potential hepatotoxicity when possible. Examples:
- Acetaminophen, particularly in the alcoholic patient
- Sulfonamides, tetracycline, and penicillins
- Amiodarone

Anticipate presence, development, or abnormalities of:

Coagulation
- Attempt to correct prothrombin time to within 2 seconds of normal.
- Consider cryoprecipitate if fresh frozen plasma is ineffective or fibrinogen abnormality exists.
- Correct thrombocytopenia approximately for procedure.
- Anticipate higher than normal blood loss for procedure.

Hemodynamics
- Anticipate relative hypovolemia, worsened by treatment of ascites.
- Assess for presence of high cardiac output, low peripheral resistance.
- Suspect portal hypertension and/or variceal bleeding, even without history.
- Anticipate depressed response to inotropes and vasopressors.
- Consider invasive monitoring.

Pharmacokinetics and Pharmacodynamics
- Altered volume of distribution may occur.
  - Decreased serum albumin, increased gamma globulins
  - Intravascular volume unpredictable, especially with ascites treatment
- Portosystemic shunted blood bypasses liver
  - Drugs highly extracted by liver especially affected
  - Increased sensitivity to sedative medications may be present.

From Dhillon A, Steadman RH. Liver disease. In: Fleisher LA. *Anesthesia and Uncommon Diseases*. 6th ed. Philadelphia: Saunders; 2012:198-199.

circulatory dysfunction. It is clearly established that it has a functional nature, and that it is related to intense renal vasoconstriction.[26] Prognosis is very poor once disease has progressed to this stage. Further failure of the liver to clear nitrogenous compounds (ammonia) from the blood contributes to the development of progressive mental-status changes (encephalopathy), ultimately leading to coma and death if untreated. Anesthetic preparation and management in cirrhosis is given in Box 30-8.

Perioperative Considerations in Liver Disease

Preoperative Assessment

Preoperative assessment of patients with hepatic dysfunction necessitates the collection of diagnostic laboratory markers and physical characteristics indicative of the type and severity of liver disease present. Acute derangements in hepatic function should be identified and the risks of surgery must be weighed against the risk of postponing the planned procedure until the physical status of the patient is improved. Urgent or emergent surgery may preclude a rigorous diagnostic workup, so it is incumbent on the anesthetist to focus on the implications of the disease process and prioritize care to minimize further physiologic insult.

TABLE 30-8 MELD Score Prediction of 90-Day Mortality

MELD Score	Mortality
Greater than 40	71.3%
30-39	52.6%
20-29	19.6%
10-19	6%
Less than 9	1.9%

MELD, Model for end-stage liver disease.

The Model for End-stage Liver Disease (MELD) score and the Child-Pugh score have been reported to be correlated with postoperative morbidity and mortality in patients with end-stage liver disease.[27] The Child-Pugh score was described earlier (refer to Table 30-3). MELD is a scoring system that assesses the severity of chronic liver disease and is useful in prioritizing recipients for liver transplant by predicting outcome based on the calculated score. MELD uses the patient's values for serum bilirubin, serum creatinine, and the INR for prothrombin time to predict survival (interpretation of MELD score is given in Table 30-8).

$$\text{MELD} = 3.78\,[\text{Ln serum bilirubin (mg/dL)}] + 11.2\,[\text{Ln INR}] + 9.57\,[\text{Ln serum creatinine (mg/dL)}] + 6.43$$

The MELD calculation is more cumbersome than Child-Pugh, and online calculators are available (e.g., http://www.mayoclinic.org/meld/).

MELD scores have largely replaced the older Child-Pugh scoring system, although systemic reviews comparing MELD and Child-Pugh are inconclusive, particularly in nontransplant settings.[28] Multivariate analysis of a 2007 study of 772 patients with cirrhosis undergoing major digestive, orthopedic, or cardiovascular surgery (586 patients underwent gastrointestinal surgery) revealed that the MELD score, American Society of Anesthesiologists' physical status, and age were predictors of mortality.[27]

The existence of jaundice, prolonged prothrombin time, ascites, encephalopathy, hypoalbuminemia, portal hypertension, renal insufficiency, hyponatremia, infection, and anemia have been proposed as risk factors.[29] In patients with cirrhosis undergoing surgery, preoperative assessment is crucial. The high risk of mortality and morbidity can be reduced by addressing coagulopathy, ascites, renal dysfunction, hyponatremia, hepatic encephalopathy, malnutrition, pulmonary conditions, cardiac conditions, anemia, and administering antibiotic prophylaxis.[29]

Past or current jaundice, ascites, hepatitis, blood transfusion, or substance abuse can be relevant information obtained in the patient history and physical examination. Reviewing previous anesthetic records also may provide guidance for developing an anesthetic plan. Physical signs, such as petechiae, jaundice, ascites, dependent edema, altered mental status, and asterixis (tremor of the wrist indicative of hepatic encephalopathy), suggest the presence of significant liver disease. Laboratory assessment may include the following:
- Albumin (normal, 3.5 to 5 g/dL)
- Bilirubin
- PT/INR
- Creatinine

- Serum liver enzyme levels: alanine transaminase (ALT) and aspartate aminotransferase (AST), alkaline phosphatase, lactic dehydrogenase, γ-glutamyl transpeptidase
- Complete blood count
- Serum electrolyte and glucose levels
- Blood type and screen or crossmatch based on planned surgery and patient condition

Effects of Hepatic Dysfunction on Other Organ Systems

Cardiovascular Considerations

Cardiovascular complications of cirrhosis include cardiac dysfunction and abnormalities in the central, splanchnic, and peripheral circulation and (hemodynamic) changes caused by humoral and nervous dysregulation.[30] Increased levels of endogenous vasodilators such as vasoactive intestinal peptide, ferritin glucagon, and others result in a hyperdynamic circulatory state. Cardiovascular changes associated with liver disease include the following:

- Increased cardiac output
- Decreased systemic vascular resistance
- Decreased arterial blood pressure
- Systemic collateral circulation
- Arteriovenous shunting
- Portal hypertension
- Esophageal varices
- Cardiomyopathy
- Congestive heart failure

Fluid Balance and Renal Considerations

Severe hepatic disease confers a derangement in fluid balance, manifesting as ascites and edema. Ascites is the most common complication of cirrhosis and is associated with increased risk of infections, renal failure, and poor long-term outcome.[31] Absolute intravascular volume typically may be described as increased, but therapeutic paracentesis, diuretic therapy, and arteriovenous shunting create a relative hypovolemia. Severe hepatic disease (e.g., advanced cirrhosis) may result in impairment of compensatory mechanisms that initiate displacement of blood from the hepatic vascular reservoir into systemic circulation in response to sympathetic stimulation or hemorrhage.

Perioperative concerns focus on intravascular volume and electrolyte imbalances. Diuretic therapy should be instituted in the presence of volume overload with attention to maintaining normotension and electrolyte balance. Perioperative preservation of adequate renal perfusion is of the utmost importance. Water restriction, controlled isotonic intravenous fluid administration, and potassium replacement may be necessary components of the preoperative plan of fluid therapy.

Fluid and electrolyte disturbances associated with liver disease include the following:

- Hypoalbuminemia
- Sodium retention
- Progressive decline in renal function
- Decreased free water clearance
- Dilutional hyponatremia
- Hypokalemia

Intraabdominal ascites exerts a profound influence on several organ systems, including the renal system. As cirrhosis progressively worsens, excessive hydrostatic pressure develops within lymphatic and hepatic venous systems. This phenomenon, coupled with impaired albumin synthesis, produces decreased plasma oncotic pressure within the liver vasculature and an exudative process results. Protein-rich fluid accumulates within the peritoneum, resulting in electrolyte abnormalities. The misplacement of fluids within peritoneum establishes an osmotic gradient leading to a relative intravascular hypovolemia and sodium retention.

TABLE 30-9 Summary of Current Pharmacologic Treatment Options for HRS

Treatment Mechanism	Pharmacologic Option
Vasoconstriction of splanchnic circulation	Octreotide Midodrine Albumin 20%
	Ornipressin Albumin 20%
	Terlipressin Albumin 20%
Renal vasodilation	Misoprostol Adenosin-1 receptor antagonist
Selective angiotensin II type I receptor antagonist	Losartan

Adapted from Kashani A, et al. Fluid retention in cirrhosis: pathophysiology and management. *QJ Med.* 2008;101:71-85.
HRS, Hepatorenal syndrome.

Hepatorenal syndrome (HRS) is a clinical condition of renal failure that occurs in patients with chronic liver disease, advanced hepatic failure, and portal hypertension; it is characterized by impaired renal function and marked abnormalities in arterial circulation and in the activity of vasoactive systems.[32] Hepatorenal syndrome may occur as a consequence of gastrointestinal hemorrhage, sepsis, or surgery or as a result of aggressive diuretic therapy, all of which place patients at risk for derangements in renal perfusion. Signs include progressive ascites, azotemia, oliguria, and eventually multisystem organ failure. Hepatic transplantation remains the only definitive treatment for hepatorenal syndrome, and supportive therapy must be instituted until an organ match is made. The aim of most HRS therapy is to increase renal blood flow through renal vasodilation and vasoconstriction of splanchnic circulation.[32] Current treatment options for hepatorenal syndrome are listed in Table 30-9.

Hematologic Considerations

Anemia is commonly encountered in advanced hepatic disease. The reduction in red blood cells is due to hemolysis, folate deficiency, hemorrhage, and bone marrow suppression. Multiple factors can contribute to the development of thrombocytopenia, including splenic platelet sequestration, bone marrow suppression by chronic hepatitis C infection, and antiviral treatment with interferon-based therapy.[33] Reductions in the level or activity of the hematopoietic growth factor thrombopoietin (TPO) also may play a role. Failure of hepatic synthetic processes results in clotting-factor deficiencies, decreased blood viscosity, and enhanced fibrinolysis resulting from decreased clearance of fibrinolytic factors.

In the setting of hepatic dysfunction, excessive blood transfusion may exacerbate encephalopathy, owing to the breakdown of red blood cells and the subsequent increase of protein-rich by-products in the plasma—by-products ordinarily metabolized by hepatocytes. When indicated, FFP, platelet, and cryoprecipitate transfusion should be undertaken to correct coagulation deficiencies before surgery.[34]

Respiratory Considerations

Decline in pulmonary function can be predicted in patients with severe hepatic disease. Arterial hypoxemia is common in the

context of hepatic disease; it is often multifactorial (e.g., ascites, hepatic hydrothorax, and chronic obstructive pulmonary disease in patients with alcoholism).[35] The hepatopulmonary syndrome (HPS) is defined as the triad of liver disease, arterial deoxygenation, and widespread pulmonary vasodilation.[36] HPS can, however, appear in patients with acute[37] and chronic noncirrhotic hepatitis.[38] The exact pathogenesis of HPS is being explored, but it is reported in 15% to 20% of patients with cirrhosis being evaluated for orthotopic (living related donor) liver transplantation. One of the characteristics of HPS is intrapulmonary vascular dilation. The intrapulmonary vascular dilation significantly affects pulmonary gas exchange, and consequently leads to hypoxia and raised mortality of cirrhotic patients.[39] Preoperative focus is on baseline measurement of oxygen tension or saturation and improvement of reversible pulmonary dysfunction (e.g., elective thoracentesis/paracentesis). Preoperative sedatives and opioids should be carefully considered or omitted based on underlying pathology and the patient's current physical status.

Central Nervous System Considerations

Hepatic encephalopathy is a chronically debilitating complication of hepatic cirrhosis and encompasses a wide spectrum of potentially reversible neuropsychiatric abnormalities seen in patients with liver dysfunction. Neurologic impairment stems from various metabolic abnormalities that are a direct result of the failing liver. Inability to clear neurotoxins (e.g., ammonia, short-chain fatty acids, mercaptans, manganese) derived in the gut results in a cascade of systemic maladies, including alterations in mental status that range from subtle personality change to coma. Ammonia is produced in the gastrointestinal tract by bacterial degradation of amines, amino acids, purines, and urea. Once formed, ammonia is detoxified by hepatocytes in the liver. In hepatic failure, there is a decrease in functioning hepatocytes. The alterations in hepatic portal flow (shunting) that accompanies cirrhosis permit entry of ammonia into the systemic circulation. Ammonia, for example, causes neurotransmitter abnormalities and induces injury to astrocytes that is partially mediated by oxidative stress. These disturbances lead to astrocyte swelling and brain edema, which appear to be involved in the pathogenesis of neurologic manifestations.[40] It is noteworthy that the mechanism of encephalopathy cannot fully be attributed to ammonia; some patients with encephalopathy have normal ammonia levels, yet others with elevated ammonia levels have no encephalopathic symptoms. Research into the pathogenesis of hepatic encephalopathy is ongoing, but therapy continues to focus on pharmacologic reduction of ammonia levels with nonabsorbable disaccharides (e.g., lactulose) and antimicrobial agents (e.g., neomycin, rifaximin) that reduce bacterial production of ammonia and other bacteria-derived toxins through suppression of intestinal flora.[41] Given the presence, or potential worsening, of altered mental status, benzodiazepine and other sedatives should be avoided when possible.

Intraoperative Anesthetic Considerations

Monitoring

After thorough preoperative evaluation, anesthetic management of patients with liver disease requires consideration of the underlying pathophysiology and the attendant alterations in pharmacokinetics/pharmacodynamics for each medication administered.

Use of routine intraoperative monitoring may be sufficient for patients with mild hepatic dysfunction undergoing minor surgery. As previously discussed, morbidity and mortality is higher in patients with advanced liver disease. Regarding electrocardiography (ECG) monitoring, a five-cable ECG lead system is preferred over a three-cable ECG system in such patients in that it allows monitoring of a true chest lead. With the former, only a modified chest lead can be used. The ECG lead recognized as being most sensitive in detecting early evidence of ischemia is V_3.[42-45] In patients who have sustained an intraoperative myocardial infarction (MI), V_4 is the most sensitive.[45] Limb lead III is preferred over other limb leads for discerning significant ST segment changes.[42-44,46] Each of these recommendations presumes the anesthesia provider has properly configured the respective computerized ST segment analysis software (e.g., verified the ST point has been positioned over the J point, electrodes have been properly placed on the body). Given the potential for hemodynamic lability related to alterations in intravascular status, ascites, electrolyte irregularities, cardiac comorbidity (e.g., cardiomyopathy), attention should be paid to ST segment analysis for signs of cardiac ischemia. In the absence of an ST segment fingerprint, leads III and V_3 are advocated for the detection of ST segment elevation or depression.[47]

Invasive hemodynamic monitoring may be indicated for patients with cirrhosis and other conditions of severe hepatic dysfunction. Arterial cannulation permits beat-to-beat measurement of blood pressure and provides immediate access for blood withdrawal if laboratory analysis is indicated intraoperatively. Patients with liver cirrhosis frequently require hemodynamic monitoring including cardiac output (CO) assessment, particularly when admitted to the intensive care unit or when undergoing surgery.[48] Arterial cannulation also permits usage of minimally invasive cardiac output monitors (e.g., FloTrac). The reliability of noninvasive cardiac monitors is not universally demonstrated and may be considered unreliable in cirrhotic patients with hyperdynamic circulation.[49] Cirrhosis is associated with a pattern of alterations in the cardiovascular system, known as *cirrhotic cardiomyopathy*, which is characterized by a hyperdynamic circulation, elevated baseline CO, reduced peripheral vascular resistance, and decreased ventricular response to physiologic, pharmacologic, and surgical stressors.[50,51] Furthermore, cirrhotic patients commonly have peripheral autonomic neuropathy, which may result in pronounced hemodynamic instability.[51,52]

Surgery such as liver transplant (discussed later) or hepatic resection require additional preparation in anticipation of extensive blood loss. As such, large-bore peripheral and central venous access is necessary for rapid fluid administration, administration of pressor medications, and invasive monitoring (e.g., central venous pressure [CVP], pulmonary artery catheter), especially if cardiac disease is present. Transesophageal echocardiography (TEE) monitoring also may be used in the absence of esophageal varices or significant coagulopathy.

Additional considerations for hepatic comorbidity may necessitate blood glucose monitoring (e.g., hypoglycemia during hepatic vascular occlusion), forced air and fluid warming to prevent hypothermia (related to prolonged surgery with an open abdomen coupled with large blood loss and fluid replacement), and coagulation profile monitored and corrected with fresh frozen plasma (FFP) as necessary.

Anesthetic Technique and Medication Choices

In patients with severe hepatic disease, hepatic arterial blood flow does not increase when portal blood flow and/or oxygen content in portal venous blood are decreased. This could lead to a decrease in hepatic blood and oxygen supply, with subsequent hepatic oxygen deprivation.[53] Any anesthetic plan must be focused on the maintenance of arterial blood pressure and cardiac output. Often it is not the specific anesthetic agents chosen that matter most, rather the care in which they are administered. General anesthesia can

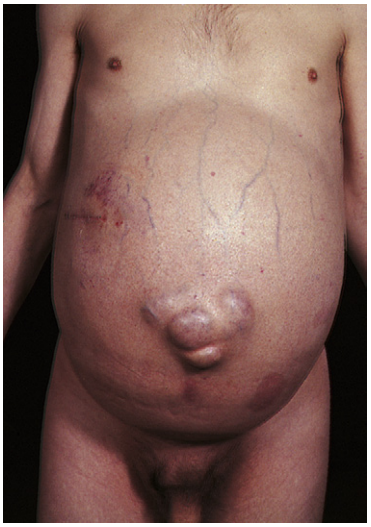

FIGURE **30-4** Ascites in a patient with alcoholic cirrhosis showing distended abdomen; dilated superficial collateral veins; hemorrhagic scratch marks due to pruritus and coagulopathy; umbilical varices; plaster in left iliac fossa indicating diagnostic paracentesis. (From Forbes A, et al, eds. *Atlas of Clinical Gastroenterology*. 3rd ed. Oxford: Mosby Ltd; 2005.)

be performed safely for patients with liver disease; regional anesthesia also can be used, but coagulopathy should be considered as a contraindication to many types of nerve blockade.

Volatile anesthetic considerations were discussed earlier, with an emphasis on selecting agents with little or no metabolism (e.g., desflurane, sevoflurane, isoflurane).

Nitrous oxide may be avoided in open abdominal cases because of the potential for expansion of the bowel and theoretic risk of exacerbating a venous embolism resulting from positional entrainment of air. Propofol has been used safely in patients with liver disease and may be a consideration for an induction agent. A midazolam induction may confer hemodynamic stability, but this benzodiazepine is NOT a prudent choice in the face of hepatic dysfunction because of impaired metabolism. Other benzodiazepines (e.g., lorazepam, oxazepam) do not require hepatic oxidation—only hepatic glucuronidation. Therefore, impaired liver function is less likely to result in lorazepam accumulation to an extent that would cause adverse reactions[54] and therefore would be a reasonable choice for sedation, although it is not ideally suited for induction of anesthesia.

Neuromuscular blockade selection should be based on patient physical status and the nature of the surgery (e.g., elective or urgent/emergent). Rapid sequence induction may be prudent in the cirrhotic patient with impaired gastric function and increased abdominal pressure related to ascites (Figure 30-4). In chronic liver failure, succinylcholine may exhibit a prolonged duration of action because of decreased synthesis of plasma cholinesterase by the liver. Due to the longer half-life of plasma cholinesterase (14 days), decreases are less likely in acute liver failure. Induction or maintenance with nondepolarizing neuromuscular blocking drugs (e.g., rocuronium) should be titrated cautiously with the expectation that duration of action will be extended if hepatic metabolism and clearance is impaired. Vecuronium is eliminated by the liver, and in cirrhotic patients, its onset is delayed,[55] its clearance is decreased,[56] and the duration of large doses is prolonged compared with controls.[56-58] Similar effects are seen with rocuronium. Liver disease increases the volume of distribution and elimination half-life of rocuronium, but not its clearance. The increased elimination half-life in patients with liver disease prolong rocuronium's duration of action, particularly with larger initial doses or prolonged administration. However, onset time is not altered by the presence of liver disease, preserving a desirable property of rocuronium.[59] A better option after intubation may be cisatracurium, which is metabolized independently of hepatic function and relies on Hoffman elimination (sensitive to temperature and pH).

Opioids are dependent on hepatic metabolism and should be administered cautiously. Coexisting pulmonary derangement may be worsened postoperatively by prolonged sedative and respiratory depressant effects of opioids used perioperatively. The CYP3A4 system is the primary metabolizer of fentanyl. Administration of CYP3A4 substrates or inhibitors can increase opioid concentrations, thereby prolonging and intensifying analgesic effects and adverse opioid effects, such as respiratory depression.[60] Hepatic dysfunction has a direct impact on the CYP metabolic system.

Morphine is metabolized in a phase II reaction, undergoing glucuronidation in the liver, and should be titrated cautiously or avoided in patients with significant liver disease. Elimination of alfentanil is reduced in patients with liver disease; its volume of distribution is increased, and protein binding is reduced by the lack of alpha-1-acid glycoprotein.[15] Remifentanil has a very short half-life due to its metabolism by nonspecific esterases in the blood and is not reliant on hepatic or renal function. Perhaps the most compelling evidence of no effect of hepatic dysfunction on the pharmacokinetics of remifentanil is that its kinetics do not change during the anhepatic phase of orthotopic liver transplantation.[61]

DISEASES OF THE BILIARY TRACT

Biliary tract disease is often characterized by a suppression or stoppage in bile flow. The most common cause of cholestasis is obstruction of the biliary tract outside the liver. Symptomatic presentation of obstruction and/or an inflammatory process can be attributed to gallstones, stricture, tumor, infection, or ischemia. Gallstone formation is most likely caused by physicochemical derangements in the formation of bile. Approximately 90% of gallstones appear as radiolucent structures composed of hydrophobic cholesterol crystals. Calcium bilirubinate generally accounts for the composition of the remaining percentage. Stones composed of calcium bilirubinate are usually seen in patients with cirrhosis and hemolytic anemia. An estimated 15 to 20 million adults in the United States have biliary tract disease, as evidenced by the presence of gallstones.[62]

Anatomic and Physiologic Overview

The biliary tract is the excretory conduit for the liver. It is composed of (1) the intrahepatic ducts, which collect bile from the liver segments; (2) the coalescence of the intrahepatic ducts and the right and left hepatic ducts; (3) the common hepatic duct, which is formed by the junction of the right and left hepatic ducts in the liver hilum; (4) the gallbladder, which serves as a reservoir of bile; (5) the cystic duct, which joins the gallbladder to the common bile duct; and (6) the common bile duct, which begins at the junction of the cystic duct and the common hepatic duct and terminates in the lumen of the duodenum.[62]

The gallbladder is a pear-shaped organ capable of holding 30 to 60 mL of fluid and is attached to the liver in a shallow depression at the inferior junction of the right and left hepatic lobes. The gallbladder drains into the cystic duct, which is usually 1 to 5 cm long and arises from the narrow end, or infundibulum, of the gallbladder. The cystic duct drains into the common hepatic duct. The common bile duct arises from the junction of the cystic duct and common hepatic duct and is approximately 6 mm

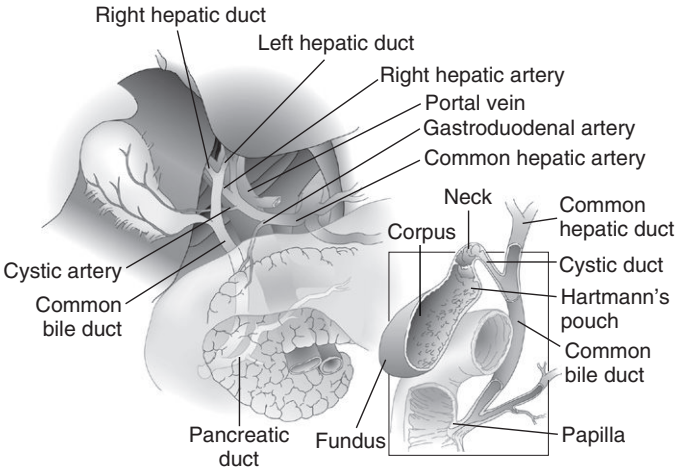

FIGURE **30-5** Anatomy of the biliary tract. (From Townsend CM, et al, eds. *Sabiston Textbook of Surgery*. 18th ed. Philadelphia: Saunders; 2008:1548.)

in diameter. It passes behind the duodenum to the right of the gastroduodenal artery, traversing the head of the pancreas before entering the second part of the duodenum. The distal common bile duct may join with the pancreatic duct before entering the duodenum via the ampulla of Vater (Figure 30-5). At the termination, these ducts are enveloped in smooth muscle, the sphincter of Oddi, which provides a barrier to intestinal bacteria to maintain the sterile environment of the biliary tract. At this point, biliary tract obstruction can occur from a pancreatic tumor.

Arterial blood supply to the gallbladder is furnished by the cystic artery, which is a branch of the right hepatic artery. The biliary ducts receive their blood supply distally from the gastroduodenal, retroduodenal, and posterosuperior pancreatoduodenal arteries and proximally from the right hepatic and cystic arteries. Venous drainage flows into the portal vein. Lymphatic drainage flows into a cystic duct node located between the cystic duct and the common hepatic duct.

The area known as the *cystohepatic triangle (Calot's triangle)* is bound by the common hepatic duct, the liver, and the cystic duct and is a critical region that contains the cystic artery, the right hepatic artery, the cystic duct lymph node, and sometimes an aberrant right segmental bile duct. This area must be carefully dissected during cholecystectomy, so damage to these vital and friable structures can be avoided.

The gallbladder mucosa secretes a protective mucus that prevents caustic damage by bile salts. After food is ingested, the gallbladder contracts, emptying its contents (bile) into the duodenum to assist in the digestive processes. Regulation of gallbladder contraction is primarily hormonal through the action of cholecystokinin. The release of cholecystokinin from duodenal cells is mediated by the presence of intraluminal amino acids and fat. Vagal stimulation also serves a role (secondary to the role of cholecystokinin). Indeed, vagotomy is associated with impaired gallbladder contraction and increased prevalence of gallstones.[34]

Bile is the combined secretory product of the hepatocyte and biliary tract epithelial cell and has three main functions: (1) to emulsify and enhance absorption of ingested fats and fat-soluble vitamins; (2) to provide an excretory pathway for bilirubin, drugs and toxins, and immunoglobulin A (IgA); and (3) to maintain duodenal alkalization. The combined output of the ductal cells and hepatocytes is 500 to 1000 mL/day. The bile ducts, gallbladder, and sphincter of Oddi modify, store, and regulate the flow of bile. The liver produces 500 to 1000 mL of bile per day and excretes it into the bile canaliculi. The gallbladder concentrates and stores hepatic bile during the fasting state and delivers bile into the duodenum in response to a meal. Because the usual capacity of the gallbladder is only about 30 to 60 mL, the remarkable absorptive capacity of the gallbladder accounts for its ability to store much of the bile produced each day.[62] Absorbed bile is returned via the portal venous system to the liver.

The hepatocytes secrete bilirubin (the metabolic waste product of heme metabolism), cholesterol, bile salts, lecithin, water, and electrolytes. The epithelial cells contribute water and electrolytes. Vagal stimulation, secretin, cholecystokinin, and gastrin stimulate ductular cell secretion and increase bile flow. In addition, bile acids furnish a positive-feedback mechanism in the elaboration of hepatocyte and ductular secretion. Gallbladder filling during fasting occurs with relaxation and contraction of the sphincter of Oddi. The sphincter of Oddi is a complex structure that is functionally independent from the duodenal musculature. It creates a high-pressure zone between the bile duct and the duodenum. The sphincter regulates the flow of bile and pancreatic juice into the duodenum, prevents the regurgitation of duodenal contents into the biliary tract, and diverts bile into the gallbladder. Vasoactive intestinal peptide produces relaxation of the sphincter of Oddi, whereas somatostatin, an inhibitory peptide, produces contraction. In states of prolonged fasting, the risk of gallstone formation increases because of the lack of cholecystokinin stimulation and consequent biliary stasis.[62]

Cholecystitis

Cholecystitis symptoms are usually the result of obstruction, infection, or both. Obstruction can be extramural (e.g., pancreatic cancer), intramural (e.g., cholangiocarcinoma), or intraluminal (e.g., choledocholithiasis). Acute cholecystitis is related to gallstones in 90% to 95% of cases. Obstruction of the cystic duct leading to biliary colic is the initial event in acute cholecystitis. If the cystic duct remains obstructed, the gallbladder distends, and the gallbladder wall then becomes inflamed and edematous. Obstruction of the cystic duct by gallstones results in a triad of sudden right upper quadrant tenderness, fever, and leukocytosis.

Inspiratory effort usually accentuates the pain (Murphy sign). Increases in plasma bilirubin, alkaline phosphatase, and amylase levels frequently occur. Ileus and localized tenderness may indicate perforation with peritonitis. Leukocytosis and fever are often present. Jaundice indicates complete obstruction of the cystic duct. Symptoms are frequently confused with those of myocardial infarction. Differential diagnosis is accomplished through serial ECG evaluations and laboratory analysis of serum enzymes specific to cardiac muscle. Cholescintigraphy (a contrast study that evaluates gallbladder excretion of a radiographically labeled substance) and ultrasonography are often used for clinical confirmation of the diagnosis.[34]

For most patients, the treatment of acute cholecystitis is cholecystectomy, but for those who are critically ill, the risk of general anesthesia may be greater than the benefit of a surgical procedure. An alternative, temporary treatment for these high-risk patients is decompression and drainage of the gallbladder through the insertion of a cholecystostomy tube. This minimally invasive procedure can be performed with local anesthetic infiltration and intravenous sedation.[63]

Patients with symptoms indicative of acute cholecystitis are often volume depleted because of intolerance of oral intake, vomiting, and possible preoperative nasogastric evacuation of gastric contents. Dehydration calls for preoperative intravenous fluid replacement. Gastric suction may be warranted in the presence of

ileus. The presence of free abdominal air, as determined by abdominal radiography or symptoms of an acute abdomen (e.g., fever, ileus, rigid and painful abdomen, vomiting, dehydration), suggests a ruptured viscus, possibly including perforation of the gallbladder. Under these circumstances, emergency exploratory laparotomy is undertaken.

Cholelithiasis and Choledocholithiasis

Acute obstruction of the common bile duct often produces symptoms similar to those seen in patients with cholecystitis. Recurrent bouts of acute cholecystitis induce the development of fibrotic changes in gallbladder structure, thereby impeding the ability of the gallbladder to adequately expel bile. Presence of Charcot's triad (i.e., fever and chills, jaundice, right upper quadrant pain) aids in establishing the diagnosis of acute ductal obstruction. Weight loss, anorexia, and fatigue complete the symptomatology. Diagnostic modalities include radiography, transhepatic cholangiography, ultrasonography, cholescintigraphy, and computed tomography (CT) scan. A dilated common bile duct and biliary tree are typically observed in these studies.

The use of endoscopic retrograde cholangiopancreatography (ERCP) in patients with suspected common bile duct stones not only confirms the diagnosis but also provides ductal clearance of the stones and sphincterotomy before subsequent laparoscopic cholecystectomy. It is relatively more complex than routine endoscopies and requires adequate patient sedation, analgesia, and patient cooperation. Patients undergoing ERCP have been found to be more anxious as compared with those undergoing a routine esophagogastroduodenoscopy (EGD). Restlessness and lack of cooperation have been reported to be one of the causative factors for post-ERCP complications such as duodenal perforation and pancreatitis. The choice of sedative is chiefly governed by the user and the patient history. Similarly, the level of sedation is also dependent on the clinical condition of the patient and the degree of patient cooperation.[64] Patients presenting for ERCP often have comorbidities. Endoscopic clearance of stones from the common bile duct can avoid the need for an open operation if expertise in laparoscopic common bile duct exploration is not available. Patients with worsening cholangitis caused by ascending bacterial infection of the biliary system, ampullary stone impaction, biliary pancreatitis, multiple comorbidities, and cirrhosis are considered good candidates for preoperative endoscopic therapy.[62]

Anesthetic Considerations in Gallbladder and Biliary Tract Disease

Removal of gallstones is undertaken not only for relief of symptoms but also for prevention of further sequelae, including cholecystitis, cholangitis, jaundice, pancreatitis, and peritonitis, all of which may result from stasis or impediment to bile flow. Contraindications to laparoscopic cholecystectomy include coagulopathy, severe chronic obstructive pulmonary disease, end-stage liver disease, and congestive heart failure.

Since the introduction of laparoscopic cholecystectomy, the number of cholecystectomies performed in the United States has increased from about 500,000 per year to 700,000 per year. More than 90% of cholecystectomies are performed laparoscopically. Laparoscopic cholecystectomy is now often performed in the relatively healthy patient on an outpatient basis with either discharge later in the day of surgery or after an overnight stay in the hospital. Postoperative pain management is typically less challenging with laparoscopic surgery.

Induction is standard or rapid-sequence induction with oral endotracheal intubation. The use of abdominal carbon dioxide insufflation to effect adequate exposure of anatomic structures mandates general endotracheal intubation anesthesia to effectively seal the airway and prevent passive aspiration of gastric contents. Maintenance requires muscle relaxation with appropriate reversal. An orogastric (OG) tube should be inserted to decompress the stomach. Prophylactic antiemetics are needed due to the peritoneal irritation of insufflation, opioid use, and intravascular volume depletion. The peritoneal cavity must be insufflated for surgical exposure.

Insufflation of the abdomen with carbon dioxide impedes diaphragmatic excursion, causing a decrease in functional residual capacity, closing capacity, and increased peak inspiratory pressure. Retroperitoneal insufflation may lead to hypotension and necessitates repositioning of the trocar. Insufflation with carbon dioxide causes a rise in the carbon dioxide partial pressure unless ventilation is controlled. Abdominal insufflation may lead to hypercarbia in the presence of inadequate ventilation. Special attention should be paid to the possibility of needed adjustments in ventilator settings with insufflation. In the setting of intraabdominal insufflation, applying an alternative ventilatory strategy using pressure control ventilation (PCV) rather than a volume control mode may best serve to prevent alveolar derecruitment (measured at the bedside by a pressure-volume curve method) by providing a physiologic minute ventilation while minimizing the risk of barotrauma. The use of a reverse Trendelenburg position during laparoscopic cholecystectomy may induce a variable degree of hemodynamic compromise by impeding venous return. Occult hemorrhage is also possible and may go undetected.

Insufflation also leads to increased intraabdominal pressure. An intraabdominal pressure of 20 to 25 cm H_2O produces increases in cardiac output and CVP secondary to changes in the volume of the venous return of blood. An intraabdominal pressure greater than 30 to 40 cm H_2O may lead to decreased CVP and reduced cardiac output secondary to reduced right ventricular preload. Insufflation to a pressure of approximately 15 mmHg is routine. Abdominal insufflation also displaces the abdominal viscera and diaphragm in a cephalad direction, placing extra pressure on the lower esophageal sphincter (LES) and thereby increasing the risk of gastric reflux.

All maintenance anesthetic drugs may be used. Some surgeons request that nitrous oxide not be used to reduce the risk of bowel expansion, which could hinder surgical exposure. In the presence of hepatic dysfunction, isoflurane, desflurane, and sevoflurane are safe. The choice of muscle relaxant depends on the patient's ability to tolerate possible side effects of the drug, the drug's dependence on hepatic clearance, and the length of the procedure to be performed. Awake extubation is performed after the patient's airway reflexes are adequate. The laparoscopic approach offers the benefit of reduced postoperative pain secondary to smaller abdominal incisions. Patients may experience shoulder pain from pneumoperitoneum, which is usually self-limiting. Evacuation of the pneumoperitoneum with a Valsalva maneuver prior to closing will assist in alleviating postoperative pain. Severe postoperative pain may be reduced by patient-controlled analgesia, intercostal nerve blocks, or neuraxial opioid administration. Abdominal pain or other symptoms originally attributed to the gallbladder may persist or recur months or years after cholecystectomy.

Open cholecystectomy may be indicated for patients who are emergently ill, in the presence of infection, or patients in whom laparoscopy poses a particularly formidable technical challenge (e.g., in cases of morbid obesity or intraabdominal adhesions secondary to previous abdominal surgery or peritonitis). Patients who undergo open cholecystectomy often experience

more complications, including a greater likelihood of severe postoperative pain and respiratory splinting (caused by the use of a right subcostal or upper abdominal midline incision), with the risk of postoperative respiratory embarrassment in the susceptible patient. Patients who have experienced severe traumatic injury or who require aggressive intensive care for multiorgan disease are at particular risk for developing acute cholecystitis secondary to the stress of severe illness. Patients with significant comorbidities, including advanced age, who undergo prolonged or complex surgical procedures (e.g., trauma, cardiac surgery with cardiopulmonary bypass, abdominal aneurysm repair) that are complicated by perioperative hemodynamic lability have also been identified to be at added risk for ischemia of the abdominal viscera. The result may be the development of an acute, postoperative abdominal crisis. Under this circumstance, exploratory laparotomy for an acute abdomen may reveal necrosis and perforation of the gallbladder. This places the patient at extreme risk for developing peritonitis. The acute critical nature of the presenting illness, superimposed upon preexisting patient comorbidities, is another factor potentially complicating perianesthetic management of the patient.[34]

Full-stomach precautions should be used during the induction of and emergence from anesthesia, particularly in the presence of abdominal distention or ileus. Patients with jaundice require a more thorough preparation, owing to the likelihood of a variable degree of hepatic dysfunction. This may make for greater susceptibility to hemorrhage, exaggerated drug effects, and fluctuation in hemodynamics. Invasive hemodynamic monitoring and preparation for blood product transfusion are influenced by the patient's clinical status.

Common bile duct exploration may be carried out in conjunction with cholecystectomy if necessary. Glucagon may be requested by the surgeon for its spasmolytic effect in the GI system and its ability to relax the sphincter of Oddi. Note that Glucagon may cause nausea at doses greater than 2 mg.

DISEASES OF THE ESOPHAGUS

Anatomic and Physiologic Overview

Esophagus is derived from the Greek words *oiso*, which is the future tense of *phero* (to carry), and *phagein* (food).[65] Approximately 18 to 25 cm long, the esophagus is a hollow, muscular tube that serves to carry food or liquid to the stomach. The esophagus extends through three segments: cervical, thoracic, and abdominal. The cervical esophagus is bordered anteriorly by the trachea, bilaterally by the common carotid arteries, internal jugular veins, and vagal nerves, and posteriorly by cervical muscles. Proximally, the esophagus begins where the inferior pharyngeal constrictor merges with the cricopharyngeus, an area of skeletal muscle known functionally as the upper esophageal sphincter.[66] At rest, the upper esophageal sphincter prevents entrainment of air by creating a zone of high pressure through muscle contraction.

Although collapsed when unused, the esophagus is capable of expanding to permit passage of substances, yet it remains the narrowest of the digestive tubes. Peristaltic action continues to push solid matter distally toward the stomach. The lower esophageal sphincter (LES), contracted at rest to prevent passage of gastric contents proximally into the esophagus, relaxes to permit passage of food into the stomach.

Sympathetic and parasympathetic innervation regulates esophageal muscle tone. Peristaltic activity is regulated by parasympathetic innervation via the vagus nerves. Esophageal muscular contraction and relaxation of the LES is regulated by stimulation of cranial nerves IX, X, and XI. Sympathetic fibers act on Auerbach's (myenteric) plexus to modulate motor activity.

Esophageal Disorders

Disorders affecting esophageal motility or sphincter tone may create generalized symptoms of dysphagia, heartburn, or chest pain. Primary esophageal motility disorders include achalasia and gastroesophageal reflux disease (GERD). Achalasia is characterized by impaired relaxation of the lower esophageal sphincter and may develop secondary to systemic disease states, including diabetes, stroke, amyotrophic lateral sclerosis, and certain connective tissue diseases, such as amyloidosis and scleroderma. Chronic achalasia results in dilation of the distal esophagus, and regurgitation becomes more frequent when larger amounts of food and fluid are retained. GERD is a consequence of the failure of the normal antireflux barriers to protect against frequent and abnormal amounts of gastroesophageal reflux. Symptoms range from heartburn to extraesophageal manifestations (e.g., pulmonary, ear, nose, or throat symptoms).

Chronic GERD can result in abnormal epithelial changes in the esophagus that are predisposed to malignancy. Termed *Barrett's esophagus*, damage to the esophageal epithelium results in columnar epithelium replacing the normal stratified squamous cells in the distal esophagus. These changes create no symptoms but are a cautionary risk factor associated with adenocarcinoma of the esophagus.

In many patients, GERD may be managed conservatively with pharmacologic therapy, and surgery is withheld until medical management proves unsuccessful. Medication therapy may include antacids, mucosal protective medications, histamine (H_2) receptor blockers, proton pump inhibitors, and prokinetics designed to facilitate emptying of the stomach. Aside from failed medical therapy, other surgical indications include mechanically defective cardiac sphincter, recurrence of symptoms after discontinuing treatment, and unacceptable side effects related to medications.

Hiatal Hernia

Hiatal hernia refers to conditions in which elements of the abdominal cavity, most commonly the stomach, herniate through the esophageal hiatus into the mediastinum.[67] Hiatal hernias are classified as type I to type IV. Type I, the sliding type, is formed by the movement of the upper stomach through an enlarged hiatus. In type II, the paraesophageal type, the esophagogastric junction remains in normal position, but all or part of the stomach moves into the thorax and assumes a paraesophageal position. A type III has been identified that combines the features of sliding and paraesophageal hernias (Figure 30-6). Type IV hiatal hernias are present when other organs, such as the colon or small bowel, are contained in the hernial sac formed by a large paraesophageal hernia.[68]

The contribution of hiatal hernia to GERD is controversial,[69] but data confirm the importance of hiatal hernia in patients with more severe esophagitis, peptic stricture, or Barrett's esophagus. Several surgical approaches may be used to reduce and correct hiatal hernia although the laparoscopic Nissen fundoplication remains common. The Collis-Nissen (elongation gastroplasty) may be superior to the Nissen fundoplication for select patients with Barrett's esophagus because of the reflux-induced shortening of the esophagus.[70] Anesthetic management may include aspiration prophylaxis, discussed previously. Application of cricoid pressure has been shown to decrease LES; however, normal gastric pressures remain; consequently, the value of cricoid cartilage pressure in rapid sequence induction has been questioned, although it remains a frequent technique in clinical practice.[71]

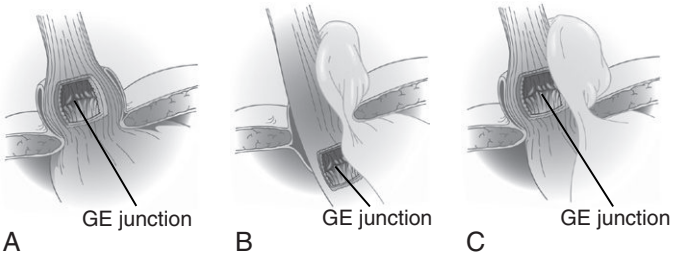

FIGURE **30-6** Three types of hiatal hernia. **A,** Type I, or sliding hernia. **B,** Type 2, or rolling hernia. **C,** Type 3, or mixed hernia. *GE*, Gastroesophageal. (From Townsend CM, et al, eds. *Sabiston Textbook of Surgery: The Biological Basis of Modern Surgical Practice*. 19th ed. Philadelphia: Saunders; 2012:1068.)

Anesthetic Considerations in Esophageal Disease

Special considerations may be necessary for patients with active esophageal disease. Occult disease (asymptomatic) is generally less concerning compared with patients with uncontrolled disease states that manifest with reflux symptoms. A preoperative history of symptoms that indicate the presence of gastric reflux warrants aspiration prophylaxis during induction and emergence surrounding general anesthesia. Although best practice data does not support a specific regimen, modifying acidity and/or volume of gastric contents remains a common preoperative practice. To gain maximum benefit, it is imperative to have an understanding of the pharmacokinetic/pharmacodynamic profile of selected preoperative medications.

Rapid sequence induction with cricoid pressure may serve to hasten protection of the airway with a cuffed endotracheal tube and limit opportunity for aspiration of gastric contents. Usage of a laryngeal mask airway (LMA) remains controversial in patients with active reflux disease. The absence of definitive airway protection with LMA must be carefully considered, and a reasonable indication against endotracheal intubation should be present prior to implementation.

DISEASES OF THE STOMACH

Anatomic and Physiologic Overview

The principal function of the stomach is to prepare ingested food for digestion and absorption before it is moved into and through the small intestine. The initial period of digestion requires that solid components of a meal be stored for several hours while they undergo a reduction in size and break down into their basic metabolic constituents.

Receptive relaxation is a process whereby the proximal portion of the stomach relaxes in anticipation of food intake. This relaxation enables liquids to pass easily from the stomach along the lesser curvature, whereas the solid food settles along the greater curvature of the fundus. In contrast to liquids, emptying of solid food is facilitated by the antrum, which pumps solid food components into and through the pylorus. The antrum and pylorus function in a coordinated fashion, allowing entry of food components into the duodenum and also returning material to the proximal stomach until it has been processed appropriately for delivery into the duodenum.

In addition to storing food, the stomach participates in digestion of a meal. An example of this is the enzymatic breakdown of starch through the activity of salivary amylase. For this to work, the pH within the center of the gastric bolus needs to be greater than pH 5. Peptic digestion metabolizes a meal into fats, proteins, and carbohydrates by breaking down cell walls. Although the duodenum and proximal small intestine are primarily responsible for digestion of a meal, the stomach clearly facilitates this process.[72]

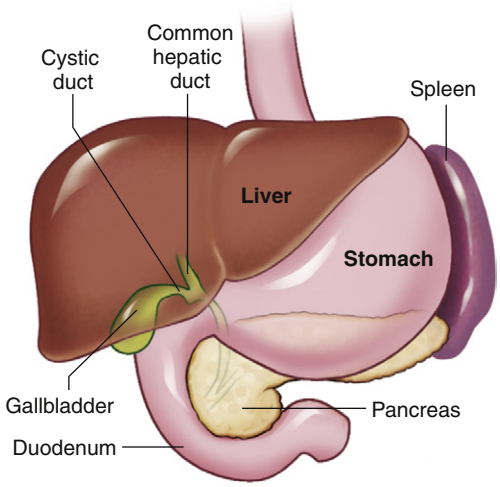

FIGURE **30-7** Position of the stomach relative to the other principal organs of the upper abdomen. (From Patton KT, Thibodaux GA. *Anatomy & Physiology*. 8th ed. St Louis: Mosby; 2013:862.)

The stomach is essentially composed of three sections. The thin-walled and distensible proximal portion (fundus) is located in the upper abdomen and has primarily a storage function. The body of the stomach represents the largest portion and is also referred to as the *corpus*. The body also contains most of the parietal cells and is bound on the right by the relatively straight lesser curvature and on the left by the longer greater curvature. The thick-walled distal portion (antrum) of the stomach is responsible for the mixing of food and its slow release through the pyloric sphincter into the duodenum. The liver is positioned right and ventral to the stomach and left and lateral to the spleen. The biliary tract courses posterior to the stomach (Figure 30-7).

Most of the blood supply to the stomach is from the celiac artery. There are four main arteries: the left and right gastric arteries along the lesser curvature and the left and right gastroepiploic arteries along the greater curvature. In addition, a substantial quantity of blood may be supplied to the proximal stomach by the inferior phrenic arteries and by the short gastric arteries from the spleen (Figure 30-8). Major autonomic innervation is furnished by two branches of the vagus nerve, the right posterior (celiac) branch and the left anterior (hepatic) branch.

The gastric wall consists of an external serosal layer that covers an inner oblique, a middle circular, and an outer longitudinal layer of smooth muscle. The middle layer of smooth muscle is circular and is the only complete muscle layer of the stomach wall. At the pylorus, this middle circular muscle layer becomes progressively thicker and functions as a true anatomic sphincter between the stomach and duodenum.

The submucosa lies between the muscularis externa and mucosae and is a collagen-rich layer of connective tissue that is the strongest layer of the gastric wall. The submucosa contains the rich anastomotic network of blood vessels, lymphatics, and Meissner's plexus of autonomic nerves. The mucosa consists of surface epithelium, lamina propria, and muscularis mucosae. The latter is on the luminal side of the submucosa and is probably responsible for the rugae that greatly increase epithelial surface area. It also marks the microscopic boundary for invasive and noninvasive gastric carcinoma.[72]

Within the gastric mucosa reside the glands responsible for the significant physiologic role played by the stomach during the digestive processes. The functions of the glands and the cells lining the glands vary according to the region of the stomach in which they

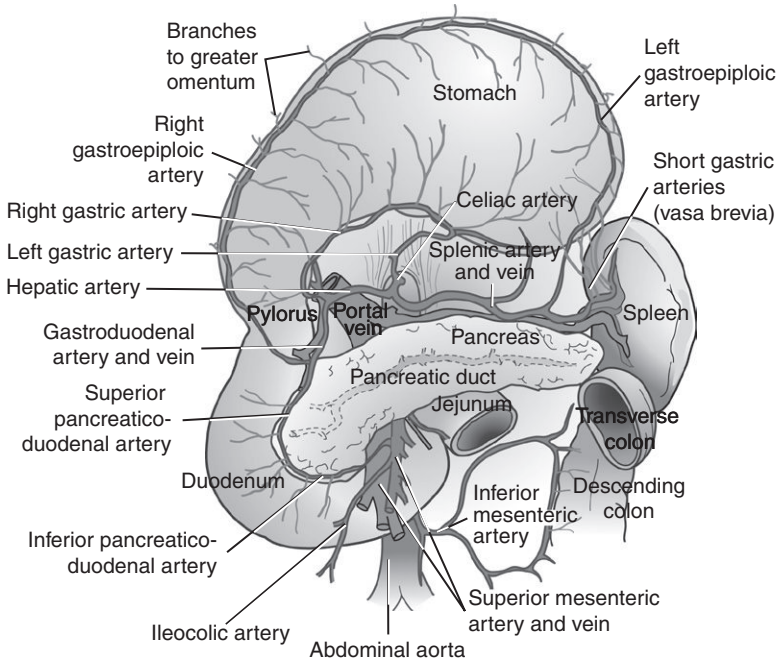

FIGURE **30-8** Blood supply to the stomach and duodenum with anatomic relationships to the spleen and pancreas. (From Yeo CJ, et al. *Shackelford's Surgery of the Alimentary Tract*. 7th ed. Philadelphia: Saunders; 2013:641.)

are found. Within the fundic mucosa lie mucus-secreting glands that provide a protective barrier to the acid outflow of the parietal cells, which are located in the same region of the stomach. The endocrine function of the stomach is apparent through the secretions (pepsinogen) of the chief cells and the secretions (serotonin) of other cells. Within the antrum are cells that secrete mucus (surface epithelial cells and mucous cells) and gastrin (G cells). The two important sphincters are the LES at the gastroesophageal junction and the pyloric sphincter at the gastroduodenal junction.

The stomach is very distensible, can store up to 1.5 liters of fluid without any increase in gastric pressure, and normally stores food for up to 4 hours. The sight and smell of food stimulate acid and pepsinogen production. Gastrin is the major hormonal regulator of the gastric phase of acid secretion after a meal. Gastrin is released by the G cells in response to gastric distention, which stimulates parietal-cell acid (hydrochloric acid) secretion. The duodenum and upper jejunum also secrete a small amount of gastrin. Luminal acid suppresses gastrin feedback (negative feedback).

Pepsinogen and gastrin release are vagally mediated. Acid in duodenal contents induces the release of secretin, an effect that inhibits gastrin release even more and inhibits further acid production. Acid in the antrum also stimulates the release of somatostatin. Somatostatin is able to directly inhibit parietal cell acid secretion but can also indirectly inhibit acid secretion through inhibition of gastrin release and down-regulation of histamine release. Pancreatic bicarbonate release is also stimulated by duodenal acidity.

Gastric acid secretion by the parietal cell is regulated by three local stimuli: acetylcholine, gastrin, and histamine. These three stimuli account for basal and stimulated gastric acid secretion. Acetylcholine is the principal neurotransmitter modulating acid secretion and is released from the vagus and parasympathetic ganglion cells. Gastrin has hormonal effects on the parietal cell and stimulates histamine release. Histamine has paracrine-like effects on the parietal cell and plays a central role in the regulation of acid secretion by the parietal cell after its release from enterochromaffin-like (ECL) cells. Somatostatin exerts inhibitory actions on gastric acid secretion. Release of somatostatin from antral D cells is stimulated in the presence of intraluminal acid at a pH of 3 or less. After its release, somatostatin inhibits gastrin release and also modifies histamine release from ECL cells. In some patients with peptic ulcer disease (PUD), this negative feedback response is defective. Consequently, the precise state of acid secretion by the parietal cell is dependent on the overall influence of the positive and negative stimuli.[72]

Other gastric functions include providing a barrier against ingested pathogens. This goal is accomplished through the maintenance of a highly acidic environment and through a functional role in immunosurveillance. The stomach heats or cools ingested substances as needed for the maintenance of normothermia. Parietal cells also secrete intrinsic factor (in addition to hydrochloric acid), which facilitates ileal vitamin B_{12} absorption.

Peptic Ulcer Disease

A gastric ulcer is defined by the loss of mucosa (including muscularis mucosae) due to inflammation. Ulcers may extend into the submucosa and even muscularis propria. Of course, all ulcers begin as erosions, but not all erosions progress to ulcers. Ulcers may be acute or chronic. Peptic ulcers are considered chronic and are most often solitary. They may occur in any portion of the GI tract that is exposed to acid-peptic juices. Approximately 98% of peptic ulcers occur in the stomach and duodenum.

It is now believed that 90% of duodenal ulcers and roughly 75% of gastric ulcers are associated with *H. pylori* infection. *H. pylori* is detected in the stomach of almost all patients with duodenal peptic ulcer and in more than 90% of gastric ulcer patients who are not nonsteroidal antiinflammatory drug (NSAID) users (after *H. pylori* infection, ingestion of NSAIDs is the most common cause of PUD). Eradication of *H. pylori* facilitates healing of peptic ulcers, and essentially, prevents their recurrence.[73]

The most common complications of peptic ulcer disease, in order of prevalence, are hemorrhage, perforation, and obstruction.

Approximately one third of patients experience at least one of these complications during the course of their peptic ulcer disease; pyloric channel ulcers are the ones most commonly associated with complications, particularly obstruction. Bleeding occurs when the ulcer erodes underlying blood vessels. Ulcers may perforate into adjacent organs, such as the pancreas (more common) or liver.

Gastric outlet obstruction may develop as a result of distortion and narrowing of the pyloric area caused by fibrosis, edema, or smooth muscle spasm resulting from chronic ulcer disease. It occurs almost exclusively in patients with long-standing peptic ulcers of the pyloric channel or duodenum. Surgical repair or endoscopic pyloric dilation are often necessary to alleviate the symptoms of gastric outlet obstruction.[73,74]

A chronic overabundance of hydrochloric acid and pepsin (from various causes) results in erosion of the protective mucous layer of the stomach and duodenum, eventually leading to ulcerative lesions extending beyond the mucosal barrier into the submucosa and muscularis epithelial layers and sometimes into the serosal layer. In the case of LES incompetence, ulcerative involvement of the esophagus may develop.

A chronic ulcerative lesion in the duodenum constitutes duodenal ulcer disease. Because of similarity of symptoms and responses to therapy, this classification is also placed on lesions that occur before the pylorus in the lower antrum of the stomach. Men 45 to 65 years of age and women older than 55 years of age have the highest incidence of duodenal ulcer disease. Affected patients possess twice the number of acid-secreting parietal cells.[75]

Gastritis

Stress gastritis, an inflammatory disorder of the gastric mucosa, has been referred to as stress ulcerations, stress erosive gastritis, and hemorrhagic gastritis. These lesions may lead to life-threatening gastric bleeding and by definition occur after physical trauma, shock, sepsis, hemorrhage, or respiratory failure. They are characterized by multiple, superficial (nonulcerating) erosions that begin in the proximal or acid-secreting portion of the stomach and progress distally. They also may occur in the setting of central nervous system disease such as that seen with Cushing's ulcer or as a result of thermal burn injury involving more than 30% of the body surface area (Curling's ulcer).

Although the precise mechanisms responsible for the development of stress gastritis remain to be fully elucidated, current evidence suggests a multifactorial etiology including drugs, chemicals, or *H. pylori* infection. These stress-induced gastric lesions appear to require the presence of acid. Stress is considered present when hypoxia, sepsis, or organ failure occurs. Other factors that may predispose to the development of these lesions include impaired mucosal defense mechanisms against luminal acid such as a reduction in blood flow, a reduction in mucus, a reduction in bicarbonate secretion by mucosal cells, or a reduction in endogenous prostaglandins.[72] *H. pylori* has been identified as a major etiologic factor of gastritis-associated disease, as well as gastric and duodenal ulcers and gastric carcinoma. Epidemiologic findings indicate a higher prevalence of this organism in older adults, individuals of lower socioeconomic status, and those born outside the United States. Infected patients undergoing stress are at greatest risk for exacerbation of the infection, with potential development of gastric and duodenal ulceration. At present, despite the numerous exposures of anesthesia providers to potential oral and ambient routes of transmission, *H. pylori* has not been recognized as a serious occupational hazard.[75] All these factors render the stomach more susceptible to damage from luminal acid with the resultant hemorrhagic gastritis.

Any patient with upper GI bleeding requires prompt and definitive fluid resuscitation with correction of any coagulation or platelet abnormalities. If blood is required, it should be administered without delay, and if there are specific clotting abnormalities or platelet deficiencies, fresh frozen plasma and platelets should likewise be administered. In patients being treated for sepsis, broad-spectrum antibiotics, in conjunction with source control of the infection, need to be undertaken. Treatment of the underlying sepsis plays a major role in treating the underlying gastric erosions. Saline lavage of the stomach through a nasogastric tube will help remove any pooled blood and prevent gastric distention, which stimulates gastrin release. Nasogastric decompression also removes noxious substances such as bile and pancreatic juice that could potentially further compromise the stomach. More than 80% of patients who present with upper GI hemorrhage stop bleeding using this approach. When the nasogastric tube aspirate is clear, indicating that bleeding has ceased, intraluminal gastric pH should be maintained at greater than 5.0 with antisecretory agents. If the pH can be maintained above 5.0, more than 99.9% of acid will be neutralized, and pepsin will be inactive. Usually this involves the use of proton pump inhibitors or, alternatively, H_2-receptor antagonists with or without combination antacid therapy. There is little evidence to suggest that endoscopy with electrocautery or heater probe coagulation has any benefit in the therapy of bleeding from acute stress gastritis.[72]

Gastric mucosal acidosis has been commonly reported in critically ill patients with respiratory failure and underlying coagulopathy, hepatic cirrhosis, hyperparathyroidism, obstructive airway disease, rheumatoid arthritis; patients undergoing prolonged, complex surgical procedures; and patients undergoing cardiopulmonary bypass. Gastritis associated with gastric mucosal acidosis is associated with increased perioperative morbidity and mortality. The splanchnic viscera is particularly vulnerable to decreased circulatory blood flow in the presence of inflammation, with the potential for breakdown of intestinal barrier function. This occurrence results in translocation of bacteria and endotoxin into the bloodstream, with consequent systemic sepsis. Ischemia and acidosis of the gut is the primary causative factor for erosion of gut barrier function.[34]

Therapeutic Options in Peptic Ulcer Disease

The clinician has three major goals when faced with a patient with ulcer disease: symptoms need to be relieved, the ulcer needs to heal, and recurrence needs to be prevented. The major medical therapies and treatments of choice used for the control of peptic ulcer disease focus on *H. pylori*. Adjuncts include oral antacids, H_2-receptor antagonists, proton pump inhibitors, sucralfate, and antibiotics. A proton pump inhibitor such as omeprazole is used in duodenal ulcer management. EGD and surgical treatment are reserved for patients who continue to experience intractable symptoms despite aggressive medical therapy or for treatment of complications. These complications are often of an urgent nature and consist of GI hemorrhage, ulcerative perforation into adjacent structures such as the pancreas or jejunum, and obstruction.[76,77]

Antacid use in the medical treatment of peptic ulcer disease has potential complications of interest to the anesthetist. Antacids may produce an acid rebound in which gastric acid secretion may increase after acid is neutralized by calcium-containing antacids. Another condition that may result from antacid therapy is the milk-alkali syndrome. In this condition, hypercalcemia, alkalosis, and an elevated blood urea nitrogen level may develop from the daily ingestion of large quantities of calcium-containing antacids

TABLE 30-10 Proton Pump Inhibitors

Generic Name	Trade Name	Adult Dosage Range	Available Dosage Forms*	Dose Adjustment in Renal Dysfunction	Drug Interactions and Comments
Esomeprazole	Nexium	20 mg daily	Capsule: 20, 40 mg	No	Cefuroxime, cefpodoxime, digoxin, dihydropyridine calcium channel blockers, iron salts, itraconazole, ketoconazole, sucralfate
Lansoprazole	Prevacid	15-30 mg daily or bid	Capsule: 15, 30 mg	No	Same as esomeprazole plus theophylline
Omeprazole	Prilosec	20-40 mg daily or bid	Capsule: 10, 20, 40 mg	No	Same as esomeprazole plus benzodiazepines, cilostazol, citalopram, clarithromycin, cyclosporine, disulfiram, methotrexate, phenytoin, sulfonylureas, theophylline, warfarin
Pantoprazole	Protonix, Protonix IV	40-80 mg daily	Tablet: 40 mg Injection: 40 mg/vial	No	Same as esomeprazole
Rabeprazole	Aciphex	20 mg daily	Tablet: 20 mg	No	Same as esomeprazole plus cyclosporine

Adapted from Townsend CM, et al, eds. *Sabiston Textbook of Surgery: The Biological Basis of Modern Surgical Practice*. 19th ed. Philadelphia: Saunders; 2012; Rakel RE, Rakel DP. *Textbook of Family Medicine*. 8th ed. Philadelphia: Saunders; 2011.
*All oral forms are delayed release.

and milk. Manifestations of this syndrome include skeletal muscle weakness and polyuria. Ingestion of large quantities of aluminum-containing antacids may result in acute hypophosphatemia because of increased binding of intestinal phosphorus. Skeletal muscle weakness and fatigue follow chronic overuse, resulting in pathologic fractures and osteoporosis.[34]

Hydrochloric acid secretion is blocked by H_2 antagonists, thereby promoting the healing of duodenal ulcers. All four available H_2 antagonists (cimetidine, ranitidine, famotidine, and nizatidine) suppress basal acid output as well as acid output stimulated by meals. After intravenous administration, all four agents are eliminated principally through renal excretion. For cimetidine and famotidine, it is recommended that the doses be cut in half in patients whose creatinine clearance is 15 to 30 mL/min. For nizatidine and ranitidine, the dose should be halved if the creatinine clearance is less than 50 mL/min.[76] A noteworthy side effect is the alteration of cytochrome P-450 enzyme activity in the liver; this alteration may result in prolongation of the effects of concurrently administered drugs that rely on hepatic metabolism and elimination by means of this mechanism. Famotidine is the H_2 antagonist least likely to cause this effect. Other side effects of H_2 antagonists include decreased hepatic blood flow, leukopenia and thrombocytopenia, mental confusion, interstitial nephritis, hepatitis, bradycardia, and hypotension.

The proton pump inhibitors are the most effective antisecretory agents and are listed in Table 30-10. Sucralfate, the aluminum salt of sulfated sucrose, not only binds to ulcers but also increases the gastric mucous layer, thereby promoting healing processes. It has been shown to be equally efficacious when used with H_2 antagonists and antacids and is relatively devoid of side effects.

Misoprostol is a synthetic prostaglandin and may be used as a prophylactic therapy to prevent ulcers in patients taking NSAIDs. *H. pylori* is a species of gram-negative spiral bacteria sensitive to combination therapy with a variety of antibiotics. About 80% of upper GI bleeds are self-limited. Laparoscopic repair is indicated when medical therapy is unsuccessful.

Gastric Ulcer Disease

Gastric ulcers develop as a result of degeneration of the stomach's mucosal barrier to gastric acid. Gastric ulcers can occur anywhere in the stomach, and may or may not be associated with increased gastric acid secretion. Pain and anorexia predispose the patient to metabolic derangements and weight loss. The most frequent complication of gastric ulceration is perforation. Most perforations occur along the anterior aspect of the lesser curvature. In general, older patients have increased rates of perforations, and larger ulcers are associated with more morbidity and higher mortality rates. Similar to duodenal ulcer, gastric outlet obstruction can also occur in patients with type II or III gastric ulcer.[72] Surgery, consisting of antrectomy with pyloroplasty and vagotomy, is undertaken if the patient's condition does not respond to medical therapy.

Gastric Neoplastic Disease

Gastric cancer is the second most common type of cancer worldwide. In the United States, gastric cancer is the seventh most frequent cause of cancer-related death. Most gastric neoplasms are malignant. The incidence of these neoplasms according to type is adenocarcinoma, 95%; lymphoma, 4%; and leiomyosarcoma, 1%. The epigastric pain is similar to pain caused by benign ulcers and similarly may mimic angina. Typically, however, the pain is constant, nonradiating, and unrelieved by food ingestion. More advanced disease may present with weight loss, anorexia, fatigue, or vomiting. Symptoms often reflect the site of origin of the tumor. Endoscopic mucosal resection has become the treatment of choice for early gastric cancer (EGC), and usually is performed in association with endoscopic ultrasonography for staging. Advanced adenocarcinoma is defined as a tumor that invades the gastric wall beyond the submucosa. Most patients are men (male-to-female ratio of 2:1) in their fifth to seventh decades of life. Clinically, symptoms include epigastric pain, dyspepsia, anemia, and weight loss. Hematemesis and symptoms of gastric outlet obstruction are not uncommon. Female patients may develop metastatic ovarian lesions (Krukenberg tumors) composed of diffuse-type cancer cells. Unfortunately, the majority of patients with gastric cancer in the United States are diagnosed at an advanced stage.[78]

Surgical resection remains the primary curative treatment for gastric cancer and represents the best chance for long-term survival. In addition, surgical resection often provides the most effective palliation of symptoms, particularly those of obstruction. In general, total gastrectomy is performed for proximal gastric tumors and diffuse gastric cancer, and partial gastrectomy is reserved for tumors in the distal stomach. Despite increased morbidity and mortality, arguments in favor of an extended lymphadenectomy include the fact that removal of a larger number of lymph nodes

results in more accurate pathologic staging, and that failure to remove these lymph nodes leaves tumor behind in as much as one third of patients.[78]

Anesthetic Considerations in Gastric Disease

Despite advances in medical therapy designed to inhibit acid secretion and to eradicate *H. pylori*, surgery remains important in managing these patients. Patients undergoing surgery for gastric disease are generally either acutely ill and require emergency surgery, as in the case of a bleeding gastric ulcer, or stable and require elective surgical treatment of gastric carcinoma or intractable ulcer disease. Many procedures are performed laparoscopically. Limitations to the laparoscopic approach include the risk of peritonitis and dense adhesions. Acutely ill patients are more likely to be hemodynamically unstable and dehydrated. Elective surgical patients may have a variable degree of debilitation and anemia. Aspiration precautions in both groups are warranted during anesthesia.

Hypovolemia should be corrected with the administration of appropriate colloid, crystalloid, or blood products before the induction of anesthesia. Suggested laboratory tests include complete blood count, electrolytes, blood urea nitrogen, glucose, magnesium, calcium, phosphate, prothrombin time, and partial thromboplastin time. Other tests are performed based on history and physical examination. Preparations for the perioperative transfusion of blood products must be undertaken before anesthesia and surgery. Expect a moderate fluid shift with moderate to large fluid losses. Two large-bore intravenous catheters (14- to 16-gauge) are indicated.

Clinical anemia and coagulopathy should be corrected with packed red blood cells and appropriate blood products (e.g., FFP, cryoprecipitate, platelets). The use of invasive monitoring (i.e., that using a pulmonary artery catheter, central venous pressure line, or arterial line) is determined by the presence of preexisting, age-related, or acquired compromise in the function of other organ systems. Potential postoperative complications include hemorrhage, hypovolemia, hypothermia, atelectasis, and ileus. A postoperative stay in the intensive care unit may be necessary, especially in the case of peritonitis-caused fluid shifts and the need for large-volume fluid resuscitation.

The anesthetic technique used in gastrectomy may include preoperative epidural catheter placement as an intraoperative adjunct and for use in postoperative analgesia. Procedures other than total and partial gastrectomy performed for gastric disease include the following:

- Billroth I (gastroduodenostomy): resection of the distal stomach with reconstruction via end-to-end gastroduodenostomy
- Billroth II (gastrojejunostomy): resection of the distal stomach with reconstruction via end-to-side gastrojejunostomy
- Laparotomy with oversewing of the ulcer and application of an omental patch

Vagotomy is usually performed for gastric ulcer surgery to decrease gastric acid secretion and allow ulcer healing. The vagus nerve can be transected at the main vagal trunks (truncal), which interrupts transmission to the top of the stomach and other abdominal viscera, or selectively, in that only gastric vagal nerves are interrupted. Anesthetic technique is general or laparoscopic; esophageal dilators are used to facilitate traction on the stomach. A nasogastric (NG) tube is placed after induction.

Gastrostomy

Gastrostomy establishes a permanent or temporary artificial opening into the stomach that exits the skin of the abdominal wall and is surgically placed for the purpose of gastric decompression and nutritional support. Patients who require placement of a gastrostomy tube (permanent or temporary) are often neurologically incapacitated or otherwise markedly debilitated and are likely to have compromised command of their airway reflexes. This general finding, along with the need to insufflate the stomach, places the patient at greater risk for aspiration.

Gastrostomy placement is performed percutaneously at the bedside, in the endoscopy suite, or in the operating room. Endoscopic guidance is used with percutaneous placement of the gastrostomy tube. Any tube feedings should be stopped at least 8 hours prior to the procedure. A bite block should be used. As a primary procedure, gastrostomy placement is commonly undertaken with sedation and local anesthesia at the incisional site and in the back of the throat. General endotracheal anesthesia is indicated in patients who require laparotomy in conjunction with endoscopic placement and in those for whom percutaneous placement under local anesthesia with sedation may be contraindicated (e.g., the comatose patient). If general anesthesia is used, the endotracheal tube (ETT) may need to be held as the surgeon inserts and withdraws the gastroscope.

PANCREATIC DISEASE

Physiologic Overview

The pancreas is about 20 cm long, with its head tucked into the curve of the duodenum and its tail touching the spleen. The body lies behind the stomach. The pancreas functions in both an exocrine digestive enzyme and endocrine hormonal capacity.

The exocrine functions of the pancreas include protein secretion and electrolyte secretion. The exocrine function of the pancreas is primarily the continuous transductal secretion of 2.5 liters of clear, colorless, bicarbonate-rich (pH 8.3) pancreatic juice per day. The ionic composition consists largely of sodium, potassium, bicarbonate, and chloride, with smaller concentrations of phosphate, sulfate, zinc, and calcium. The principal function of pancreatic juice is duodenal alkalinization to promote optimal activity of pancreatic enzymes.

Arrival of acidic chyme (partially digested gastric contents) into the duodenum and jejunum stimulates the release of the hormones cholecystokinin-pancreozymin (CCK-PZ) and secretin. Both hormones are produced in the duodenum, jejunum, and ileum. Secretin causes the pancreas to release bicarbonate and water, and CCK-PZ, released in response to the presence of fats and partially digested proteins in the duodenum, stimulates elaboration of the pancreatic enzymes necessary for further intestinal digestive processes. Trypsinogen, produced by pancreatic cells, is converted to the active enzyme trypsin in response to the release of enterokinase by the gastric mucosa. Trypsin is responsible for the conversion of large ingested proteins into smaller peptides and amino acids in preparation for intestinal absorption.[34] The major pancreatic enzyme groups are listed in Table 30-11.

Secretion of the aqueous and enzymatic components of pancreatic juice is controlled by hormonal and parasympathetic stimuli. Administration of vagolytic agents (e.g., atropine, glycopyrrolate) or ganglionic blocking agents, along with physical interruption of the vagus nerve, may induce a decreased response to secretin. Vagotomy also has been shown to result in a decrease in the release of pancreatic bicarbonate in response to duodenal acidity.

The endocrine function of the pancreas consists primarily of regulation of the plasma glucose level through the release of glucagon and insulin. Endocrine cells of the pancreas reside in the islets of Langerhans, and the adult human pancreatic islet contains multiple types: the A (alpha) cell secretes glucagon, the B (beta) cell secretes insulin, the D (delta) cell secretes somatostatin (growth

TABLE 30-11 Major Pancreatic Enzyme Groups*

Enzyme Group	Enzyme, Proenzyme, or Precursor
Proteolytic	Trypsinogen (trypsin), chymotrypsinogen (chymotrypsin), procarboxypeptidase A (carboxypeptidase A), procarboxypeptidase B (carboxypeptidase B), proaminopeptidase (aminopeptidase), proelastase (elastase)
Amylolytic	α-Amylase
Lipolytic	Lipase, prophospholipase A_2 (phospholipase A_2), carboxylesterase lipase, procolipase (colipase)
Nucleolytic	Deoxyribonuclease, ribonuclease
Other	Trypsin inhibitor

*Precursor molecules are listed, with products in parentheses.

hormone–releasing inhibitory factor), which is responsible for controlling the plasma levels of both insulin and glucagon, and gastrin, whereas the D_2 (delta-2) cell secretes vasoactive intestinal peptide (VIP), and the PP (or F) cell secretes pancreatic polypeptide (PP).[79] The chief physiologic function of the endocrine pancreas might be starkly summarized as regulation of body energy (a role largely achieved by hormonal control of carbohydrate metabolism). Simply stated, insulin is the hormone of energy storage and glucagon the hormone of energy release. Insulin stores energy by decreasing blood glucose levels, increasing protein synthesis, decreasing glycogenolysis, decreasing lipolysis, and increasing glucose transport into cells (except beta cells, hepatocytes, and central nervous system cells). Glucagon releases energy by increasing blood glucose levels through stimulation of glycogenolysis, gluconeogenesis, and lipolysis.

α-Adrenergic sympathetic stimulation has been shown to be inhibitory to insulin secretion. β-Adrenergic sympathetic and cholinergic blockade are inhibitory to insulin secretion as well. Arterial hypoxemia, hypothermia, traumatic stress, and surgical stress all suppress insulin secretion through α-adrenergic stimulation. Insulin secretion is enhanced by parasympathetic vagal stimulation, β_2-adrenergic sympathetic activation, and cholinergic drug administration.

Anesthetic considerations in patients with derangements in pancreatic endocrine function, such as diabetes mellitus, are outside the scope of this chapter. The present discussion is directed toward anesthetic considerations germane to patients with inflammatory or neoplastic disease of the pancreas.

Acute Pancreatitis

The cause of pancreatitis is multifactorial. Common causes include alcohol abuse, direct or indirect trauma to the pancreas, ulcerative penetration from adjacent structures (e.g., the duodenum), infectious processes, biliary tract disease, metabolic disorders (e.g., hyperlipidemia and hypercalcemia), vascular and autoimmune causes, toxic causes, and certain drugs (e.g., corticosteroids, furosemide, estrogens, and thiazide diuretics). In industrialized nations, 80% of acute pancreatitis cases are caused by alcohol abuse or gallstones. Although 35% to 40% of attacks are induced by gallstones, only 3% to 7% of patients with gallstones develop pancreatitis. The incidence of gallstone pancreatitis is increased in white females older than 60 years and is highest among patients with small gallstones (less than 5 mm diameter). Severe acute pancreatitis (SAP) is associated with organ failure, local complications, prolonged intensive care stay, and mortality rates greater than 25%. In patients with SAP, the multiple organ dysfunction syndrome (MODS) is the main cause of death.[80]

Patients who have undergone extensive surgery involving mobilization of the abdominal viscera are at risk for development of postoperative pancreatitis, as are patients who have undergone procedures involving cardiopulmonary bypass. Patients who have received large doses of calcium intraoperatively, particularly after cardiopulmonary bypass, also have been shown to be at risk for development of postoperative pancreatitis.[81] Hypothetically, the pathophysiologic mechanism may involve a syndrome of induced autodigestion. In fact, acute pancreatitis is characterized as a severe chemical burn of the peritoneal cavity.

It is generally believed that acute pancreatitis is triggered by obstruction of the pancreatic duct and that the injury begins within pancreatic acinar cells. That injury is believed to include, and possibly be the result of, intraacinar cell activation of digestive enzyme zymogens, including trypsinogen. The pathophysiology of acute pancreatitis can be grouped into three phases. The first phase is characterized by the premature activation of trypsin in acinar cells. The second phase is the inflammatory response of the pancreas, which is disproportionate to the response of other organs to a similar insult. In the third phase, systemic activation of the immune system and remote organ dysfunctions occur.[80] Aberrant activation or release of pancreatic enzymes or injury to the acinar cells caused by one or more of the aforementioned etiologic factors produces a syndrome that results in hemorrhage, edema, and necrosis of the pancreas.

Enzymes implicated as major culprits in the syndrome of pancreatitis are those activated by trypsin, enterokinase, and bile acids. These enzymes are necessary for proteolysis, elastolysis, and lipolysis. The inappropriate elaboration of these enzymes results in pancreatic inflammation, which is caused by vascular breakdown, coagulation necrosis, fat necrosis, and parenchymal necrosis. Cardiovascular complications of acute pancreatitis can lead to pericardial effusions, alterations in cardiac rhythmicity, signs and symptoms mimicking acute myocardial infarction, thrombophlebitis, and cardiac depression. Acute pancreatitis also predisposes patients to the development of acute respiratory distress syndrome and disseminated intravascular coagulopathy.[6]

The pain of pancreatitis may be severe and difficult to control. Most patients require narcotic medications. Meperidine and its analogs are probably preferable to morphine in this setting because morphine can induce spasm of the sphincter of Oddi, which could, at least theoretically, worsen biliary pancreatitis. Pancreatic pain may radiate from the midepigastric to the periumbilical region and may be more intense when the patient is in the supine position. Abdominal distention is often seen and is largely attributable to the accumulation of intraperitoneal fluid and paralytic ileus. Nausea, vomiting, and fever are common symptoms. Hypotension is seen in 40% to 50% of patients and is attributable to hypovolemia secondary to the loss of plasma proteins into the retroperitoneal space. Acute renal failure secondary to dehydration and hypotension may occur.

Immediate circulatory and electrolyte resuscitation restores the microcirculation and represents one of the most powerful and effective interventions, especially in patients with severe acute pancreatitis. Fluid losses can be enormous and can lead to marked hemoconcentration as well as hypovolemia. Inadequate fluid resuscitation during the early stages of pancreatitis can worsen the severity of an attack and lead to subsequent complications. The fluid depletion that occurs in pancreatitis results from the additive effects of losing fluid both externally and internally. The external fluid losses are caused by repeated episodes of vomiting and worsen by nausea that limits fluid intake. Repeated vomiting can result in a hypochloremic alkalosis. Internal fluid losses, which are usually

even greater than the external losses, are caused by fluid sequestration into areas of inflammation (i.e., the peripancreatic retroperitoneum) and into the pulmonary parenchyma and soft tissues elsewhere in the body. These latter losses result from the diffuse capillary leak phenomenon that is triggered by proinflammatory factors released during pancreatitis. Total fluid losses may be so great that they lead to hypovolemia and hypoperfusion, and as a result, a metabolic acidosis can develop.[82]

In patients with severe acute pancreatitis, the magnitude of the proinflammatory response correlates with the severity and concomitant course of disease. A simple predictive tool is C-reactive protein (CRP). A CRP level exceeding 150 mg/L, a cutoff level that has been arbitrarily chosen, within the first 72 hours correlates with the occurrence of necrotizing pancreatitis and the degree of severity.[83]

During the first several days of a severe attack, circulating levels of many proinflammatory factors, including cytokines and chemokines, are elevated. This so-called cytokine storm, in many cases, triggers the systemic immune response syndrome, and as a result, the hemodynamic parameters of these patients may resemble those of sepsis associated with other disease states. Heart rate, cardiac output, and cardiac index usually rise, and total peripheral resistance falls. Hypoxemia also can occur as a result of the combined effects of increased intrapulmonary shunting and a pancreatitis-associated lung injury that closely resembles that seen in other forms of acute respiratory distress syndrome (ARDS). Fluid management, although critical, may be particularly difficult when hypovolemia is combined with the respiratory failure of ARDS.[82]

Severely ill, malnourished patients are often given parenteral nutritional support. Pain is controlled with synthetic opioids, such as fentanyl, which are preferable to morphine. Morphine-induced spasms of the Oddi sphincter may exacerbate bile obstruction and stasis. Normeperidine, the metabolite of meperidine, causes analeptic activity and makes meperidine unattractive for pain management in these patients. Epidural analgesia may be selectively appropriate.[82]

Patients with gallstone pancreatitis can be divided into two groups: those who have or have had gallbladder-derived problems (cholecystitis or biliary colic) and those whose only problems are purely related to stones in the biliary ductal system (i.e., cholangitis and pancreatitis). Patients in the first group undergo cholecystectomy because that operation will prevent additional gallbladder attacks as well as eliminate the source of stones that might trigger another attack of pancreatitis. Patients in the second group, however, do not necessarily require cholecystectomy because their problem relates only to ductal stones. Theoretically, they could be treated simply by endoscopic stone clearance combined with endoscopic sphincterotomy, so that future stones are passed without becoming impacted in the ampulla and triggering either pancreatitis or cholangitis. Indeed, for poor surgical risk patients, the endoscopic approach is generally recommended. Good surgical risk patients are better managed by cholecystectomy.

The choice of anesthetic technique and the extent to which monitoring modalities are used are based on an assessment of the patient's history, the severity of disease, and the degree of preexisting physical compensation. Special attention should be paid to correcting significant intravascular volume deficits. The presence of labile hemodynamics and altered hepatic function also must be discerned and appropriate modifications made to the anesthetic plan—for example, ensuring stable arterial pressure, using anesthetic agents and adjuvants that require minimal hepatic biotransformation, ensuring adequate oxygenation, and replacing electrolytes and blood volume.

Chronic Pancreatitis

Chronic pancreatitis is traditionally defined as having permanent and irreversible damage to the pancreas, with histologic evidence of chronic inflammation, fibrosis, and destruction of exocrine (acinar cells) and endocrine (islets of Langerhans) tissue. Chronic pancreatitis is believed to reflect repeated episodes of subclinical acute pancreatitis with unrecognized pancreatic necrosis evolving into pancreatic fibrosis.

The most common etiology of chronic pancreatitis is alcohol use (70% of cases), with the risk increasing logarithmically with increasing alcohol use. Other causes include tobacco use (increased risk of pancreatic calcifications), genetic mutation, autoimmune disease, and obstruction of the main pancreatic duct by tumors, scars, stones, or duodenal wall cysts.[84]

Chronic pancreatitis is strongly suggested by the classic diagnostic triad of steatorrhea, pancreatic calcification (evidenced radiographically), and diabetes mellitus. Steatorrhea does not occur until pancreatic lipase secretion is less than 10% of the maximum output. The most common clinical problem in chronic pancreatitis is abdominal pain causing loss of appetite that results in weight loss and malnutrition. The clinical picture may also include hepatic disease, as evidenced by jaundice, ascites, esophageal varices, derangements in coagulation factors, serum albumin, and transferase enzymes. A disturbance in pancreatic exocrine function, with consequent enzymatic insufficiency, results in malabsorption of fats and proteins in the intestine. Patients with chronic pancreatitis also have a predisposition for pericardial and pleural effusions.[82]

Many of the patients with chronic pancreatitis are alcoholics who, even before the onset of pancreatitis, had hypoalbuminemia and hypomagnesemia. Those problems are exacerbated by the losses of pancreatitis. The measured values for serum albumin may be even further depressed as fluid losses are treated with albumin-free crystalloid solutions. Although hypocalcemia is common, particularly during a severe attack, the low total serum calcium is usually attributable to the low levels of circulating albumin, and no treatment is needed when ionized calcium is normal. Occasionally, however, ionized calcium levels also may be depressed, and tetany as well as carpopedal spasm can occur. This necessitates monitoring the electrocardiogram (ECG) for cardiac rhythm disorders (e.g., lengthened QT interval with possible reentry dysrhythmias). Under those circumstances, aggressive calcium repletion is indicated.[82]

Endocrine insufficiency is another consequence of chronic pancreatitis and is especially common after pancreatic resection. About half of all patients with chronic pancreatitis develop insulin-dependent diabetes. Unlike type I diabetes, insulin-producing beta cells and glucagon-producing alpha cells are injured, leading to an increased risk of prolonged and severe hypoglycemia with overzealous insulin treatment.[84]

Pancreatic abscesses develop from infected peripancreatic collections of fluid. Abscesses are usually secondary manifestations of chronic pancreatitis and warrant surgical drainage to prevent spread of the infectious contents to the subphrenic and pericolic spaces. Fistula formation is possible, particularly into the transverse colon. Severe intraabdominal hemorrhage is also possible as a result of erosion into major proximal arteries.

Pancreatic Pseudocysts

Most pseudocysts communicate with the pancreatic ductal system and contain a watery fluid that is rich in pancreatic digestive enzymes. Typically, patients with pseudocysts have persistent elevations of circulating pancreatic enzymes. Recent reports have

shown that many pseudocysts eventually resolve without complications and that intervention is not mandatory in all cases unless the pseudocysts are symptomatic, enlarging, or associated with complications. The likelihood that a pseudocyst will resolve spontaneously, however, is dependent on its size. Large pseudocysts (i.e., greater than 6 cm in diameter) are more likely to become symptomatic either because they are tender or because of their mass effect on adjacent organs. Those that compress the stomach or duodenum may cause gastric outlet obstruction with nausea and vomiting. Those that reduce the capacity of the stomach frequently cause early satiety, whereas those impinging on the bile duct can cause obstructive jaundice. Pancreatic pseudocysts that erode into a neighboring vessel can result in formation of a pseudoaneurysm with *hemosuccus pancreaticus* and upper gastrointestinal bleeding.

Most patients who develop symptomatic pseudocysts are best managed by pseudocyst drainage. Internal drainage can be accomplished either endoscopically (by transpapillary drainage, cystogastrostomy, or cystoduodenostomy) or surgically (by cystogastrostomy, cystoduodenostomy, or Roux-en-Y cystojejunostomy). The approach chosen depends primarily on the locally available expertise as well as the location of the pseudocyst, but endoscopic drainage may be preferable in poor surgical risk patients.

Surgical Therapy for Pancreatitis

Depending on the cause of pancreatitis, several surgical approaches can be made. Endoscopic therapy is used to improve drainage of the pancreatic duct. This can be done through pancreatic duct sphincterotomy, stent placement, or pancreatic duct stone removal (including extracorporeal shock wave lithotripsy [ESWL]). Open surgical therapy in chronic pancreatitis is most often considered for intractable abdominal pain for which medical therapy has failed, complications involving adjacent organs, failure of endoscopic management of pseudocysts, and internal pancreatic fistulas.

Surgical drainage of a pancreatic pseudocyst is usually undertaken after a period of maturation of the cyst (usually 6 weeks with acute pancreatitis). Pseudocysts with chronic pancreatitis are generally mature at the time of diagnosis, and delay is not necessary to allow for maturation. The procedure consists of formation of a cystogastrostomy, cystojejunostomy, cystoduodenostomy, or possibly distal pancreatectomy. The location of the pseudocyst dictates the extent and type of procedure used for providing drainage of cystic contents into the gastrointestinal tract. Percutaneous external drainage, guided by CT, is reserved for cases in which the pseudocyst is particularly friable.[85]

Pancreatic Tumors

Pancreatic cancer affects 25,000 to 30,000 people in the United States each year, occurs more often in men than in women, and is more common among blacks than whites. The generation most commonly associated with pancreatic cancer is between 60 and 80 years of age (80%), whereas less than 2% occur in people younger than 40 years. Other risk factors include a family history of pancreatic cancer or a history of either hereditary or chronic pancreatitis, cigarette smoking, and occupational exposure to carcinogens. The incidence of diabetes mellitus is increased in patients with pancreatic cancer, but some studies have indicated that diabetes is a risk factor for the development of pancreatic cancer, whereas others have argued that diabetes may be a manifestation of the cancer. Coffee drinking, which was once considered a risk factor, is no longer thought to play a role in the development of pancreatic cancer.[82]

Eighty to ninety percent of all pancreatic tumors can be accounted for by ductal adenocarcinoma, and an even greater percentage of the malignant tumors are ductal adenocarcinoma. Most ductal cancers (70%) arise in the pancreatic head or uncinate process. They are generally resected by pancreaticoduodenectomy, with or without preservation of the pylorus and proximal duodenum. Ductal cancers originating in the body or tail of the pancreas are often larger and more likely to have spread before their presence is known.[82]

Pancreatic cancers are insidious tumors that can be present for long periods and grow extensively before they produce symptoms. Once symptoms appear, they are determined by the location of the tumor in the pancreas. Those in the head or uncinate process of the pancreas cause bile duct, duodenal, or pancreatic duct obstruction. Because the head of the pancreas is most often the locus of the tumor, biliary obstruction is likely, resulting in progressive painless jaundice. The patient may have symptoms that are vague and nonspecific and include dull, aching, midepigastric or back pain. Anorexia and fatigue are often present and are associated with weight loss. Other symptoms include unexplained episodes of pancreatitis, nausea, vomiting, and steatorrhea. If the tumor spreads beyond the pancreas, peripancreatic nerve plexuses may cause abdominal or back pain. In the presence of peritoneal carcinomatosis or portal vein occlusion, ascites may occur. New-onset diabetes mellitus is occasionally the first symptom of an otherwise occult pancreatic cancer. Recent studies have suggested that this form of diabetes may be mediated by a factor released from the tumor that either inhibits insulin release from islets or induces peripheral insulin resistance. Unexplained migratory thrombophlebitis (Trousseau's syndrome) may be associated with pancreatic and other types of malignancy. It is probably a paraneoplastic phenomenon that results from a tumor-induced hypercoagulable state.[82]

Laboratory studies usually show elevated bilirubin and alkaline phosphatase levels. Radiographic evidence is generally nonspecific; needle biopsy during CT is most helpful in achieving diagnosis. Percutaneous transhepatic cholangiography and endoscopic retrograde cholangiopancreatography are useful diagnostic modalities. Endoscopic retrograde cholangiopancreatography is the most useful modality for defining lesions of the body and tail of the pancreas or of the duodenum and ampulla.[85]

Insulinoma is the most common functioning tumor of the pancreas, and affected patients have a multitude of symptoms referable to hypoglycemia including seizures and coma (symptoms of catecholamine release), mental confusion and obtundation, or both. Hypersecretion of insulin is a major manifestation of this disease and results in profound hypoglycemia. The diagnostic hallmark of the syndrome is the so-called Whipple triad, namely, symptoms of hypoglycemia (catecholamine release) and low blood glucose (40-50 mg/dL) and relief of symptoms after the IV administration of glucose.

Treatment of insulinoma is surgical and performed by either open or laparoscopic approaches except in patients with advanced metastatic disease, and involves distal pancreatectomy, subtotal pancreatectomy, or removal of all but a small portion of pancreatic tissue around the rim of the duodenum (Child procedure).[85]

If neoplastic disease is determined to be respectable, that is, without involvement of mesenteric vessels or infiltration into the mesenteric arterial root or hepatobiliary structures, a pancreaticoduodenectomy (Whipple procedure) may be performed. This

procedure involves excision of the head of the pancreas, the entire duodenum, the proximal portion of the jejunum, the distal third of the stomach, the gallbladder, and the distal half of the common bile duct. A Whipple procedure also can be performed for malignancies of the common bile duct, traumatic injury to the pancreas, or benign obstructive chronic pancreatitis.[86]

Zollinger-Ellison syndrome (ZES; gastrinoma), a neoplasm primarily arising from the duodenum, releases overabundant quantities of gastrin, resulting in the secretion of massive quantities of hydrochloric acid from the parietal cells. This condition is associated with severe, intractable ulcer pain. If other endocrine neoplasias are present (i.e., thyroid or parathyroid adenoma, pituitary adenoma, insulinoma), the condition is referred to as *multiple endocrine neoplasia type I*.

Omeprazole therapy is so effective that surgery is performed only for tumor removal, and every patient with ZES is a candidate for a tumor removal operation until proved otherwise because of systemic illness or widespread metastases. Although gastrinomas have a high rate of malignancy, they are more apt to be cured than cancer of any other abdominal viscera. During anesthetic induction for excision of gastrinoma, a rapid-sequence technique is recommended because of the likelihood of a large volume of stagnant, acidic intragastric fluid. Electrolyte and intravascular volume derangements (e.g., from severe diarrhea) should be anticipated and corrected before surgery. Attention also should be given to intraoperative monitoring of electrolyte and fluid balance. Hypokalemia and metabolic alkalosis are likely to be present if the patient has been vomiting and is dehydrated. Furthermore, preparations for the treatment of patients with known or suspected derangements in endocrine function must be included in the anesthetic plan, to include blood glucose monitoring, vigilance for and timely correction of swings in vital signs and physiologic parameters, maintenance of normothermia and normocarbia, maintenance of an appropriately anesthetized state, and maintenance of renal function.[34]

Gastrinoma is the second most common islet cell tumor and is the most common symptomatic, malignant endocrine tumor of the pancreas. Having said that, current information is that gastrinomas in the duodenum are 3 to 10 times more common than in the pancreas, and although up to 70% of duodenal gastrinomas have lymph node metastases, only 5% have liver metastases. Although gastrinomas have a high rate of malignancy, they are more apt to be cured than cancer of any other abdominal viscera.

Anesthetic Considerations in Pancreatic Disease

The patient undergoing surgical treatment of pancreatic disease exhibits a variable clinical picture, from jaundiced and stable with a painless pancreatic mass to severely ill with multiorgan system involvement. Patients may have severe, acute abdominal pain with possible intestinal obstruction or ileus. Aspiration precautions should be in effect during induction of anesthesia and emergence from anesthesia, and an NG tube should be placed after induction. Because these patients are likely to be diabetic (secondary to beta-cell dysfunction) or hypoglycemic (as in the case of insulinoma), perioperative assessment of serum glucose and institution of appropriate control measures are warranted. Patients with pancreatitis are usually hypotensive and hypovolemic. As such, aggressive blood product and crystalloid resuscitation may be necessary throughout the perioperative period and likely will necessitate placing invasive hemodynamic lines to guide therapy and monitor central pressures.

Severe electrolyte disorders may be present and include hypocalcemia, hypomagnesemia, hypokalemia, and possibly hypochloremic metabolic alkalosis. The serum hematocrit value may be falsely increased secondary to hemoconcentration, or it may be decreased secondary to the presence of a bleeding diathesis. Coagulation parameters, including platelet count, prothrombin time (PT), activated partial thromboplastin time (aPTT), and fibrinogen level, should be assessed at regular intervals perioperatively. Preserving renal function mandates the preoperative assessment of blood urea nitrogen, serum creatinine, and 24-hour creatinine clearance (if possible); urinalysis also should be performed. Intraoperatively, a urine output of at least 0.5 to 1 mL/kg/hr should be maintained.

Thorough assessment of preexisting pulmonary status is vital. Pleural effusions, $\dot{V}/\dot{Q}$ mismatching, and atelectasis may be seen and can progress to respiratory failure. A significant incidence of postoperative respiratory morbidity is associated with upper abdominal surgery, especially in association with a preoperative debilitated state and splinting secondary to pain. Pulmonary assessment includes arterial blood gas analysis, chest radiography, and pulmonary function tests when appropriate.

Cardiovascular assessment should assimilate related findings from the assessment of other organ systems so that the degree to which functional hemodynamic impairment may need to be corrected is fully appreciated. Correction of preexisting hemodynamic disturbances entails restitution of plasma volume and the oxygen-carrying capacity of the blood. Ischemic changes noted on the ECG must be treated promptly. ECG changes mimicking myocardial ischemia are often seen in those with pancreatitis.[34]

The celiac plexus transmits visceral afferent impulses from the upper abdominal organs, including the pancreas. Celiac plexus block may be performed in patients with chronic pancreatitis, but its effects are short-lived. A combination of glucocorticoid and long-acting local anesthetic such as bupivacaine are commonly used. Celiac plexus neurolysis also may be performed using an injection of absolute alcohol and administered under CT or ultrasound guidance.[84]

Pancreatectomy

Pancreatectomy is performed for a variety of reasons including ductal obstruction, pancreatic stones or cysts, trauma, benign or malignant tumors, chronic pancreatitis, and endocrine tumors. Complete surgical excision is the only definitive treatment of ductal pancreatic cancer.

In a partial pancreatectomy, part of the pancreas, the duodenum, the gallbladder, and part of the bile duct are removed. The tail of the pancreas is joined to a portion of the small bowel. In a total pancreatectomy, the distal portion of the stomach, the gallbladder, part of the bile duct, the spleen, and the surrounding lymph nodes are removed. The remaining distal portion of the stomach is reanastomosed to a portion of the small intestine.[86]

General endotracheal anesthesia is preferred for pancreatectomy, and muscle relaxants are used. The presence of increased intraabdominal pressure requires a rapid sequence induction. The use of nitrous oxide should be avoided because of expansion of air-filled spaces in the bowel. An epidural is advised with a level of T9 to T10 for postoperative pain control because it seems to improve the surgical outcome.[87] An even better choice may be the use of intrathecal morphine. One study also showed that intrathecal morphine for major hepato-pancreato-biliary surgery is associated with a lower incidence of postoperative hypotension, reduced perioperative intravenous fluid requirement, and shorter hospital stay compared with thoracic epidural anesthesia.[88]

Patients undergoing extensive pancreatic surgery often require postoperative ventilatory support and intensive care unit

monitoring because of the magnitude and length of the procedure, as well as the patient's preexisting cardiopulmonary status.[34] Pancreatic transplants are discussed later in this chapter.

DISEASES OF THE INTESTINAL TRACT

Anatomic and Physiologic Overview of the Small Intestine

The overall length of the small intestine is between 5 and 7 meters and extends from the pylorus to the ileocecal valve. The small intestine is divided into three functional anatomic and physiologic segments. The first segment, the duodenum, begins at the pylorus and has a length of approximately 20 cm. The duodenum joins the second segment, the jejunum, which has a length of approximately 100 to 110 cm, at a suspensory ligament called the treitz ligament. The third and longest segment of the small intestine is the ileum, which has a length of approximately 150 to 160 cm and ends at the ileocecal valve. The jejunum has a larger lumen and is thicker than the ileum with a less extensive blood supply (one or two vascular networks versus four or five in the ileum).[89]

The mesentery, which is rich in lymphatics and blood vessels, is a peritoneal membrane that tethers the ileum and jejunum to the posterior abdominal wall and facilitates intestinal motility. Branches of the superior mesenteric artery provide the primary arterial supply to the jejunum and ileum and to the proximal transverse colon. Venous drainage is primarily furnished by the superior mesenteric vein. This vessel joins the splenic vein posterior to the pancreas, and empties into the portal circulation to the liver. Lymphatic drainage from the bowel wall originates from the central bowel wall lacteal and continues through the superior mesenteric nodes into the cisterna chyli and ultimately drains into the thoracic duct.

The wall of the small intestine is composed of the mucosa, submucosa, muscular layer (muscularis), and serosa. The serosal outermost layer is composed of visceral peritoneum. This layer is formed in the jejunum, ileum, and anterior duodenum and is analogous to the pericardium and pleura that surround the heart and lungs, respectively. There is fluid containing space between the visceral peritoneum and the parietal peritoneum, which aids in lubricating for organ movement. The muscular layer is made up of an outer longitudinal layer and a thin circular layer of smooth muscle, both continuously present along the length of the small intestine. The Auerbach (myenteric) plexus, which primarily controls gross gastrointestinal motility, lies between the two muscular layers. The strongest component of the bowel wall is the submucosa, which consists of fibroelastic connective tissue. Within it lies the Meissner plexus, which controls local blood flow and gastrointestinal secretions. The innermost layer, the mucosa, is composed of transverse folds with millions of villi. These intraluminal projections are the functional units of the intestines and greatly increase the absorptive surface.

The mucosa is further subdivided into three distinct layers:

1. *Muscularis mucosae*. The deepest layer, composed of a thin muscular sheet.
2. *Lamina propria*. A continuous connective tissue layer between the muscularis mucosae and the epithelium. This layer serves as a support epithelium and immunogenic barrier. Constituents of this layer include plasma cells (which produce immunoglobulins), macrophages, and lymphocytes.
3. *Epithelial layer*. Covers the villi and lines the Lieberkühn crypts. The functional units of the intestines, villi, contain goblet (mucus-secreting), absorptive, and endocrine cells. The villi also secrete enzymes necessary for digestion and are useful in nutrient absorption. Cell turnover takes 3 to 7 days.

The intestinal mucosa provides a barrier to the entry of pathogens. The lamina propria provides a rich reservoir of IgA (the secretory immunoglobulin) and plasma cells (responsible for synthesis of IgA). IgA antigen binding initiates mucus secretion, which prevents intestinal bacterial and viral uptake. Furthermore, IgA binds with, disables, and facilitates enzymatic destruction of bacteria. Binding with and preventing entry of toxins is another role of IgA. Lymphocytes, which are instrumental in the elaboration of a specific antibody to a given antigen, are found in Peyer patches, which are located in the intestinal wall.[90]

An additional function of small intestinal mucosa is the production of a rich supply of hormones that regulate gastrointestinal function (Table 30-12).

Both divisions of the autonomic nervous system innervate the small intestine, but innervation is primarily parasympathetic through the vagus nerve and celiac ganglia. Parasympathetic stimulation is responsible for pain sensation, increased motility, secretion, and intestinal reflexes (e.g., relation of the lower esophageal sphincter). Splanchnic nerves from the celiac plexus provide sympathetic innervation, the activation of which inhibits motility and produces vasoconstriction. Sympathetic nerve tracts are also responsible for carrying afferent pain impulses. Intrinsic motor innervation is mediated by the myenteric plexus (Auerbach plexus) and the submucosal plexus (Meissner plexus). The enteric nervous system also plays an important role in the gastrointestinal tract. The enteric nervous system is the network of neurons found within the walls of the gastrointestinal tract, including neurons in the pancreas and gallbladder. The enteric nervous system contains as many nerve cells as the spinal cord, and is unique in its extraordinary degree of local autonomy. The high degree of local autonomy allows digestion and peristalsis to continue in the event of spinal cord transection or spinal anesthesia. Spinal anesthetic inhibition of sympathetic preganglionic fibers from T8 through L3 yields a contracted small intestine that may afford superior surgical conditions.

The intestinal inhibitory reflex responds to abnormal distention by decreasing motility proximal to the locus of distention. This reflex may have significant indirect clinical implications (e.g., aspiration risk).[90] Physiologic functions of the small intestine are summarized in Box 30-9.

Chyme from the stomach stimulates intestinal movements that mix in secretions from the liver, pancreas, and intestinal glands. A basic electrical rhythm in the longitudinal smooth muscle layer initiates action potentials in the circular muscular layers of the small intestine. This activity sets forth the muscular contractions that constitute small-bowel motility. Both segmental contractions, which mix chyme with digestive enzymes and expose it to the villi's absorptive surfaces, and peristaltic (propulsive) contractions to move chyme toward the large intestine are present.

Malabsorption Syndromes

The two most important goals of the small intestine are the efficient absorption of nutrients and maintaining the movement of chyme and indigestible substances along the small intestine. Approximately 85% to 90% of the water entering the gastrointestinal tract is absorbed in the small intestines. Malabsorption syndromes interfere with nutrient absorption in the small intestine through mucosal disruption. Numerous disorders of the small intestine manifest as derangements in absorption. Primary clinical signs include unexplained weight loss, steatorrhea, and diarrhea. These disorders affect the absorption of the major constituents of ingested nutrients, including amino acids, carbohydrates, and fats.[6]

TABLE 30-12 Gastrointestinal Hormones

Hormone	Location	Major Stimulants of Peptide Secretion	Primary Effects	Diagnostic and Therapeutic Uses
Gastrin	Antrum, duodenum (G cells)	Peptides, amino acids, antral distention, vagal and adrenergic stimulation, gastrin-releasing peptide (bombesin)	Stimulates gastric acid and pepsinogen secretion; stimulates gastric mucosal growth	Gastrin analog (pentagastrin) used to measure maximal gastric acid secretion
Cholecystokinin (CCK)	Duodenum, jejunum (I cells)	Fats, peptides, amino acids	Stimulates pancreatic enzyme secretion; stimulates gallbladder contraction; relaxes sphincter of Oddi; inhibits gastric emptying	Biliary imaging of gallbladder concentration
Secretin	Duodenum, jejunum (S cells)	Fatty acids, luminal acidity, bile salts	Stimulates release of water and bicarbonate from pancreatic ductal cells; stimulates flow and alkalinity of bile; inhibits gastric acid secretion and motility and inhibits gastrin release	Provocative test for gastrinoma; measurement of maximal pancreatic secretion
Somatostatin	Pancreatic islet (D cells), antrum, duodenum	Gut: Fat, protein, acid, other hormones (e.g., gastrin, CCK) Pancreas: Glucose, amino acids, CCK	Universal "off" switch; stimulates release of all GI secretion and motility; stimulates gastric acid secretion and release of antral gastrin; stimulates growth of intestinal mucosa and pancreas	Treatment of carcinoid; diarrhea and flushing; decreases secretion from intestinal fistulas (particularly pancreatic fistulas); ameliorates symptoms associated with hormone-overproducing endocrine tumors; treatment of esophageal variceal bleeding
Gastrin-releasing peptide (mammalian equivalent of bombesin)	Small bowel	Vagal stimulation	Universal "on" switch; stimulates release of all GI hormones (except secretin); stimulates GI secretin; stimulates growth of intestinal mucosa and pancreas	
Gastric inhibitory polypeptide	Duodenum, jejunum (K cells)	Glucose, fat, protein adrenergic stimulation	Inhibits gastric acid and pepsin secretion; stimulates pancreatic insulin release in response to hyperglycemia	
Motilin	Duodenum, jejunum	Gastric distention, fat	Stimulates upper GI tract motility; may initiate the migrating motor complex	
Vasoactive intestinal peptide	Neurons throughout GI tract	Vagal stimulation	Primarily functions as a neuropeptide; potent vasodilator	
Neurotensin	Small bowel (N cells)	Fat	Stimulates pancreatic and intestinal secretion; inhibits gastric acid secretion; stimulates growth of small and large bowel mucosa	
Enteroglucagon	Small bowel (L cells)	Glucose, fat	Glucagon-like peptide-1: stimulates insulin release; inhibits pancreatic glucagon release; Glucagon-like peptide-2: potent enterotropic factor	
Peptide YY	Distal small bowel, colon	Fatty acids, CCK	Inhibits gastric and pancreatic secretions; inhibits gallbladder contraction	

From McKenzie S, Evers BM. Small intestine. In: Townsend CM, et al, eds. *Sabiston Textbook of Surgery: The Biological Basis of Modern Surgical Practice*. 19th ed. Philadelphia: Saunders; 2012.
CCK, Cholecystokinin; *GI*, gastrointestinal.

Fat malabsorption results in deficiency in the uptake of fat-soluble vitamins (vitamins A, D, E, and K). Deficiency in vitamin K manifests through hypoprothrombinemia. This condition is often evidenced through bleeding dyscrasias. Vitamin B_{12} deficiency results in anemia (which also may be encountered in patients with impaired iron absorption), neuropathy, and glossitis. Protein malabsorption may result in the development of peripheral edema and ascites. Tetany, osteomalacia, and pathologic fractures result from calcium deficiency caused by vitamin D malabsorption and calcium malabsorption because fatty acids bind calcium. In the setting of steatorrhea, pancreatic replacement enzymes are often effective in decreasing fat loss.[72]

The cause of malabsorption syndromes is multifactorial. The basic underlying defect is either disruption of intestinal mucosal

BOX **30-9**

Synopsis of Physiologic Functions (Digestion and Absorption) of the Small Intestine

Protein
- Initiated in the stomach
- Completed in the duodenum and jejunum; further hydrolysis (via intracellular peptidases) of peptides to free amino acids occurs before entry into the portal vein (approximately 90% of intact peptides)

Carbohydrates
- Initiated by salivary amylase
- Digested by pancreatic amylase in the duodenum; absorption completed by brush border of the intestinal microvilli (through conversion of monosaccharides into absorbable hexoses)

Fats
- Digestion and absorption of lipid (primarily triglycerides) occurs almost entirely in the small intestine by two processes:
  - Lipolysis
  - Formation of micelles
- Facilitated by pancreatic bicarbonate and bile salts

Water and Electrolytes
- 10 L of water enters small bowel daily; most of this volume is absorbed
- Net absorption of water facilitated primarily via osmosis; another mechanism involves passive diffusion through luminal pores under the influence of hydrostatic pressure
- Sodium absorption occurs essentially in conjunction with bulk flow of water (primarily in the jejunum); this process occurs with concomitant hydrogen ion extrusion
- Bicarbonate secretion and chloride ion absorption occur in conjunction with sodium absorption
- Electrical neutrality is maintained
- Calcium ion absorption (facilitated by an acidic environment) occurs primarily in the duodenum and jejunum via active transport; enhanced by vitamin D and parathyroid hormone
- Passive potassium absorption occurs primarily in the jejunum
- Absorption of iron occurs primarily in the duodenum

Other Vitamins and Minerals
- Ascorbic acid—absorbed in the ileum and coupled to sodium
- Cobalamin (vitamin B_{12})—absorbed in the distal ileum and linked to glycoprotein carrier molecules (especially intrinsic factor)
- Folate—absorbed in the proximal jejunum in conjunction with sodium
- Biotin—absorbed in the proximal small bowel as a result of sodium-linked active transport
- Thiamine (vitamin B_1)—absorbed predominantly in the duodenum
- Vitamin B_6—absorbed in the proximal small bowel
- Niacin, pantothenate, and riboflavin—absorbed passively (mechanism incompletely understood)

Modified from McKenzie S, Evers BM. Small intestine. In: Townsend CM, et al, eds. *Sabiston Textbook of Surgery: The Biological Basis of Modern Surgical Practice*. 19th ed. Philadelphia: Saunders; 2012.

integrity, such as from disease processes, or loss of absorptive surface area caused by extensive surgical resection of the small intestine (i.e., short gut syndrome). With regard to alterations in small-intestine absorption secondary to surgical resection, the particular part of the small bowel resected and the amount removed have a significant bearing on the degree to which deficiencies in minerals, vitamins, and electrolytes are clinically manifested and of concern to the anesthetist.

Maldigestion Syndromes

Maldigestion syndromes are generally caused by failure of the chemical processes of digestion that take place in the intestinal lumen or at the brush border of the intestinal mucosa. The most common causes include pancreatic, lactase, or bile salt deficiency. Diseases more likely to result in malabsorption syndromes (failure to absorb and transport digested nutrients) may be differentiated from those responsible for maldigestion (failure of the chemical digestive process). The hallmark of maldigestion is steatorrhea. Significant pancreatic disease is usually present when a maldigestion syndrome exists, because the pancreas has a large functional reserve in both normal and disease states. Chronic pancreatitis is the major and most common cause of pancreatic insufficiency. Cystic fibrosis, fistulas, gallstones, ischemic enteritis, and neoplastic disease processes, however, are also etiologic factors.[90]

Anatomic and Physiologic Considerations of the Large Intestine

The large intestine is approximately 3 to 5 feet long, consists of the cecum, appendix, colon, rectum, and anal canal, and may be recognized not only by its size and position but also by the presence of three strips of longitudinal muscle called *teniae coli* and the numerous outpouchings (haustrations) formed by the circular muscles of the colon. The arterial supply comprises the superior mesenteric artery (which perfuses the right side of the midtransverse colon), the inferior mesenteric artery (which perfuses the midtransverse colon to the superior rectum), and the internal iliac artery (which perfuses the middle and lower rectum). Venous drainage parallels arterial drainage, with the middle and superior veins contributing to the portal venous system. The myenteric plexus regulates motor and secretory activity independently of the extrinsic system. Sympathetic innervation is derived from T10 to T12 (right colon), L1 to L3 (left colon), and the presacral nerves arising within the preaortic plexuses (rectum). Parasympathetic innervation is primarily from the vagus nerve (right and transverse colon) and from nerve fibers arising from S2 to S4 (descending colon, sigmoid colon, and rectum). A rich endowment of lymphatics is present throughout the length of the colon and rectum.[34]

The primary function of the large colon is to store and expel waste products. Approximately 500 to 700 mL of chyme are delivered from the ileum to the cecum each day. Another function performed largely in the right colon is the absorption of sodium and water. All but 100 to 200 mL of the 1 to 2 L of ileal effluent presented to the large colon per day is reabsorbed through diffusion and active transport.

Sodium absorption occurs through active transport against a gradient and is enhanced by minerals, corticoids, glucocorticoids, and fatty acids that are produced by indigenous bacteria. Conservation of sodium is so efficient in the large colon that a normal individual may require only 5 mEq/day in order to remain in sodium balance. However, a patient presenting with an ileostomy necessitates a greater intake of sodium (80 to 100 mEq/day) to approximate the high sodium content lost as ileal effluent. The

loss of the normal colonic reabsorption of sodium chloride and water (e.g., after colectomy) may eventually exceed the small intestine's compensatory capacity to increase absorption, and clinical derangements in electrolyte balance follow.

Potassium is passively absorbed and secreted across the electrochemical gradient, whereas chloride is absorbed as the complementary ion to sodium and in exchange for bicarbonate. Potassium is lost through passive diffusion in the colonic mucoid secretions. Significant potassium loss is likely to occur, therefore, in the presence of colitis and villous adenoma, two disease processes notable for mucoid stools.

Inflammatory Bowel Disease

In the United States, about 1 million individuals have inflammatory bowel disease, and approximately 30,000 new cases are diagnosed each year.[91] The two major types of inflammatory bowel disease are Crohn's disease and ulcerative colitis, which have different clinical features and manifestations (Table 30-13).

Crohn's disease can involve any part of the gastrointestinal tract from the mouth to the anus but most commonly it affects the distal ileum and proximal large colon. Th1-mediated inflammation with activation of leukocytes and cytokines causes injury. Involved leukocytes subsequently release proinflammatory substances including prostaglandins, leukotrienes, proteases, and nitric oxide with resulting injury. Progression of the disease leads to neutrophil infiltration of the crypts with resulting abscess formation and crypt destruction. Symptoms of Crohn's disease may initially be described as irritable bowel. Abdominal pain and diarrhea are the most common signs (more than five stools per day), with passage of blood and mucus. If the ileum is involved, patients may have right lower quadrant tenderness, and the individual may be anemic due to decreased vitamin B_{12} absorption.

The deeper layers of the intestinal mucosa are typically involved, a situation that leads to derangements in colonic absorption. Owing to the loss of functional absorptive surfaces in the large colon, patients with Crohn's disease are often deficient in magnesium, phosphorus, zinc, and potassium. They also have deficiencies secondary to the loss of absorptive capability in portions of the small intestine. Protein-losing enteropathy is often encountered, as is anemia resulting from occult blood loss and deficiencies in vitamin B_{12} and folic acid. Disturbance in the enterohepatic circulation of bile in the terminal ileum is reflected in complex nutrient deficiencies, including proteins, zinc, magnesium, phosphorus, fat-soluble vitamins, vitamin D, calcium (leading to bone disease), and vitamin B_{12}. This state is typical of patients with chronic Crohn's disease. Folate deficiency also may be present in patients who receive sulfasalazine preparations.

Fistulas often develop between inflamed portions of the intestine and adjacent abdominal structures. Abdominal and pelvic abscesses, rectocutaneous fistulas, and perirectal abscesses have a high incidence in these patients. Increased calcium oxalate absorption in the terminal ileum frequently occurs, resulting in a high rate of renal calculi and cholelithiasis.[92,93] Medical therapy for Crohn's disease includes a variety of drugs and is given in Box 30-10.

Surgery is performed when medical treatment fails or when complications supervene. Although effective in the relief of complications, surgical resection of the diseased colon and ileum does not alter the progression of the disease. The primary goal of surgical management is to limit the operation to the correction of the presenting complication, which could include bowel obstruction, fistulas, abscesses, perforation, and symptoms that indicate widespread symptomatic disease (for which total colectomy and ileal resection may be warranted). Surgical resection of small intestinal segments can lead to short bowel syndrome, with accentuated complications of malabsorption, diarrhea, and nutritional deficiencies.

Most patients with Crohn's disease eventually undergo surgery, and a large number require repeat or continued procedures. The recurrence rate at 10 years after surgery is 50%. A high likelihood of repeat surgery involves areas of the remaining bowel proximal

TABLE 30-13 Diagnosis of Crohn's Colitis Versus Ulcerative Colitis

Observation	Crohn's Colitis	Ulcerative Colitis
Symptoms and Signs		
Diarrhea	Common	Common
Rectal bleeding	Less common	Almost always
Abdominal pain (cramps)	Moderate to severe	Mild to moderate
Palpable mass	At times	No (unless large cancer)
Anal complaints	Frequent (>50%)	Infrequent (<20%)
Radiologic Findings		
Ileal disease	Common	Rare (backwash ileitis)
Nodularity, fuzziness	No	Yes
Distribution	Skip areas	Rectum extending upward and continuously
Ulcers	Linear, cobblestone, fissures	Collar-button
Toxic dilation	Rare	Uncommon
Proctoscopic Findings		
Anal fissure, fistula, abscess	Common	Rare
Rectal sparing	Common (50%)	Rare (5%)
Granular mucosa	No	Yes
Ulceration	Linear, deep, scattered	Superficial, universal

From McKenzie S, Evers BM. Small intestine. In: Townsend CM, et al, eds. *Sabiston Textbook of Surgery: The Biological Basis of Modern Surgical Practice*. 19th ed. Philadelphia: Saunders; 2012.

BOX 30-10

Agents Used to Treat Crohn's Disease

5-Aminosalicylate Acids (5-ASAs)
- Sulfasalazine
- Sulfa-free (mesalamine, olsalazine, balsalazide)

Antibiotics
- Metronidazole
- Ciprofloxacin

Glucocorticoids
- Classic
- Novel (controlled ileal-release budesonide)

Immune Modulators
- 6-Mercaptopurine, azathioprine
- Methotrexate
- Cyclosporine

Biologic Response Modifiers
- Infliximab

From Sands BE. Crohn's disease. In: Feldman M, et al, eds. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*. 9th ed. Philadelphia: Saunders; 2010:1960-1970.

to the area of a previous anastomosis. Patients with a long history of Crohn's disease are also shown to have a higher risk of intestinal carcinoma.[94]

Ulcerative colitis (UC) is a chronic inflammatory disease that causes ulceration of the colonic mucosa and extends proximally from the rectum into the colon. It is a disease characterized by remissions and exacerbations. UC is more prevalent in females and white populations and has a peak incidence between ages 20 and 40 years. The disorder is speculated to have a strong familial genetic predisposition, but psychological factors have also been implicated in its cause. UC lesions are limited to the mucosa and are not transmural. Inflammation begins at the crypt of Lieberkühn with infiltration and release of inflammatory cytokines from neutrophils, lymphocytes, plasma cells, macrophages, eosinophils, and mast cells.[95]

Symptoms usually include abdominal pain, fever, and bloody diarrhea. Loss of absorptive mucosal surface and decreased colonic transit time can lead to large volumes of watery diarrhea. Ulcerative colitis is typically chronic with periods of remission and exacerbation. Ulcerative colitis has relatively low-grade symptoms, such as bloody stools with purulent mucus, malaise, diarrhea, and pain. In approximately 15% of patients, however, ulcerative colitis with acute, fulminating characteristics may occur. Under this circumstance, continuous severe abdominal pain, profuse rectal hemorrhage, and high fever are seen. Associated symptoms include nausea and vomiting, anorexia, and profound weakness. Physical signs usually include dehydration, pallor, and weight loss. Severe blood loss may result in hypotension and shock.

Associated with an acute onset of fulminating ulcerative colitis is toxic megacolon, which is characterized by severe colonic distention that causes shock. In patients with this condition, the distended bowel lumen (greater than 5.5 to 6 cm on a supine abdominal film) provides an environment conducive to bacterial overgrowth. This condition, coupled with erosive intestinal inflammation and perforation, allows for the systemic release of bacteria-produced toxins. Clinical signs and symptoms of toxic megacolon include fever, tachycardia, abdominal distention, pain, ileus, and dehydration. Electrolyte derangements, anemia, and hypoalbuminemia are also commonly present. If there is no significant improvement within a short period of medical treatment, patients arrive in the operating room for subtotal colectomy with an end ileostomy. Patients with toxic megacolon due to Crohn's disease undergo surgical treatment similar to those with toxic megacolon due to ulcerative colitis.[96]

Patients with chronic ulcerative colitis are at increased risk for the development of left-sided carcinoma of the colon. An increased incidence of large-joint arthritis is seen in patients when the disease is clinically active. Concomitant liver disease, as evidenced by fatty infiltrates and pericholangitis, also may complicate the clinical picture. Other extracolonic manifestations of ulcerative colitis include iritis, erythema nodosum, and ankylosing spondylitis.

Therapy for ulcerative colitis is initially medical. As with Crohn's disease, sulfasalazine preparations, antidiarrheal agents, immunosuppressive agents, and corticosteroids are the cornerstones of medical therapy. Nicotine may have a protective effect in UC but not in Crohn's. Both Crohn's disease and ulcerative colitis result in systemic disorders such as anemia and nutritional deficiencies, which are handled in the same supportive manner. In both diseases, surgical resection is reserved for patients with intractable complications. Whereas surgery for Crohn's disease is nondefinitive and complication oriented, proctocolectomy with ileostomy is generally curative for ulcerative colitis and eliminates the risk of malignancy and long-term steroid use.[97]

Anesthetic Considerations in Inflammatory Bowel Disease

Anesthetic management of patients with inflammatory bowel disease begins with optimization of the patient's medical status. Correction of anemia, fluid depletion, electrolyte and acid-base disorders, and nutritional assessment are mandatory. Possible extracolonic complications (e.g., sepsis, liver disease, coagulopathy, anemia, arthritis, hypoalbuminemia, and other metabolic derangements) also must be considered during planning and perioperative management.

Patients on long-term steroid therapy may require prophylactic steroid coverage. Nitrous oxide should be avoided due to the possibility of bowel distention associated with its prolonged intraoperative use. Many patients require total parenteral nutrition (TPN) and bowel rest because eating may worsen symptoms. As such, the anesthetist should be aware of complications from parenteral nutritional therapy (e.g., hyperglycemia or hypoglycemia, increased carbon dioxide production, renal or hepatic dysfunction, nonketotic hyperosmolar hyperglycemic coma, and hyperchloremic metabolic acidosis). Any preexisting TPN infusion should be maintained throughout the perioperative period at the ordered infusion rate. Correction of fluid, electrolyte, and hematologic derangements may be necessary before surgery. Periodic laboratory assessment of metabolic status (i.e., serum glucose and electrolytes) should be performed and guide corrective interventions for derangements. The severity of extracolonic influence on the function of other organ systems dictates appropriate technique and drug selection, as well as the extent to which invasive monitoring is used. Increased intraluminal pressure caused by the administration of anticholinesterases for reversal of neuromuscular blockade has been shown to have no effect on colonic suture lines. No particular anesthetic technique is mandated; however, the use of a combined technique (epidural and general anesthesia) is attractive for both intraoperative use and postoperative analgesia needs.[98]

Diverticulitis and Diverticulosis

Diverticulosis of the colon is characterized by the presence of numerous asymptomatic mucosal herniations or outpouchings in the large colon, with the highest prevalence noted in the left (sigmoid) colon (65%). The colonic mucosa herniates through the smooth muscle layers. Structural weakness of the colonic wall, usually where arteries penetrate the tunica muscularis to nourish the mucosal layer, and intraluminar hypertension are two mechanisms theorized to be responsible for the development of diverticulosis.

Diverticulitis is inflammation of diverticula; this syndrome manifests as abdominal pain with ileus and other symptoms that indicate an acute abdomen, such as nausea, vomiting, diarrhea, rigid abdominal distention, and dehydration. Diverticulitis occurs in only 1% of patients with diverticulosis. Inflamed diverticula may be localized or more widespread and may involve the mesentery and other abdominal organs. Progression of symptoms may lead to hypovolemia, hypokalemia, and shock. The presence of free intraperitoneal air, as evidenced on radiographic abdominal films, suggests perforation. Air in the retroperitoneum may be indicative of paracolic abscess. Both conditions require urgent surgical exploration. Abscess formation and visceral perforation indicate the need for urgent surgical intervention.[89]

Surgical treatment of diverticulitis is reserved for severe symptoms that are refractory to aggressive medical therapy. Intravenous corticosteroids, antibiotics, and fluid replacement are attempted

initially. Exploratory laparotomy with colectomy may be necessary under emergent conditions of acute bleeding, recurrent bleeding that fails to cease spontaneously, or sepsis. The goals of surgical exploration include fecal diversion and abscess drainage, as well as resection of the diseased colon.[34]

Complications of diverticulitis, which occur in up to 25% of patients, frequently necessitate surgical intervention. Such complications include bowel obstruction; fistulas between the sigmoid colon and the skin, bladder, vagina, or small intestine; abscesses; and peritonitis. Abscess formation after colonic obstruction and perforation is generally confined to the pelvis and may involve such structures as the abdominal wall and the subdiaphragmatic spaces. Abscess formation may be extensive; it may include the deep pelvic organs and the hip and thigh. Patients with pelvic abscesses caused by diverticulitis have significant pain, fever, and leukocytosis.

Bleeding is uncommon in patients with diverticular disease, but when present, it often defies localization through endoscopy and even laparotomy. A bleeding diathesis in diverticular disease may be either occult or massive and is caused by erosion of the vessels adjacent to the diverticulum. Elective colon resection is usually considered in patients with recurrent episodes of acute diverticulitis. After a second attack of acute diverticulitis, the prevalence of complications associated with the disease approaches 50%, and the associated mortality rate is twice that of an initial attack. Diverticulitis, when present in the right colon or cecum, often mimics acute appendicitis. Surgery for appendectomy, therefore, may uncover the presence of an inflamed diverticulum or diverticulitis, necessitating extension of the procedure so that colonic resection can be performed.[34]

Abdominal Compartment Syndrome

Abdominal compartment syndrome (ACS) develops when there is abnormally high intraabdominal pressure (greater than 20 mmHg) with associated organ dysfunction. Also known as intraabdominal hypertension, ACS can be diagnosed by measuring intraabdominal pressures (IAP) with a bladder manometer. Normal IAP is less than 10 mmHg. At pressures greater than 10 mmHg, hepatic arterial blood flow significantly decreases. Cardiovascular perturbations occur at 15 mmHg. Oliguria occurs at 15 to 20 mmHg and anuria at 40 mmHg. Organ dysfunction develops with these increased pressures lasting greater than 6 hours. IAP greater than 20 to 30 mmHg can result in organ failure and death.[99]

ACS is associated with abdominal trauma, hemoperitoneum, mesenteric arterial thrombosis, acute pancreatitis, intestinal obstruction, visceral edema (as occurs in sepsis and shock), and massive fluid volume replacement. Causes of chronic ACS include ascites, pregnancy, and intraabdominal tumors. Resuscitative efforts and exposure of the open abdomen induces mesenteric edema formation and bowel dilation. Under these conditions, attenuation and prevention of worsening ischemic injury to the abdominal viscera are avoided through delayed closure until gross abdominal distention is resolved.

Cardiac output is decreased secondary to decreased cardiac preload (venous return), elevated systemic vascular resistance, and elevated intrathoracic pressure. Reflex tachycardia is a baroceptor-mediated response to decreased preload, with resultant diminished diastolic filling and coronary perfusion. Intracranial filling pressures are increased. Decreased thoracic compliance and decreased lung volumes result from impaired diaphragmatic descent. The outcome is increased pulmonary shunt fraction, atelectasis, and pulmonary edema. Impairment in renal function results from compression of the kidney and diminished glomerular perfusion. The end consequence is multiple organ failure.

Treatment of ACS is urgent decompressive laparotomy, and may be performed at the bedside if the patient is too unstable to move. However, surgical decompression is ideally performed in the operating room. One study showed that overall mortality after surgical decompression was 46%, with preoperative renal failure, lower preoperative IAP, and late decompression being predictive of death. This underscores the point that once the diagnosis of ACS is made, prompt intervention is needed, and if medical interventions are futile or judged to be inadequate, prompt decompression is mandatory.[100]

Affected patients often have myriad medical problems that may significantly influence outcome. The possibility of ACS subsequent to resuscitative "damage-control" laparotomy used in the traumatically injured patient is always a consideration. Under this circumstance, immediate life-threatening injuries are primarily addressed, and then the patient is returned to the operating room from the intensive care unit at a later date. This occurs after a period in which hemodynamic stabilization is accomplished.[34] Definitive repairs of associated, less life-threatening injuries are then undertaken, often in stages. During this time, the abdomen may be left open but packed and sealed with sterile dressings, along with a drainage appliance to resolve postresuscitation intraabdominal edema.[34] The patient may undergo repeated returns to the operating room for dressing changes until conditions are conducive for abdominal wound closure. Providing anesthesia care for these patients can be extremely challenging. Intraoperative monitoring is directed toward maintenance of hemodynamic stability and includes knowledge of the patient's preoperative hemodynamic profile. If the patient is still receiving mechanical ventilatory support, it is of utmost importance to provide intraoperative ventilation as closely as possible to the mode being administered in the intensive care unit. This is particularly vital in the patient with ARDS. This may require a modification of the anesthesia delivery ventilator to approximate as closely as possible the minute ventilation, Fio_2, inspiratory/expiratory (I:E) ratio, ventilatory rate, and level of positive end-expiratory pressure the patient has been receiving. In this way, the potential for perioperative deterioration of previously accomplished improvement in the patient's ventilatory status is minimized. Invasive monitors brought with the patient, such as an arterial line, central venous catheter, and pulmonary artery catheter, should be used for perioperative management. Opioids and inhalation agents are used with discretion in accordance with patient tolerance. Adequate muscle relaxation and amnesia with a benzodiazepine or scopolamine assume priority in the pharmacologic anesthetic management of the physiologically labile patient. Other vasoactive agents are included as indicated for hemodynamic support. Best practice caveats for the anesthetic management of these patients are provision of intraoperative stability and preservation of preoperative homeostatic compensation.

One serious but rare complication of surgical decompression is the so-called "reperfusion syndrome" in which the patient develops severe hypotension and acidosis immediately after the abdomen is decompressed as a result of the release of acidotic blood from the mesenteric beds.[100] Reperfusion washout of by-products of anaerobic metabolism releases an array of cardiac depressant and vasodilatory mediators into the general circulation. Proper preparation is required and includes optimization of intravascular volume, acid-base status, and arterial oxygenation.[101]

Mortality rate in ACS approaches 42%, with most patients succumbing to secondary systemic inflammatory response syndrome,

sepsis, and MODS. Other causes of death include respiratory failure (i.e., ARDS) and the consequences of added stress imposed on cardiac function in susceptible patients.[101]

Anesthetic Considerations in Elective Surgery of the Colon

Using either a laparoscopic or anterior open approach, the surgeon mobilizes the colon and ligates the associated blood vessels. The diseased bowel is removed, and the remaining ends of the distal and proximal colon can be anastomosed together, or alternatively a colostomy or ileostomy may be created. Preoperative elimination of fecal mass and bacterial flora are critical to avoid postoperative infection. The night before admission, the patient can lavage with isotonic and isosmotic solutions orally or by way of a nasogastric tube. Cleansing enemas also may be ordered. These techniques often are used for elective procedures in conjunction with dietary changes that emphasize the intake of fluids and low-residue foodstuffs and that culminate in the intake of only clear liquids for 24 to 48 hours before surgery. Intravenous and oral antibiotics used for bowel cleansing commonly include drugs of the aminoglycoside family (e.g., neomycin, erythromycin) and/or a combination of the cephalosporins and metronidazole.

Awareness of this preoperative preparation in patients who undergo elective bowel surgery is critical because aggressive preoperative bowel preparation predisposes a patient to water and electrolyte imbalances that may have a deleterious influence on perioperative cardiovascular function, hemodynamics, and systemic organ perfusion, particularly if the patient is elderly or debilitated. Depending on how chronic the disease process is, anemia resulting from frank or occult bleeding may be present. Malnutrition with hypoalbuminemia also may be present before surgery.

Preoperative nasogastric drainage may be required if an adynamic colon or obstruction is present. This preoperative intervention may be superimposed on a dehydrated patient or one who is electrolyte depleted, resulting in hypochloremic hypokalemic alkalosis. The resulting fluid and electrolyte derangements may be of sufficient magnitude to require postponement of the procedure until volume and electrolyte resuscitation has been accomplished.

Carcinoma of the Colon

Cancer of the colon is a highly treatable and often curable disease when localized to the bowel. It is the second most frequently diagnosed malignancy in the United States, as well as the third most common cause of cancer death in both men and women. Most colorectal cancers develop from adenomatous polyps. Surgery is the primary treatment and results in cure in approximately 50% of patients. The location and amount of resection depends on the site of the cancer. If the rectum is involved, a permanent colostomy will be created. Recurrence after surgery is a major problem and often is the ultimate cause of death. The prognosis of patients with colon cancer is clearly related to the degree of penetration of the tumor through the bowel wall and the presence or absence of nodal involvement. Carcinoma of the colon accounts for approximately 50,000 deaths annually, and more than 145,000 new cases are diagnosed annually.[96] The etiology is multifactorial and includes a strong environmental correlation with diet (high red meat intake, low dietary fiber intake) and genetic predisposition. Inflammatory bowel disease is usually associated with a greater predisposition to colonic carcinoma. Occult stool testing for blood is a standard screening method. Rectal examination and colonoscopic examination with biopsy are important diagnostic modalities. Genetic markers in stool and blood are being developed.

Right-sided colonic lesions grow along one wall of the cecum and ascending colon and often cause symptoms including pain, a palpable mass in the lower right quadrant, anemia, and dark-colored blood mixed with stool. Persistent blood loss and anemia with fatigue are common, and obstruction is unlikely because the feces are more liquid. Bleeding is usually less profuse than in patients with diverticular disease. Left-sided colonic lesions grow circumferentially and symptoms include progressive abdominal distention, pain, vomiting, constipation, cramps, and bright red blood on the stool. Obstruction is common but occurs slowly.[89]

Volvulus of the Colon

Volvulus is a twisting of the bowel on its mesenteric pedicle, resulting in an occlusion of the blood supply. This condition usually affects a freely mobile colonic segment and a fixed point or set of points about which the colon twists. Approximately 75% of colonic volvulus affects the sigmoid colon, and is often associated with fibrous adhesions in the small intestines.[89]

Although colonic volvulus is relatively rare in the United States, it is responsible for 5% of large bowel obstruction cases. Symptoms usually suggest the presence of acute or subacute bowel obstruction (e.g., sudden onset of acute, severe, colicky abdominal pain, vomiting, and distention). Acute strangulation of the bowel is suggested by generalized severe abdominal pain, hypovolemia, and fever. Initial therapy starts with appropriate resuscitation followed by decompression through placement of a rectal tube through a proctoscope or the use of a colonoscope. This treatment has a high success rate (70% to 80%) and allows resection as an elective procedure, which can be accomplished with reduced morbidity and mortality. If detorsion of the volvulus cannot be accomplished with either a rectal tube or colonoscope, laparotomy with resection of the sigmoid colon with the formation of an end colostomy and a mucous fistula (Hartmann's operation) is required.[96]

Many patients with this condition are elderly (seventh to eighth decade) or are debilitated individuals and are referred from long-term care facilities. Associated disease processes include Alzheimer disease, Parkinson disease, multiple sclerosis, paralysis, pseudobulbar palsy, chronic schizophrenia, and dementia. Medications taken on a long-term basis by these institutionalized patients may include psychotropic drugs, which are known to affect intestinal motility.

Ischemic Bowel Disease

Ischemic injury to the GI tract occurs whenever the oxygen or vascular supply cannot meet the metabolic demands of the tissue. GI ischemia has many causes, including inadequate perfusion, narrowing of blood vessels from any cause, bowel obstruction and distention, drug effects, and infections that can mimic ischemic damage. Most ischemic episodes result from nonocclusive ischemic bowel disease (low-flow states), and in these cases, no vascular lesion or specific cause for ischemia can be demonstrated on pathologic examination.[102] Surgical iatrogenic causes, such as interruption of the inferior mesenteric artery as a result of aortic cross-clamping during abdominal aortic surgery, are also responsible. Prolonged hemodynamic lability in patients with significant comorbidities such as advanced age, chronic diabetes, hypertension, and atherosclerotic disease places them at even greater risk for the consequences of ischemic bowel disease. Any part or length of bowel can be affected depending on the cause and duration of hypoxia and the state of the collateral circulation. The extent, severity, and prognosis of the syndrome of ischemic bowel disease are variable. Localized or segmental ischemia is often present. Differentiation of ischemic colitis from infectious processes, diverticulitis, or inflammatory bowel disease may be difficult.

Definitive diagnosis depends on endoscopic examination with biopsy. Exclusion of bowel perforation in the differential diagnosis is made through radiographic or ultrasonographic examination of the abdomen for the presence of free air.

Patients with ischemic bowel disease are usually elderly. Symptoms of ischemic bowel disease typically include fever, vomiting, rectal bleeding, and abdominal cramping pain and may be present for weeks or months. The development of sudden rectal bleeding associated with left-sided abdominal pain and peritoneal signs strongly suggests the presence of this disease process. Concomitant ischemic heart disease and peripheral vascular disease are often present in these patients.[103] Supportive measures are initially undertaken if bowel necrosis is not suspected. This includes antibiotic therapy and fluid resuscitation. In patients in whom perforation or necrosis is suspected, emergency laparotomy is indicated, with possible bowel resection and temporary or permanent colostomy. Stable patients may be candidates for vascular reconstructive procedures.[6]

Diseases of the Rectum and Anus

Diseases of the anorectal region may include neoplastic lesions. Rectal carcinomas are defined as tumors occurring up to 15 cm from the anal opening. If biopsy findings are consistent with localized adenocarcinoma, abdominal-perineal resection of the rectum and sigmoid colon with permanent colostomy may be curative. Squamous cell carcinomas of the rectum are effectively treated with chemotherapy and radiation, as well as local excision. Rectal carcinoma can spread through the rectal wall to nearby structures (the prostate and vagina), especially in the lower third of the rectum due to the lack of a serial covering. Surgical proctectomy is another treatment option.

Other rectal diseases include rectal prolapse, which is characterized by full-thickness eversion of the rectal wall through the anus and is repaired with rectosigmoidectomy or proctopexy. Rectal prolapse is seen most often in the elderly and females. Another rectal disease is perirectal abscess, which requires drainage; this may be performed on either an inpatient or an outpatient basis.

Perirectal fistulas typically develop secondary to infectious disease processes that cause abscess formation. Four types are generally recognized: extrasphincteric, suprasphincteric, transsphincteric, and intersphincteric. Initial therapy is incision and drainage with delayed fistulectomy to facilitate healing of the abscess.[34]

Hemorrhoids are a common affliction and have been described and treated for more than 4000 years. The refined, low-fiber diet of Western nations makes hemorrhoids extremely common in the United States, where 1 in 25 to 30 individuals is afflicted. Hemorrhoidal tissue is composed of vascular, mucosal, and muscular tissues. Although frequently attributed to varicosities, all three elements compose the hemorrhoid. There are two types of hemorrhoids: internal and external. Internal hemorrhoids originate above the dentate line, are covered with mucosa, and lack sensory innervation. Internal hemorrhoidal prolapse may be painless. Gangrenous, strangulated, extruded, or thrombosed internal hemorrhoids, however, may be extremely painful. Treatment is usually by rubber band ligation or surgical excision. External hemorrhoids originate below the dentate line and are covered with squamous epithelium that makes them easily recognizable because their covering matches the surrounding skin. The inferior rectal nerve innervates external hemorrhoids. A thrombosed external hemorrhoid appears as a bluish mass covered by epidermis. Acute thrombosis occurs suddenly and is usually very painful. Significant bleeding is uncommon but may occur if spontaneous rupture occurs. Increased pressures from straining or trauma from constipation or diarrhea may exacerbate external hemorrhoids. Distention and trauma predispose the hemorrhoidal venous plexus to stasis with ensuing clot formation and edema.[104] Surgical excision is the treatment of choice.

Anesthesia for most perirectal and perianal procedures may be effectively provided by regional techniques such as spinal subarachnoid block or epidural blockade, as well as by local anesthesia infiltration with sedation. A particularly useful technique is a saddle block with hypobaric bupivacaine. In some cases, general endotracheal anesthesia may be necessary. Anesthetic considerations must include the influence of patient position (e.g., prone, jackknife, or lithotomy position) on intraoperative cardiovascular and respiratory dynamics.

Radiation Enteritis

Radiation therapy is commonly used as adjuvant therapy for various abdominal and pelvic cancers. In addition to tumor cells, however, other rapidly dividing cells in the intestinal epithelial lining may be affected by radiation. Surrounding normal tissue such as the small intestinal epithelium may sustain severe, acute, and chronic deleterious effects. The amount of radiation appears to correlate with the probability of developing radiation enteritis. Radiation damage tends to be acute and self-limiting, with symptoms consisting mainly of diarrhea, abdominal pain, and malabsorption. The late effects of radiation injury are the result of damage to the small submucosal blood vessels with a progressive obliterative arteritis and submucosal fibrosis, resulting eventually in thrombosis and vascular insufficiency. Operative intervention may be required in a subgroup of patients with the chronic effects of radiation enteritis. Indications for operation include obstruction, fistula formation, perforation, and bleeding, with obstruction being the most common presentation. Operative procedures include a bypass or resection with reanastomosis, sometimes under emergent conditions. The presence of adhesions and the induced increased friability of the intestinal tissues predispose affected patients to increased intraoperative bleeding and tissue third spacing. Radiation enteritis can be a relentless disease process. Almost half of patients who survive their first laparotomy for radiation bowel injury require further surgery for ongoing bowel damage. Up to 25% of these patients die of radiation enteritis and complications from its management.[90]

Appendicitis

The appendix arises from the apex of the cecum. The length of the appendix varies from 2 to 20 cm, and the average length is 9 cm in adults. The appendiceal artery, a branch of the ileocolic artery, supplies the appendix.[105] The appendix may assume any of a number of positions that influence the quality of symptoms and the site of pain when inflammation occurs.

Appendicitis occurs most often in individuals between 10 and 30 years of age and is the most common general surgical emergency. A slight prevalence for male patients over female patients exists. Obstruction of the appendiceal lumen is believed to be the major cause of appendicitis.

In the classic presentation of appendicitis, patients first note vague, poorly localized epigastric or periumbilical discomfort progressing to localized right lower quadrant tenderness in 80% of patients. Within 4 to 12 hours of the onset of pain, most patients also note nausea, vomiting, anorexia, or some combination of these three symptoms. If vomiting is the main symptom, the diagnosis should be questioned.[106] Patients point to localized pain at McBurney's point, which is midway between the iliac crest and umbilicus; rebound tenderness, muscle rigidity, and abdominal guarding are

noted. In the pregnant patient, Alder's sign is used to differentiate between uterine and appendiceal pain. The pain is localized with the patient supine. The patient then lies on her left side. If the area of pain shifts to the left, it is presumed to be uterine.

The major complication of untreated appendicitis is perforation, with resultant peritonitis, abscess, and portal pylephlebitis. The risk of perforation increases as the duration of the illness progresses, especially beyond 24 hours. Patients with perforation are more likely to have a higher fever, leukocytosis, and physical findings of peritonitis. The most severe complication of appendiceal perforation is septic thrombophlebitis of the portal vein, or portal pylephlebitis.

If the appendix perforates, abdominal pain becomes intense and more diffuse, and abdominal muscular spasm increases, producing rigidity. The heart rate rises, with an elevation of temperature above 39° C. Occasionally, pain may improve somewhat after rupture of the appendix, although a true pain-free interval is uncommon.[105]

Definitive treatment of appendicitis is appendectomy, which may be performed with general or regional anesthesia. The patient is frequently dehydrated and may require a brief period of fluid resuscitation and antibiotics for enteric anaerobic gram-negative bacilli before the induction of anesthesia. Laparoscopic propcedures are the most common technique for simple presentations. If an open appendectomy is performed and regional anesthesia is chosen, the analgesia level should be maintained at the T6 to T8 level. If general anesthesia is selected, muscle relaxation is necessary, and aspiration precautions that include a rapid-sequence induction should be considered. Local anesthesia with intravenous sedation may also be a useful technique.

SPLENIC DISEASE

Anatomic and Physiologic Overview

The spleen is located in the posterior left upper quadrant of the abdomen and is surrounded by the fundus of the stomach (medially), the splenic flexure of the colon (inferiorly), the left kidney and adrenal gland (posteriorly), and the diaphragm (superiorly). Attachment to these organs via suspensory ligaments, which are vascular except for the gastrosplenic ligament, provides protection and support of this organ.[34]

The normal spleen is weighs less than 250 g, decreases in size with age, normally lies entirely within the rib cage, has a maximum cephalocaudal diameter of 13 cm by ultrasonography or maximum length of 12 cm and/or width of 7 cm by radionuclide scan, and is usually not palpable. In fact, a palpable spleen is the major physical sign produced by diseases affecting the spleen and suggests enlargement of the organ.

The encapsulated spleen is divided into three zones by strands of connective tissue (trabeculae) that originate from the capsule. Each compartment contains masses of lymphoid tissue called *splenic pulp*. Each of the three splenic compartments is surrounded by a 1- to 2-mm capsule. These compartments are (1) the white pulp, which consists of lymphatic sheaths and contains lymphocytes, plasma cells, and macrophages; (2) the red pulp, which consists of large, thin-walled, highly distensible venous sinuses, also known as the *splenic sinusoids*, which ultimately form the splenic vein; and (3) the marginal zone, an ill-defined vascular space that interfaces between the white pulp and the red pulp.[34]

Total splenic blood flow is approximately 300 mL/min and comes from the splenic artery. The splenic artery is a tortuous vessel that arises from the descending aorta. The splenic artery divides into several branches within the splenorenal ligament before entering the splenic hilum, where they branch again into these trabeculae as they enter the splenic pulp. Splenic blood flow drains into the splenic vein and then contributes to portal venous blood flow.

The spleen functions in several physiologic capacities, including blood filtering, maintenance of normal erythrocyte morphology, and immune processing of blood-borne foreign antigens. The spleen is also involved in hematopoiesis until the fifth month of gestation in the fetus. In filtering blood, the splenic sinusoids remove nuclear remnants and excess cell membrane found in immature erythrocytes. Abnormal blood cells, such as those found in sickle cell disease, thalassemia, and spherocytosis, are filtered and removed by macrophages and other cells of the reticuloendothelial system. This process can occasionally lead to worsening anemia, symptomatic splenomegaly, and occasionally splenic infarction. Aged red blood cells (older than 120 days) that have lost enzymatic activity and membrane elasticity are removed by the same processes.[34]

The spleen has an important role in specific and nonspecific immune responses. Macrophages and specialized histiocytes engulf and remove foreign cells, particularly those with a layer of affixed antibody. The production of specific antibody (immunoglobulin M [IgM]) is facilitated in the white pulp through the processing of foreign antigens.[34] It is well established that people lacking a spleen are at a significantly higher risk for overwhelming postsplenectomy infection (OPSI) with fulminant bacteremia, pneumonia, or meningitis, as compared with those with normal splenic function. Asplenic subjects have defective activation of complement by the alternative pathway, leaving them more susceptible to infection.[107] Pimpl et al.[108] reviewed 37,000 autopsies over 20 years of adults who died after splenectomy and compared them with a deceased population of 403 who did not have splenectomy. These investigators found higher incidence rates of lethal pneumonia, sepsis with multiple organ failure, purulent pyelonephritis, and pulmonary embolism in the splenectomy group. They concluded that splenectomy carries a considerable lifelong risk for severe infection and thromboembolism.

The spleen has a minor role as a reservoir of platelets. This function, however, is important in only a few pathologic conditions. No significant reservoir function of red blood cells is performed by the spleen, but in the presence of sudden reductions in blood pressure, sympathetic nervous system activation can constrict the red pulp sinuses, contributing as much as 200 mL of blood to the venous circulation and increasing the hematocrit by as much as 4%.[109]

Despite its important and myriad functions, the spleen is not essential for life. Splenectomy may be performed for benign hematologic conditions including idiopathic thrombocytopenic purpura (ITP), thrombotic thrombocytic purpura, hereditary spherocytosis, hereditary hemolytic anemia, and hemoglobinopathies (e.g., thalassemia, sickle cell disease). Splenectomy also may be performed for malignancy such as Hodgkin or non-Hodgkin disease, lymphoma, certain leukemias, or for other benign conditions such as splenic abscess, splenic cysts, presence of an accessory spleen, wandering spleen, and splenomegaly (spleen greater than 20 cm longitudinally). The development of primary (having no identifiable underlying cause) or secondary (having a known cause) hypersplenism may warrant splenectomy. Hypersplenism and acute splenic sequestration are life-threatening disorders in children with sickle cell anemia and thalassemia. Symptoms of hypersplenism include fatigue, malaise, recurrent infection, and easy or prolonged bleeding. These symptoms occur from a hyperfunctional spleen that removes and destroys normal blood cells.[107]

In portal hypertension, transmitted back pressure results in hypersplenism, which leads to congestive failure of splenic

function. Treatment of the primary disease process usually provides relief of symptoms. Splenectomy, however, is often a necessary part of therapy; particularly with long-standing disorders. Splenectomy also offers a curative solution for patients with isolated splenic vein thrombosis and bleeding gastric varices.[110]

Splenic Trauma

Angiographic embolization of hemorrhaging vessels in the spleen has reduced the need for open procedures. However, the spleen is the most frequently injured abdominal organ, being involved in 25% to 60% of adults with intraabdominal trauma. Damage to the spleen is important because it is the most vascular body organ, receives 5% of the cardiac output, and because the bleeding is mostly arterial, it can produce a lethal hemoperitoneum. Unlike the liver, hemorrhage from splenic trauma is always within the peritoneal cavity.[111] Rapid deceleration or puncture from an adjacent broken rib are common causes of spleen injuries. Any patient who has sustained blunt abdominal trauma and who has left upper quadrant pain should be suspected of having sustained splenic injury. Conservative, nonoperative treatment (with avoidance of splenectomy) may be elected in minor splenic injury. The clearest indication for urgent operation is hemodynamic instability. Because there can be no standard criteria for hemodynamic instability, a general guideline is to operate for a systolic blood pressure below 90 mmHg or a pulse of more than 120 beats/minute if there is no immediate response to 1 to 2 L of crystalloid resuscitation and when physical examination, ultrasound, or diagnostic peritoneal lavage (DPL) indicates intraabdominal blood loss.[107] Splenectomy is generally avoided in children because of the greater importance of splenic function (i.e., immunologic function) in growth and development in patients of this age group.[112]

In hemodynamically stable patients with severe splenic damage and hemoperitoneum, the surgery can be performed laparascopically with no related morbidity or mortality. Anesthesia concern with the laparoscopic approach is related to respiratory distress, possibly impaired by the lateral decubitus position and by the pneumoperitoneum in patients, usually associated with multiple trauma and rib fractures. At least one study showed no negative outcomes in this respect and in fact the patients fared better postoperative respiratory compliance.[113]

In the presence of impending shock, emergency exploratory laparotomy is carried out to diagnose and treat all injuries to the abdominal viscera, including the spleen. Anesthetic management in these cases is directed by considerations given all unstable patients undergoing emergency laparotomy, particularly hemodynamic stability and renal function. A paramount consideration is maintaining physiologic hemoglobin and hematocrit levels and arterial blood pressure. Hemoglobin and hematocrit are decreased in the emergent setting, not only by hemorrhagic diathesis but also from dilution secondary to aggressive volume resuscitation with crystalloid solutions. These considerations assume an integral part in the decision to implement perioperative blood product transfusion.

Anesthetic Considerations in Elective Splenectomy

Anesthetic management for splenectomy is individualized based on the patient's medical condition. Patients who have received chemotherapy must be assessed for potential organ system complications.

Minimally invasive procedures have become standard for most splenectomies, and laparoscopy is now the procedure of choice. The spleen may be removed laparoscopically if the spleen is normal or close to normal in size. Although the operative time is significantly greater than for laparotomy, the postoperative recovery time, the risk of damage to the pancreas, the likelihood of development of subphrenic abscess and peritoneal adhesions postoperatively, and the nutritional and metabolic challenges to the patient are considerably reduced.[114]

Patients with systemic disease may be chronically ill and have decreased cardiovascular reserve. Patients who have received doxorubicin (Adriamycin) may have a dose-dependent cardiotoxicity that can be worsened by radiation therapy. Manifestations include decreased QRS amplitude, congestive heart failure, pleural effusions, and dysrhythmia. Patients may have a degree of left lower lobe atelectasis and altered ventilation. In patients treated with bleomycin, pulmonary fibrosis may occur. Methotrexate, busulfan, mitomycin, cytarabine, and other chemotherapeutic agents may cause pulmonary toxicity. Neurologically, patients may have deficits after administration of chemotherapeutic agents. Vinblastine and cisplatin can cause peripheral neuropathies. Any evidence of neurologic dysfunction should be documented. Hematologically, patients are likely to have splenomegaly secondary to hematologic disease (e.g., Hodgkin disease, leukemia). Cytopenias are common. Some chemotherapeutic agents (e.g., methotrexate, 6-mercaptopurine) may be hepatotoxic. Evaluation of liver function tests should be considered in patients considered at risk. Renally, some chemotherapeutic drugs (e.g., methotrexate, cisplatin) are nephrotoxic. Patients exposed to such agents may have renal insufficiency.

Laboratory tests that should be performed as indicated by the history and physical examination include a complete blood count, prothrombin time, partial thromboplastin time, bleeding time, platelet count, electrolytes, blood urea nitrogen, creatinine, and urinalysis. Consider aspiration prophylaxis, and administer steroids (25 to 100 mg hydrocortisone) if the patient has received them as part of a chemotherapeutic or medical treatment.

Because of the potential for large blood loss, the patient should be typed and cross-matched, and the use of cell saver is appropriate. The ability to transfuse blood products when indicated should be accommodated with the insertion of at least two large-bore intravenous lines if a central line is not placed. The extent of monitoring modalities is dictated by the patient's preexisting condition and anticipated perioperative course.

General endotracheal anesthesia (GETA) with or without an epidural for postoperative analgesia is used. GETA induction should include consideration of rapid sequence intubation as indicated. Intravascular volume should be restored before anesthetic induction. If the patient is hemodynamically unstable, etomidate or ketamine should be considered. Nitrous oxide should be avoided to prevent bowel distention. Appropriate measures also must be implemented intraoperatively to prevent any further deterioration in preexisting function. These measures include careful patient positioning, administering appropriate intravenous fluids, maintaining adequate urine output, monitoring hemoglobin and hematocrit levels, and avoiding anesthetics and adjuvants that place an extra metabolic burden on the renal or hepatic system. An epidural catheter may be beneficial in postoperative pain control in the absence of ITP.

CARCINOID TUMORS AND CARCINOID SYNDROME

Carcinoid tumors consist of slow-growing malignancies composed of enterochromaffin cells (Kulchitsky cells) and are most commonly found in the GI tract. They also may occur in the lung, pancreas, thymus, and liver.

The GI tract accounts for about two thirds of carcinoids. Within the GI tract, most tumors occur in the appendix (45%), jejunoileum (28%), rectum (16%), and duodenum (4%). Carcinoid

TABLE 30-14 Secretory Products of Carcinoid Tumors

Amines	Tachykinins	Peptides	Other
Serotonin	Kallikrein	Pancreatic polypeptide (40%)	Prostaglandins
5-HIAA (88%)	Substance P (32%)	Chromogranins (100%)	
5-HTP	Neuropeptide K (67%)	Neurotensin (19%)	
Histamine		hCG_{α}(28%)	
Dopamine		hCG_{β}	
		Motilin (14%)	

From McKenzie S, Evers BM. Small intestine. In: Townsend CM, et al, eds. *Sabiston Textbook of Surgery: The Biological Basis of Modern Surgical Practice*. 19th ed. Philadelphia: Saunders; 2012.
hCG_{α}, Human chorionic gonadotropin alpha subunit; *h*CG_{β}, human chorionic gonadotropin beta subunit; *5-HIAA,* 5-hydroxyindoleacetic acid; *5-HTP,* 5-hydroxy-L-tryptophan.

BOX 30-11

Signs and Symptoms of Carcinoid Syndrome

- Episodic cutaneous flushing (kinins, histamine)
- Diarrhea (serotonin, prostaglandins E and F)
- Heart disease
- Tricuspid regurgitation, pulmonic stenosis
- Supraventricular tachydysrhythmias (serotonin)
- Bronchoconstriction (serotonin, bradykinin, substance P)
- Hypotension (kinins, histamine)
- Hypertension (serotonin)
- Abdominal pain (small bowel obstruction)
- Hepatomegaly (metastases)
- Hyperglycemia
- Hypoalbuminemia (pellagra-like skin lesions resulting from niacin deficiency)

Modified from Hines RL, Marschall KE. *Stoelting's Anesthesia and Co-Existing Disease*. 6th ed. Philadelphia: Saunders; 2012.

tumors are capable of metastasis and are composed of multipotential cells with the ability to secrete numerous bioactive humoral agents, the most important of which are serotonin, histamine, and kinin peptides. In addition to these substances, carcinoid tumors have been found to secrete corticotropin, histamine, dopamine, neurotensin, prostaglandins, substance P, gastrin, somatostatin, pancreatic polypeptide, calcitonin, and neuron-specific enolase[105] (Table 30-14).

Adrenergic stimulation causes the release of serotonin into the circulation. It is metabolized by aldehyde dehydrogenase and monoamine oxidase to 5-HIAA (5-hydroxyindoleacetic acid), which is excreted in the urine. Elevated levels of 5-HIAA are monitored in the urine as a marker of excess serotonin production and, therefore, the presence of a carcinoid tumor. Serotonin may cause vasoconstriction or vasodilation; thus both hypertension and hypotension are possible. At normal concentrations, serotonin does not affect cardiac function; however, the elevated levels seen in carcinoid syndrome may cause both inotropic and chronotropic responses. This action is due in part to an indirect effect from the release of norepinephrine. Elevated serotonin levels also result in increased gut motility and the secretion of water, sodium, chloride, and potassium by the small intestine. Other effects attributed to elevated levels of serotonin are vomiting, bronchospasm, hyperglycemia, and prolonged drowsiness after emergence from anesthesia.[115]

Histamine release is seen predominantly in patients with gastric or foregut carcinoids and may be due to the presence of histidine decarboxylase in normal gastric mucosa. Histamine is probably responsible for the bronchospasm seen in some carcinoid patients, and it also may be the cause of flushing.[115]

Other substances thought to be released by carcinoid tumors are the kinins, especially bradykinin. Kinins are produced by the action of proteolytic enzymes, called *kallikreins*, on the inactive precursors of the kinins.[115] Lysosomal kallikrein release is triggered mainly by sympathetic stimulation. When this action occurs, the newly produced bradykinin usually is rapidly broken down and removed from the circulation by plasma aminopeptidases and kinases. When abnormally high amounts of bradykinin are released, the pathways become saturated, causing an exaggerated and prolonged effect from bradykinin. The bradykinins produce profound vasomotor relaxation, causing severe hypotension and flushing, probably via increased nitric oxide synthesis.[116] Bradykinin also causes bronchospasm, especially in known asthmatics, and frequently in the presence of cardiac disease.[117]

Normally the release of vasoactive substances causes little if any symptoms because the liver is able to rapidly inactivate these substances. If these substances reach the systemic circulation without first being metabolized by the liver, they are capable of producing carcinoid syndrome (Box 30-11).

Carcinoid syndrome may produce life-threatening perioperative hemodynamic instability. The syndrome most often occurs with primary tumors that do not drain into the portal system or with hepatic metastases (the most common site of metastasis) because they bypass metabolism in the liver. Although 25% of tumors actively secrete substances capable of causing symptoms, less than 10% of people with a carcinoid tumor develop the classic carcinoid syndrome.[118] Symptoms related to carcinoid syndrome include episodic cutaneous flushing (kinins, histamine), diarrhea (serotonin, prostaglandins E and F), heart disease, tricuspid regurgitation, pulmonic stenosis, supraventricular tachydysrhythmias (serotonin), bronchoconstriction (serotonin, bradykinin, substance P), hypotension (kinins, histamine), hypertension (serotonin), abdominal pain (small bowel obstruction), hepatomegaly (metastases), hyperglycemia, and hypoalbuminemia (pellagra-like skin lesions resulting from niacin deficiency).

Since the introduction of octreotide as a therapeutic option, the prognosis for patients with carcinoids has significantly improved. Nevertheless, carcinoid tumors may prove fatal for some patients. Death in these patients often results from pulmonary, cardiovascular, or hepatic involvement and dysfunction, rather than from carcinoid crisis. Overall survival is significantly worse for patients with cardiac involvement.

Carcinoid crisis, a life-threatening form of carcinoid syndrome, may be precipitated by physical manipulation of the tumor (including bedside palpation), chemical stimulation or tumor necrosis resulting from chemotherapy, and hepatic artery ligation or embolization.[119] It may occur spontaneously or during the induction of anesthesia. Clinical manifestations of carcinoid crisis include severe flushing with associated dramatic changes in blood pressure (BP), cardiac arrhythmias, bronchoconstriction, and mental status changes. The most effective treatment for carcinoid tumors is generally regarded as complete surgical excision of the tumor, often with partial bowel resection and mesenteric lymphadenectomy.[119] Other procedures associated with carcinoid

BOX **30-12**

Anesthetic Considerations in Carcinoid Syndrome

- The most common clinical signs are cutaneous flushing of the head, neck, and upper thorax, wheezing, blood pressure and heart rate changes, and diarrhea.
- Preoperative assessment should include complete blood count, measurement of electrolytes, liver function tests, measurement of blood glucose, electrocardiogram, and determination of urine 5-HIAA levels. Echocardiography should be performed to determine the extent of carcinoid heart disease.
- Confirmation: > 30 mg of 5-HIAA per 24-hour urine sample (normal = 3 - 15 mg/24 hr)
- Optimize fluid and electrolyte status and pretreat with octreotide as noted. Continue octreotide throughout the postoperative period. Aprotinin (kallikrein inhibitor) may be used to treat hypotension refractory to octreotide. Interferon-α has shown success in controlling some symptoms.
- Both histamine-1 and histamine-2 receptor blockers must be used to fully counteract histamine effects.
- Perioperative blockade of serotonin receptors
- Avoid histamine-releasing agents such as morphine and atracurium. Avoid sympathomimetic agents such as ketamine and ephedrine.
- Treat hypotension with an α-receptor agonist such as phenylephrine.
- General anesthesia is preferred over regional anesthesia. Patients with high serotonin levels may exhibit prolonged recovery; therefore, desflurane and sevoflurane, which have rapid recovery profiles, may be beneficial.
- Aggressively maintain normothermia to avoid catecholamine-induced vasoactive mediator release.
- Monitor intraoperative plasma glucose, because these patients are prone to hyperglycemia. Treat with insulin as is customary.
- Pay attention to procedures, treatments, and drugs that may stimulate release of vasoactive substances from tumor cells. These include tumor-debulking surgery or hepatic artery embolization to reduce tumor size and biotherapy (interferon for tumor shrinkage) or chemotherapy for systemic spread.

Modified from Mancuso K. Carcinoid syndrome and perioperative anesthetic considerations. *J Clin Anesth*. 2011;23(4):329-41;Vaughan DJ, Brunner MD. Anesthesia for patients with carcinoid syndrome. *Int Anesthesiol Clin*. 1997;35(4):129-142; Dierdorf S. Carcinoid tumor and carcinoid syndrome. *Curr Opin Anaesthesiol*. 2003;16:343-347.
HIAA, 5-Hydroxyindoleacetic acid.

syndrome include cardiac valve replacement and hepatic resection for metastatic disease.

Anesthetic Management

The primary goal during the perioperative period is to prevent the release of bioactive mediators, thereby avoiding carcinoid crisis. Most patients with carcinoid tumors undergo general anesthesia because of the need to avoid the sympathectomy associated with neuraxial anesthesia; however, both epidural and spinal anesthesia have been used successfully in these patients.[120]

Caution should be exerted in the anesthetic management of patients with carcinoid tumors because anesthesia may precipitate a carcinoid crisis characterized by hypotension, bronchospasm, flushing, and tachycardia predisposing to arrhythmias. The treatment of carcinoid crisis is IV octreotide given as a bolus of 50 to 100 mg, which may be continued as an infusion at 50 mg/hr. In addition, IV antihistamine and hydrocortisone may be of some benefit. Octreotide, a somatostatin analog, is used to blunt the vasoactive and bronchoconstrictive effects of carcinoid tumor products. Octreotide mimics somatostatin's inhibitory action on the release of several gastrointestinal hormones, as well as those derived from carcinoid tumors. Treatment for 2 weeks preoperatively with a dose of 100 mcg subcutaneously three times a day is standard. If prophylactic therapy was not used, a dose of 50 to 150 mcg subcutaneously is given preoperatively. Intraoperative infusion may be continued at 100 mcg/hr. Bolus doses of 100 to 200 mcg given intravenously may be used for intraoperative carcinoid crises. Octreotide is also beneficial if it is given for only 24 hours before surgery. If it is discontinued postoperatively, it should be weaned over the first week.[117]

Many anesthetic techniques have been used successfully in the treatment of patients with carcinoid syndrome (Box 30-12). Most patients with carcinoid tumors undergo general anesthesia because of the need to avoid the sympathectomy associated with neuraxial anesthesia; however, both epidural and spinal anesthesia have been used successfully in these patients. Successful spinal anesthesia has been reported with the use of preoperative octreotide, fluids, and low-dose spinal anesthetic supplemented with low-dose intrathecal opioids.[120] Laboratory tests should include the standard chemistry, blood count, liver function panel, blood glucose concentration, and electrocardiogram (ECG), as well as urinary 5-HIAA measurements.[115] A low threshold for further cardiac workup should be used because the reported incidence of cardiac involvement is as high as 50% to 60%.

Rapid changes in BP are often seen in carcinoid patients; therefore, in addition to standard monitors, invasive monitoring typically is required. Invasive monitors should be inserted before induction of anesthesia and continued postoperatively. Hypotension commonly associated with induction agents may trigger a carcinoid crisis, so an arterial catheter is mandatory prior to the induction of anesthesia. Increased bleeding also may be encountered, because abdominal carcinoids often have a rich vascular supply and metastases may involve vessel-rich organs such as the liver. Central venous pressure (CVP) monitoring may be very useful in these patients, especially during abdominal surgery for tumor resection. CVP monitoring may help exclude hypovolemia as a cause of hypotension and allow better attention and adjustment of fluid balance.

The release of catecholamines should be avoided. Propofol and etomidate have been used to induce anesthesia; however, propofol has a more profound effect in suppressing the sympathetic response to intubation and, as long as hypotension is avoided, may be the best induction agent in patients with carcinoid syndrome. Etomidate may have less effect on heart rate (HR) and BP, but may not suppress laryngeal reflexes. Use of histamine-releasing agents, such as morphine, thiopental, pancuronium, and atracurium, should be avoided.

Succinylcholine-induced increases in intraabdominal pressure from fasciculations may trigger mediator release; however, some researchers have not found any adverse effects with its use. Opioids that are associated with histamine release should not be

used. Furthermore, only nondepolarizing neuromuscular blocking agents that do not cause histamine release should be used. Because of its cardiovascular stability, vecuronium is a good choice, and rocuronium is an effective alternative.

A balanced technique that incorporates positive pressure ventilation, an inhalation agent, a nondepolarizing neuromuscular blocking agent, and an opioid, most commonly fentanyl, may be the best choice in patients with carcinoid. Propofol infusions also have been reported. Inhalation agents with low blood-gas solubility such as desflurane are preferred, although all available inhalation agents have been used. Nitrous oxide also is safe. A technique using high-dose opioids may be indicated because volatile anesthetics may cause myocardial depression and hypotension, resulting in release of tumor peptides. Because these patients often have chronic right ventricular (RV) valvular lesions and heart failure, one should avoid anesthetic factors that increase RV work with potential precipitation of acute RV failure. This includes hypoxemia, hypercarbia, and a light anesthetic plane.[117] Hypotension should be treated with an alpha-receptor agonist such as Neo-Synephrine to avoid beta-adrenergic activation.

TRANSPLANTATION

Transplantation is typically the definitive treatment for end-stage organ disease. Because transplant surgery and patient management is continually evolving, specific details of best practice are perishable and should be reevaluated before clinical implementation. A brief overview is provided here of selected organ transplantation procedures.

Liver Transplantation

In 2010, 6291 liver transplants were performed in the United States (Organ Procurement Transplant network, http://optn.transplant.hrsa.gov/). Ten-year (adjusted) patient survival rate of the 3487 deceased donor liver transplants (DDLT) performed in the United States in 1999 is 59.8%. Living donor liver transplant (LDLT) patient's 10-year survival (of 237 transplants) rate is 67.2%. Compared with DDLT, survival rates at 1, 3, and 5 years for LDLT are markedly higher, ranging from 94% to 85%, respectively. Despite living donor liver transplant patients having significantly higher survival rates in all time measurements, they are performed much less frequently (212 vs. 5170 in 2008) because of a limited number of willing and compatible donors.

Patients with end-stage liver disease who have exhausted medical and surgical therapy may be eligible for liver transplantation. Eligibility requirements are multifactorial but common indications/contraindications[121,122] for liver transplantation exist (Table 30-15 and Box 30-13).

Preoperative preparation and intraoperative anesthetic management for liver transplant surgery requires, at least, an understanding of the various stages of the surgery and the physiologic derangements occurring as a result of baseline hepatic dysfunction and surgically induced hematologic and metabolic insult.

Anesthetic Preparation

The comorbidities accompanying severe liver disease were discussed earlier in the chapter. Coagulopathy and anemia are baseline maladies that become more problematic in the context of significant blood loss expected during liver transplantation. Blood products need to be immediately available during surgery, and a clear line of communication needs to exist with the transfusion service (e.g., blood bank) to handle ongoing replacement requirements.

Arterial cannulation is needed for invasive BP monitoring and serial blood analysis throughout surgery. Changes in commonly monitored parameters are shown in Table 30-16. Large-bore venous access is indicated for liver transplant surgery. Often two 9-Fr introducers may be inserted for central access and a large (e.g., 8.5 Fr) antecubital catheter may be used for volume administration via a rapid infuser device (RID). If venovenous bypass will be used intraoperatively (potentially using the internal jugular if not the axillary vein), those sites should be avoided. Communication with the surgical team can clarify this decision. Pulmonary artery catheter and/or TEE may be used in many patients for managing fluid replacement and monitoring cardiac function. Normothermia should be maintained with appropriate warming devices (e.g., forced air, conductive blankets, fluid warmers, and heated venovenous bypass).

TABLE 30-15 Indications for Liver Transplantation

Indications	Examples
Acute hepatic necrosis	Viral hepatitis, drug toxicity, toxin, Wilson's disease
Chronic hepatitis	Hepatitis B, hepatitis C, hepatitis D, autoimmune hepatitis, chronic drug toxicity or toxin exposure, cryptogenic cirrhosis
Cholestatic diseases	Primary biliary cirrhosis, sclerosing cholangitis, secondary biliary cirrhosis, biliary atresia, cystic fibrosis
Alcoholic cirrhosis	May be considered for transplant if abstinence of alcohol for 6 months and ongoing therapy and evaluation
Metabolic diseases	Wilson's disease, cystic fibrosis hemochromatosis, alpha-1-antitrypsin deficiency, familial homozygous hypercholesterolemia, glycogen storage disease, tyrosinemia
Malignant diseases of the liver	Hepatocellular carcinoma, carcinoid tumor, islet cell tumor, epithelioid hemangioendothelioma

BOX 30-13

Contraindications for Liver Transplant

- Severe cardiopulmonary disease
- Active alcohol or substance abuse
- Extrahepatic malignancy
- Active/uncontrolled infection or sepsis
- Life-limiting neurologic conditions
- Uncontrolled psychiatric disorder
- Acquired immune deficiency syndrome

Surgical Transplantation and Anesthetic Management

Liver transplantation requires vascular reconstruction of the hepatic artery, the portal vein, and the hepatic venous drainage to the inferior vena cava. Biliary reconstruction usually is accomplished using an end-to-end anastomosis of the proximal donor bile duct to the distal recipient duct; however, in recipients with diseased ducts, the donor duct is usually anastomosed to the jejunum using a Roux-en-Y loop.[122] Often the surgery may be divided into three phases: preanhepatic, anhepatic, and postanhepatic (or neohepatic) phase. Anesthesia management guidelines vary between institutions (Box 30-14).

TABLE 30-16 Relative Changes in Parameters During Liver Transplantation*

Variable	Preanhepatic	Anhepatic	Neohepatic
Glucose	+	–/+	+ +
Hemoglobin	–/– –	–	–/– –
Platelets	–	–	–
Urine output	+ +	– –	+/+ +
Cardiac index	+ +	+	+ + +
Systemic vascular resistance	– –	+ +	– – –
Peripheral vascular resistance	+	– –	+
Mean arterial blood pressure	–	– –	– – –/– followed by +
Lactate	+	+	+/+ +
Potassium (K)	+	+	+ + + followed by +
Calcium (Ca)	–	– –	–
Magnesium (Mg)	–	– –	–
Sodium (Na)	+	+	+
Temperature	–	– – –	+

From Amand MS, et al. Liver transplant. In: Sharpe MD, Gelb AW, eds. *Anesthesia and Transplantation*. Boston: Butterworth-Heinemann; 1999:190; Pilla MA, et al. Anesthesia for liver surgery and transplantation. In: Longnecker DE et al, eds. *Anesthesiology*. 2nd ed. New York: McGraw Hill; 2012:1049-1080; Yost CS, Nieman CU. Anesthesia for abdominal organ transplant. In: Miller RD, et al, eds. *Miller's Anesthesia*. 7th ed. Vol. 2. Philadelphia: Churchill Livingstone, 2009:2155-2184.
**Increases:* + = mild, ++ = moderate, +++ = marked; *decreases:* – = mild, – – = moderate, – – – = marked.

Preanhepatic Phase. In conventional liver transplantation (CLTx), the preanhepatic stage starts at surgical incision and ends once cross clamps are placed on the hepatic artery, suprahepatic inferior vena cava, the infrahepatic inferior vena cava, and the portal vein. Not all surgical techniques require full venous arrest, because some centers will do a piggyback liver transplant (PLTx) in which caval clamping is avoided. In fact, recent studies have shown that with the advancement of surgical skills, refinement of surgical techniques, and improvements in anesthesiology, there are only limited indications for doing CLTx with venovenous bypass (VVB) routinely. PLTx with preservation of inferior vena cava (IVC) can be performed in almost all primary transplants and in the majority of retransplantations without the need for VVB.[123]

As ascites are drained after abdominal incision, hypovolemia may ensue, requiring volume replacement. Both crystalloid and colloid may be necessary to minimize alterations in preload. Further reduction in preload should be anticipated if flow from the inferior vena cava is halted, and appropriate fluid replacement should be instituted venous shunting or until venovenous bypass is initiated. VVB, which diverts inferior vena cava and portal venous flow to the axillary vein, attenuates the decrease in preload, improves renal perfusion pressure, lessens splanchnic congestion, and delays the development of metabolic acidosis.[124] Disadvantages of VVB, including a high complication rate (10%-30%)[125] and lack of evidence for improving clinical outcome[126], appear to limit its usage now to selected cases.

Some coagulopathy associated with liver transplantations are noted in Table 30-17. Some clinicians may choose to address correctible baseline coagulopathy during this stage and begin infusion of fresh frozen plasma (FFP). Surgically induced vascular injury

BOX 30-14

Anesthesia Guidelines for Liver Transplant at the University of Wisconsin, 2011

Preanhepatic Phase
- Anesthesia induction
- Invasive monitors (arterial catheter, pulmonary catheter vs. FloTrac/Vigilio)
- Forced air and fluid warmers on
- IV antibiotics, baseline laboratory values (including TEG), incision
- Lower CVP to 5 cm H_2O, restrict IV fluid, phlebotomy if Hgb greater than 10g/dL
- Norepinephrine (or vasopressin) to keep mean BP greater than 60 mmHg
- Dopamine (or epinephrine) to keep CO at greater than 5L/min
- Maintain Hgb at greater than 7g/dL, platelets greater than 40,000, MA (TEG) greater than 45, fibrinogen greater than 100 mg/dL
- Mannitol 0.5g/kg IV over 1 hour, prior to anticipating clamping
- Just before clamping:
  - IV heparin 3000-5000 units, if TEG is normal or hypercoagulable
  - Increase CVP to 10 cm H_2O with IVF
  - 25% albumin in severe hypoalbuminemia

Anhepatic Phase
- IV fluids to keep CVP around 5 cm H_2O
- Maintain Hgb at greater than 7g/dL
- Norepinephrine and/or vasopressin to keep mean BP greater than 60 mmHg and CO greater than 5L/min
- Bicarbonate infusion to correct base deficit
- IV calcium chloride to sustain normocalcemia

Neohepatic Phase
- Reperfusion
- When SVR is declining, IV vasopressin 1-5 unit bolus to keep mean BP at greater than 60 mmHg
- Epinephrine 20-100 mcg boluses if heart rate is less than 60/min
- Euvolemia: CVP of 5-10 cm H_2O
- Dopamine (or epinephrine) to keep CO at greater than 5L/min
- Norepinephrine and/or vasopressin to keep mean BP at greater than 60 mmHg
- TEE if needed for detailed hemodynamic assessment
- Maintain Hgb at greater than 7g/dL, platelets at greater than 40,000, fibrinogen at greater than 100 mg/dL
- TEG:
  - Protamine 30 mg IV, if R is more than twofold compared with heparinase-R
  - Maintain MA at greater than 45 mm with platelet transfusion
- If Ly30 is greater than 8%, give IV EACA 5 g over 15 min:
  - Consider indication for postoperative mechanical ventilation per usual criteria
  - Recovery in PACU (if extubated in OR) vs. ICU (if mechanically ventilated)

From Hannaman M, Hevesi Z. Anesthesia care for liver transplantation. *Transplantation Reviews*. 2011;25(1):36-43.
BP, Blood pressure; *CO*, cardiac output; *CVP*, central venous pressure; *EACA*, epsilon-aminocaproic acid; *ICU*, intensive care unit; *Ly30*, clot lysis 30 minutes; *MA*, maximum amplitude; *OR*, operating room; *PACU*, postanesthesia care unit; *SVR*, systemic vascular resistance; *TEE*, transesophageal echocardiography; *TEG*, thromboelastography.

TABLE 30-17 Coagulopathy During Orthotopic Liver Transplantation

Stage	Coagulopathy
Dissection	Preexisting coagulopathy Dilution Fibrinolysis (mild) Ionized hypocalcemia Dilution
Anhepatic	Heparin effect (with venovenous bypass) Fibrinolysis (moderate) Hypothermia Ionized hypocalcemia Fibrinolysis (severe)
Early neohepatic	Heparin effect Intravascular coagulation Dilution Hypothermia Ionized hypocalcemia
Late neohepatic	Gradual recovery

From Kang Y, Audu P. Coagulation and liver transplantation. *Int Anesthesiol Clin*. 2006;44(4):19.

and impaired clearance of activated coagulation factors caused by decreased hepatic blood flow may result in excessive activation of coagulation and consumptive coagulopathy, whereas surgical bleeding may deplete coagulation proteins and platelets, inducing dilutional coagulopathy.[127]

Prothrombin time, fibrinogen, and platelet count may be evaluated to guide correction of coagulopathy. Thromboelastography (TEG) also has been employed to define the viscoelastic properties of blood. TEG is able to provide information about platelet activation, fibrin formation, and clot retraction. It has been used extensively to guide therapy of coagulation disorders.[128] Wang et al.[129] reported that liver transplantation patients monitored via TEG used significantly less FFP, and there was a trend toward less blood loss in the TEG-monitored patients. Blood loss is typically minor in the preanhepatic stage, although patients with significant portal hypertension have a higher bleeding tendency.

Anhepatic Phase. If performed, transection of the IVC above and below the liver results in predicable hemodynamic changes: decreased cardiac output related to the decrease in venous return, and decreased arterial blood pressure. Historically, venovenous bypass was used routinely (in some centers) to facilitate venous return from the portal system and lower body to the heart via a centrifugal pump to the axillary or subclavian vein. If IVC occlusion is used and VVB is not instituted, the decreased preload may be treated with norepinephrine infusion with addition of phenylephrine for refractory low systemic vascular resistance.

Acidosis encountered during the anhepatic phase because of the accumulation of acid metabolites and reduction of perfusion can be treated with sodium bicarbonate to correct base deficit. Blood loss during this period will necessitate transfusion blood products; calcium chloride also may be infused to correct transfusion-induced hypocalcemia and to maintain blood pressure at the anhepatic phase.

The now more common piggyback liver transplant may be successfully done with an end-to-side cavocavostomy[130] with limited hemodynamic alterations typically associated with complete caval obstruction. Liver transplant surgery was historically associated with massive blood loss and hemodynamic instability. Mangus et al.[131] reported in 2007, in a retrospective review of 526 transplant patients, that piggyback hepatectomy (PGB) can be safely accomplished in nearly all liver transplant patients without venovenous bypass or vena cava clamping and with less warm ischemia. In their analysis, estimated blood loss (EBL) was 1000 mL and median transfusion requirement was 3 units packed red blood cells, 7 units fresh frozen plasma, and 6 units platelets.

Postanhepatic Phase. Reperfusion of the graft begins the neohepatic stage. Once the donor liver is implanted and blood flow is resumed, the release of portal blood flow from the graft can result in significant hemodynamic instability and post reperfusion syndrome (PRS).[132] PRS, defined as a decrease in the mean arterial pressure of more than 30% of the value observed in the anhepatic stage, is marked by hypotension, decreased systemic vascular resistance (SVR), and increased pulmonary artery pressures. The absence of portocaval shunt and the duration of cold ischemia were independent predictors of intraoperative PRS. The etiology may be an influx of a cold, acidic, hyperkalemic fluid and other mediators into systemic circulation. Electrolyte abnormalities should be addressed before reperfusion because acidosis, hyperkalemia, and hypocalcemia are commonly encountered after the transplanted liver is perfused.

Reduction in SVR may be treated with venous hydration to maintain euvolemia (e.g., CVP 5-10), norepinephrine, and/or vasopressin to maintain mean arterial blood pressure at greater than 60 mmHg. Dopamine may be needed to maintain cardiac output (e.g., greater than 4 or 5).

Coagulation status should be monitored and corrected during this phase.

Fibrinolysis (detected by elevated TEG) is most severe after reperfusion. TEG results of patients with fibrinolysis will show a decrease in maximum amplitude (MA) on the tracing. MA measures the strength of the clot, which is an overall reflection of the structural interactions and fibrinogen, interlaced with fibrin polymers. Platelet function and aggregation have the greatest effect on MA.[133] Antifibrinolytics (e.g., aminocaproic acid) and cryoprecipitate may be required. Desmopressin (1-deamino-8-D-arginine vasopressin [DDAVP]) may be administered to help improve platelet function.

Excessive hydration with crystalloid and blood components should be avoided to prevent peripheral and pulmonary edema, decreased oxygenation, and the risks associated with prolonged intubation and ventilation. Some common intraoperative complications and their management are noted in Table 30-18.

Other Intraabdominal Organ Transplants

Intestine

Intestinal transplantation occurs at a much lower rate compared with liver or kidney. In 2008, 158 intestine transplants were performed in the United States. Bowel transplantation was first attempted in the 1960s and had a low success rate until the mid-1980s, which coincided with improved immune suppressive drugs and better methods to prevent infections. The intestine has been more difficult to transplant than other solid organs; some of the possible reasons include a large number of white cells in the bowel (providing a strong stimulus for rejection) and omnipresent bacterial presence in the gut increasing the risk of infection after transplantation.

One-year patient and intestine graft survival is 89% and 79% for intestine-only recipients and 72% and 69% for liver-intestine

TABLE 30-18 Intraoperative Complications and Management

Complication	Management
Hypothermia	Use heat exchanger, fluid warmer, warming blanket, forced-air units, postoperative ventilation, warm blood flush
Hyperkalemia	Elevated by massive transfusion; administer binding resins; perform diuresis, dialysis, hyperventilation; administer sodium bicarbonate, calcium chloride, insulin, or glucose
Hypocalcemia	Administer calcium chloride or gluconate by central line, citrate in blood may bind thus lower calcium
Oliguria	Maintain adequate volume; increase renal perfusion pressure; administer mannitol, furosemide, and ethacrynic acid; renal replacement therapy
Hypotension	Maintain adequate volume, check calcium and magnesium, rule out cardiac dysfunction, administer vasopressors; transfuse blood products if anemia or coagulopathy is present monitor for emboli, vena caval compression
Hypertension	Maintain adequate anesthetic depth, reduce filling pressures, avoid long-acting agents that are used to treat hypertension
Postreperfusion syndrome	Anticipate; ensure that volume loading is not excessive; administer calcium, vasopressors
Coagulation	Monitor coagulation status throughout massive transfusion; administer platelets, fresh frozen plasma, and other antidotes as indicated

From Amand MS, et al. Liver transplant. In: Sharpe MD, Gelb AW, eds. *Anesthesia and Transplantation*. Boston: Butterworth-Heinemann; 1999:191; Pilla MA, et al. Anesthesia for liver surgery and transplantation. In: Longnecker DE, et al, eds. *Anesthesiology*. 2nd ed. New York: McGraw Hill; 2012:1049-1080; Yost CS, Nieman CU. Anesthesia for abdominal organ transplant. In: Miller RD, et al, eds. *Miller's Anesthesia*. 7th ed. Vol. 2. Philadelphia: Churchill Livingstone; 2009:2155-2184.

recipients, respectively. By 10 years, patient and intestine survival falls to 46% and 29% for intestine-only recipients, and 42% and 39% for liver-intestine recipients, respectively.[134] Given the relative infrequency of this transplant, specialty texts or current research should be reviewed for surgical and anesthetic implications of these procedures.

Pancreas

Pancreas transplantations in diabetic patients are divided into three categories: (1) simultaneously with a kidney (SPK) (75%), (2) after a previous kidney transplantation (PAK) (18%), and (3) pancreas transplantation alone (PTA) (7%). Transplantation may be performed on patients with poorly controlled diabetes mellitus with impending complications, but more often it is done concurrently for patients with end-stage renal disease undergoing simultaneous renal transplantation (Figure 30-9).

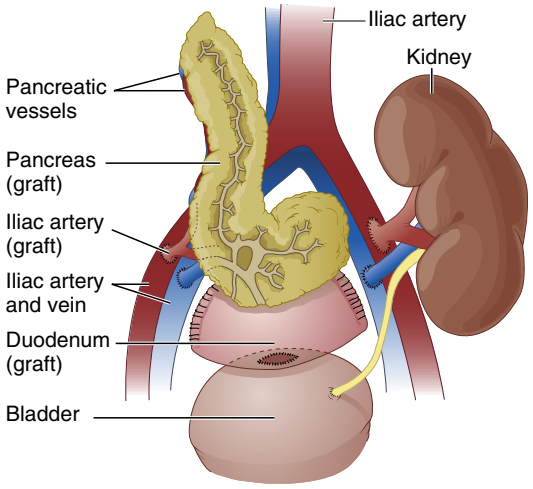

FIGURE **30-9** Simultaneous kidney-pancreas transplant. (From Carlson KK, ed. *AACN Advanced Critical Care Nursing*. St. Louis: Saunders; 2009:834.)

In 2011, Gruessener[135] reported that changes in surgical technique and immunosuppressive protocols have led to improved patient and graft survival. One year post-transplant patient survival is now over 95%, and over 83% after 5 years. The best graft survival was found in SPK with 86% pancreas and 93% kidney graft function at 1 year. PAK pancreas graft function reached 80%, and PTA pancreas graft function reached 78% at 1 year. In all three categories, early technical graft loss rates decreased significantly to 8% to 9%. Likewise, the 1-year immunologic graft loss rate also decreased: in SPK, the immunologic 1-year graft loss rate was 1.8%, in PAK, 3.7%, and in PTA, 6.0%.

As identified, pancreas-only transplantation represents a very small percentage of the overall pancreatic transplant surgeries. Anesthetic management will therefore vary depending on the organ being transplanted with the pancreas (e.g., kidney 75% of the time).

SUMMARY

Managing the anesthetic needs of patients with hepatobiliary and gastrointestinal disorders requires a thorough understanding of normal physiologic functions of the encountered organ system, as well as an appreciation for the systemic implications of pathophysiologic derangements discussed in this chapter. Advances in anesthetic and surgical management of patients are resulting in improved outcomes, but also requires ongoing inquiry by clinicians and researchers. The discussions in this chapter represent some of the most current evidence available in regard to providing quality anesthesia care and patient management.

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31 CHAPTER Anesthesia for Laparoscopic Surgery

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The advent and expansion of laparoscopic surgical techniques over the past 30 years has transformed the way in which practitioners approach the care of patients during the perioperative period. Surgeons in gynecology, urology, and general surgery are using laparoscopy to perform increasingly more complex diagnostic and therapeutic procedures (Box 31-1). In fact, in some cases laparoscopic approaches have almost entirely replaced the traditional open laparotomy. These "minimally invasive" surgical procedures offer many advantages over "open" procedures, but have also created unique challenges for the anesthesia community.

Although considered to be a relatively new phenomenon in health care, the origins of laparoscopic surgery date back over 100 years. In 1901 the first endoscopic examination of the peritoneal cavity, known at the time as "celioscopy," was attempted by the German surgeon George Kelling to evaluate the effects of pneumoperitoneum on intraabdominal hemorrhage associated with such conditions as ectopic pregnancy and bleeding ulcers.[1-3] Over the next 70 years several surgeons used laparoscopic techniques, but because of technologic limitations and a high complication rate from bowel and cautery injuries and vascular perforation, few mainstream surgeons embraced the techniques.[2] With the development of the open entry Hasson trocar in 1971 and videoscopic imagining in the mid-1980s, the safety of laparoscopy improved. Finally, in 1988 the first videolaparoscopic cholecystectomy was performed by the French surgeon Philip Mouret and the technique soon spread worldwide as the healthcare community began to realize the true benefits of laparoscopy—a safer, less painful, minimally invasive alternative to open laparotomy with a faster recovery and return to normal function.[2,4,5]

After the success of laparoscopic cholecystectomy, surgeons began to explore minimally invasive approaches to a vast array of complex intraabdominal procedures including herniorrhaphy, prostatectomy, hysterectomy, nephrectomy, and many others. These techniques are now employed by many surgical specialties in patients across the life span and with significant coexisting disease. As a result, the challenges associated with laparoscopy, such as pneumoperitoneum and unique positioning, are coupled with increasingly critical patients adding unique complexity to the anesthetic management for these procedures. Figure 31-1 depicts a classic approach to a laparoscopic appendectomy.

CREATION OF THE PNEUMOPERITONEUM

To perform laparoscopic procedures, it is necessary to create an environment in which the surgeon can clearly view all intraabdominal structures and successfully manipulate the instruments required for surgical dissection. This is accomplished through the creation of an artificial *pneumoperitoneum*—the installation of air or gas into the peritoneal cavity under controlled pressure. Although complications associated with laparoscopic surgery are rare, initial entry into the abdominal cavity and establishment of the pneumoperitoneum are responsible for a significant proportion of those that do occur.[6-9] Large multicenter studies have demonstrated the pooled risk of severe vascular or bowel injury at the time of abdominal entry to be 0.2 and 0.4 per 1000, respectively.[6,8] In addition to the risks caused by the placement of the surgical trocars, insufflation of gas into the peritoneal cavity produces significant physical stress on multiple organ systems. These physiologic effects are seen intraoperatively and can carry over into the immediate postoperative period, increasing the morbidity and mortality associated with these procedures.

Two entry methods are used most commonly for the establishment of the pneumoperitoneum during laparoscopic surgery—the closed technique or the open (Hasson) procedure.[6,8] Other techniques are available but are used less often because little evidence exists to support their superiority in respect to preventing the complications associated with needle and trocar placement. These techniques include direct entry without prior establishment of the pneumoperitoneum and the use of optical entry trocars.[10-12] The choice of technique is determined by the surgeon; however, the evidence indicates that patients who are extremely thin, obese, or known to have abdominal adhesions are at increased risk for laparoscopic entry-related injuries at the umbilical entry point, and they may benefit from an alternative entry procedure such as the open (Hasson) or left upper-quadrant (Palmer's point) entry technique.[6,13,14]

The closed technique involves the use of a spring-loaded needle known as a Veress needle to pierce the abdominal wall at its thinnest point, either in the infraumbilical or intraumbilical region. Various different techniques have been used to test for proper placement of the Veress needle including attempted saline aspiration and hanging-drop techniques. However, a review of recent case control and cohort studies of women undergoing laparoscopic procedures has shown that an intraabdominal pressure (IAP) of 10 mmHg or less reliably indicates correct placement of an umbilically placed Veress needle.[6,15-17] An appropriate nonflammable gas, usually carbon dioxide (CO_2), is then insufflated through the needle to increase the intraabdominal pressure, lift the abdominal wall, and create a space between it and the underlying organs. After insufflation of the abdomen, a trocar is inserted blindly or under direct vision to allow the surgeon to pass instruments into the abdominal cavity.[6,7]

The open technique was developed by H. M. Hasson in 1970 in an attempt to combine the benefits of laparoscopy with the safety of open laparotomy.[18] The technique involves the development of a 1- to 2.5-mm midline vertical incision that begins at the lower border of the umbilicus and extends through the subcutaneous tissue and underlying fascia.[19] The surgeon is then able to directly separate the abdominal wall from the underlying tissues,

minimizing the risk of damage to the bowel and vasculature. Once the surgeon has entered the abdominal cavity, a trocar can be placed under direct vision and sutured in place. Gas can then be insufflated directly through a side port in the Hasson trocar establishing the pneumoperitoneum.

BOX 31-1

Applications of Laparoscopy

General Surgery
- Diagnosis
- Evaluation of abdominal trauma
- Lysis of adhesions
- Cholecystectomy
- Appendectomy
- Inguinal hernia repair
- Bowel resection
- Esophageal reflux surgery
- Splenectomy
- Adrenalectomy
- Bariatric surgeries of all types

Gynecologic Surgery
- Diagnosis
- Lysis of adhesions
- Fallopian-tube surgery (sterilization, ectopic pregnancy surgery)
- Fulguration of endometriosis
- Ovarian cyst surgery
- Laparoscopic-assisted hysterectomy

Urologic Surgery
- Nephrectomy
- Varicocele

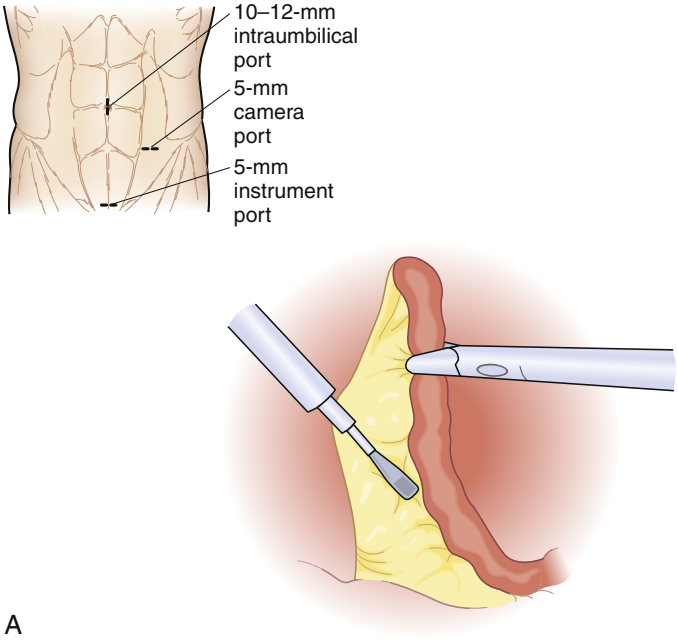

FIGURE 31-1 *Upper left*, Location of port sites for laparoscopic appendectomy. *Right*, **A,** Division of the mesoappendix using the harmonic scalpel. **B,** Placement of the appendix into a specimen bag before removal of the appendix with the umbilical port. (From Townsend CM, et al. *Sabiston Textbook of Surgery: The Biological Basis of Modern Surgical Practice*. 19th ed. Philadelphia: Saunders; 2012.)

PHYSIOLOGIC EFFECTS OF THE PNEUMPERITONEUM

As the complexity of laparoscopic surgery and the severity of illnesses in patients undergoing these procedures increase, the need to have a comprehensive understanding of the physiologic effects of pneumoperitoneum becomes paramount. The magnitude of patient response to pneumoperitoneum depends upon multiple factors, including the degree of intraabdominal pressure generated during creation of the pneumoperitoneum, the length of surgery, patient position, patient age, perioperative volume status, and the presence of preexisting pulmonary and/or cardiovascular disease.[9,20,21] Although no clinical complications have been demonstrated as being a result of transitory elevations in intraabdominal pressure, prolonged periods of high intraabdominal pressure and tension, such as those required for successful laparoscopy, have been associated with significant physiologic effects.[9,22-24] These changes occur as a result of direct mechanical pressure and the stimulation of intrinsic neurocirculatory responses. When combined with surgery-specific conditions, unique patient positioning needs (i.e., steep Trendelenburg), and variations in anesthetic technique, the net effect of intraabdominal pressure on physiologic hemostasis may be unpredictable. Fortunately, long-term clinical complications are rare.

Cardiovascular Effects

Current research has shown that creation of a pneumoperitoneum is associated with significant changes in hemodynamic parameters (Box 31-2). Consistently, increases in mean arterial pressure (MAP), systemic vascular resistance (SVR), and heart rate (HR) that are sustained over the duration of insufflation have been demonstrated.[9,20,25,26] Compression of the intraabdominal vessels and release of neuroendocrine hormones (i.e., vasopressin and renin) are implicated as causative factors in this hemodynamic response. The increases in MAP and SVR are observed regardless of whether the pneumoperitoneum is created under low pressure (12 mmHg) or high pressure (20 mmHg).[9]

Reports on the impact of abdominal insufflation on cardiac filling pressures are mixed. Several studies demonstrate increases in central pressures, whereas others show significant reductions.[20,26-28] Confounding variables, such as the use of vasodilating anesthetics and perioperative fluid restrictions, can significantly alter preload. It is known that insufflation compresses abdominal vasculature, but the extent to which this impacts venous return is not fully understood. Changes in position appear to have a greater effect on central pressures than does the pneumoperitoneum itself.[20,26] Steep Trendelenburg produces significant increases in central venous pressure because it increases hydrostatic pressure at the level of the external auditory meatus.[20]

BOX 31-2

Hemodynamic Changes Associated with Pneumoperitoneum

- Central venous pressure/LVEDP ↑ or ↓
- Mean arterial pressure ↑
- Stroke volume ↓
- Cardiac output ↑, ↓, or without change
- Systemic vascular resistance ↑
- Heart rate ↑
- QT dispersion prolonged

↑, Increased; ↓, decreased; *LVEDP*, left ventricular end-diastolic pressure.

Uniformly, studies demonstrate that creation of the pneumoperitoneum produces significant decreases in stroke volume.[26,27] These changes appear to be secondary to decreases in venous return and not changes in myocardial function. Russo et al.[26] demonstrated that in patients with healthy myocardium, left ventricular systolic function and ejection fraction as measured by transesophageal echocardiogram (TEE) were preserved regardless of surgical position. Changes in stroke volume were associated with early diastolic impairment as a result of prolonged deceleration time and augmented isovolumetric relaxation time. The decreases in stroke volume caused by increased intraabdominal pressures can be offset through adequate perioperative hydration, changes in patient position, and the application of compression stockings because these interventions augment venous return.[27]

Although it is clear that stroke volume decreases as a result of abdominal insufflation, the impact of pneumoperitoneum on cardiac output (CO) and cardiac index (CI) is variable because these parameters are influenced by a multitude of factors. In several studies, CO was maintained because reductions in stroke volume were offset by increases in heart rate and venous return, especially when patients were placed in the Trendelenburg position.[26,28] Other researchers have observed significant reductions in CI after operative insufflation pressures are achieved.[29,30] Healthy patients undergoing laparoscopic cholecystectomy have demonstrated 30% to 40% reductions in CO using a thermodilution technique.[29] In addition, significant reductions in left ventricular end-diastolic pressures have been demonstrated, which in turn negatively impact cardiac function if not accompanied by sufficient increases in heart rate.[30] Despite the variability in findings, patients who have been adequately fluid loaded and who have received therapies to augment venous return (e.g., compression stockings) experience significantly smaller reductions in CO as compared with control patients (20% versus 50%).[27]

Finally, the pneumoperitoneum appears to have an effect on the cardiac conduction system, even in healthy patients. A study by Ekici et al.[31] showed that high-pressure insufflation significantly prolonged QT dispersion (QTd) in patients undergoing laparoscopic cholecystectomy as compared with a low-pressure control group. The QTd reflects ventricular instability, and prolongation of this parameter is associated with an increased risk of arrhythmias and cardiac effects. Although these changes would not be expected to have clinical significance in healthy patients undergoing elective laparoscopic procedure, they may produce significant hemodynamic effects in elderly patients with significant cardiac disease.

Hemodynamic Changes in the Elderly

Most research on the hemodynamic effects of abdominal insufflation has been conducted in young healthy patients. Therefore, little is known about the impact of the pneumoperitoneum in the elderly population, who often present with significant comorbidity. When compared with healthy patients, patients with significant comorbidity have been shown to exhibit exaggerated hemodynamic responses to pneumoperitoneum.[32,33] The cumulative effects of carbon dioxide gas (CO_2) in the pneumoperitoneum and the reverse Trendelenburg position can result in moderate decreases in CO, as well as significant increases in filling pressures and afterload in sick patients. In one study of patients undergoing laparoscopic colorectal surgery, elderly patients exhibited greater increases in central venous pressure (CVP) and decreases in MAP, as compared with younger, healthier patients.[33] In addition, the magnitude of these changes at different time intervals was also greater in the elderly population. These findings may reflect baseline physiologic differences in organ function and compensatory mechanisms in the elderly population.[33]

Respiratory Effects

Although laparoscopic surgery is associated with a significant decrease in postoperative respiratory complications, intraoperative pulmonary function is greatly impacted by both the mechanical effects of the pneumoperitoneum and introduction of CO_2 into the intraperitoneal cavity itself. Increases in intraabdominal pressure shift the end-expiratory position of the diaphragm cephalad, decrease functional residual capacity (FRC), and create areas of atelectasis, making ventilation difficult.[34] In addition, CO_2 insufflation causes acid-base alterations that can have deleterious effects on multiple organ systems.[35]

In the presence of fixed minute ventilation, CO_2 pneumoperitoneum is associated with increases in the partial pressure of arterial CO_2 ($PaCO_2$) and end-tidal CO_2 ($ETCO_2$) with or without acidosis.[35] The increases in $PaCO_2$ are primarily caused by CO_2 absorption through the peritoneal serosa secondary to the increased intraabdominal pressure caused by the pneumoperitoneum. The resultant acidosis is considered to be respiratory rather than metabolic in nature. Studies show that during laparoscopy, decreases in arterial pH are accompanied by a rise in partial pressure of carbon dioxide (PCO_2), but not by increases in lactate or decreases in the apparent strong ion difference (SIDa).[35] These parameters return to baseline after discontinuation of CO_2 insufflation. Maximum absorption of CO_2 is noted with an intraabdominal pressure of 10 torr (mmHg pressure). $PaCO_2$ levels are noted to reach a plateau approximately 40 minutes after the induction of the peritoneum.[35-37]

A major concern during the creation of the pneumoperitoneum involves the risk of subcutaneous tracking of CO_2 through misplaced trocars or rents in the peritoneum that develop during trocar placement. Compared with intraperitoneal insufflation of CO_2, extraperitoneal insufflation (subcutaneous absorption) has been associated with an unusually rapid increase in $PaCO_2$ and exceptionally high, sustained levels of CO_2.[38-40] Cases of pneumopericardium and severe emphysema of the orbit have been documented after subcutaneous absorption of CO_2.[38,39] Factors that increase the incidence and degree include body mass index (BMI) less than 25, prolonged operative time, higher end-tidal carbon dioxide tensions, and operative approach.[40,41] Although mild hypercapnia (45 to 50 torr) is not believed to be clinically significant, profound hypercapnia with $PaCO_2$ levels in the range of 50 to 70 torr is associated with physiologic effects such as increased cerebral blood flow, peripheral vasodilation, pulmonary vasoconstriction, and increased risk of cardiac dysrhythmia.[20,42]

The mechanical effects of peritoneal insufflation impair ventilation. Insufflation of the peritoneum displaces the diaphragm in a cephalad direction, decreases functional residual capacity, decreases vital capacity, and in turn induces collapse of the dependent regions of the lungs.[34,43] Perfusion of these nonventilated alveoli causes the development of pulmonary shunt with impaired oxygenation and CO_2 elimination.[34,43] The development of atelectasis is also associated with an increase in the arterial to end-tidal PCO_2 difference.[34] Therefore, techniques such as transcutaneous carbon dioxide (P_TCO_2) monitoring may serve as a better predictor of arterial carbon dioxide ($PaCO_2$) levels than end-tidal $PaCO_2$ monitoring.[44] Increases in intraabdominal pressure also affect pulmonary compliance; in supine patients, pulmonary compliance has been observed to be reduced by 43%.[20,32]

The impact of atelectasis on gas exchange has been shown to be offset by a redistribution of perfusion away from collapsed lung

BOX **31-3**

Pulmonary Function Changes Associated with Pneumoperitoneum

- Positive inspiratory pressure (PIP) ↑
- Pulmonary compliance dV/dP ↓
- Vital capacity ↓
- Functional residual capacity ↓
- Intrathoracic pressure ↑

↑, Increased; ↓, decreased; *dV/dP*, change in volume/change in pressure.

units when the pneumoperitoneum is established.[43,44] Although the exact mechanism is not known, it appears to be the result of activation of the hypoxic pulmonary vasoconstriction (HPV) reflex.[43] Because many anesthetics inhibit the HPV reflex, increases in ventilation/perfusion ($\dot{V}/\dot{Q}$) mismatching and changes in oxygenation during laparoscopic surgery may reflect the physiologic effects of the anesthetics used, rather than the impact of the pneumoperitoneum itself. This may have implications for the choice of anesthetics used during these procedures. Physiologic pulmonary changes associated with pneumoperitoneum are listed in Box 31-3.

An additive effect is observed when general anesthesia, which in and of itself reduces FRC and pulmonary compliance, is combined with pneumoperitoneum.[34,43] The surgical position employed to facilitate exposure can either aggravate or attenuate pneumoperitoneum-induced pulmonary changes. The Trendelenburg position has been shown to increase the effects of pneumoperitoneum on pulmonary mechanics. During robotic laparoscopic prostatectomy in the steep Trendelenburg position, pulmonary compliance decreased approximately 50% and peak plateau pressures increased by 50%, and remained stable over the duration of the CO_2 insufflation.[20] In contrast, the reverse Trendelenburg position partially counteracts the effects of pneumoperitoneum on the diaphragm and improves diaphragmatic function.[45]

Another impact of pneumoperitoneum is the potential for the development of endobronchial intubation as a result of a shortening of the distance from the tip of the endotracheal tube to the carina.[46-48] Since the carina is attached to the lungs, cephalad displacement of the diaphragm compresses the lungs and shifts the position of the carina upward. Studies indicate that displacement of the tube occurs within 10 minutes of creation of the pneumoperitoneum; therefore the authors recommend reconfirmation of tracheal tube position after establishment of the pneumoperitoneum.[47,48]

Controlled mechanical ventilation is necessary to maintain normocarbia in anesthetized patients undergoing laparoscopic surgery with CO_2 pneumoperitoneum. Studies of patients in the Trendelenburg position during pneumoperitoneum reveal that a 20% to 30% increase in minute ventilation is necessary to maintain pre-pneumoperitoneum levels and prevent respiratory acidosis.[35,49] Increasing the minute ventilation by preferentially increasing tidal volume rather than increasing respiratory rate was the preferred method. In addition, the use of the pressure control (PC) modes appears to be more effective in maintaining arterial pH when compared with the volume control (VC) modes of ventilation.[50] Patients ventilated using PC were also easier to ventilate, generating significantly lower maximum peak airway pressures and increased mean airway pressures.

Patients with marginal cardiopulmonary function undergoing laparoscopic surgical procedures are at increased risk of decompensation when faced with the stress introduced by increases in intraabdominal pressure and CO_2 insufflation. Patients particularly vulnerable to the effects of exposure to prolonged CO_2 insufflation are those with increased metabolic rates (as in sepsis), large ventilatory dead space, and decreased cardiac output.[21] Patients with chronic obstructive pulmonary disease (COPD) are at increased risk of developing postoperative complications after laparoscopic procedures.[51,52] One study demonstrated the odds ratio for postoperative complication to be 1:63 in patients with significant COPD.[51] Studies also indicate that although healthy patients experience minor changes in $Paco_2$ and $ETco_2$ during CO_2 insufflation, patients with COPD show significantly higher levels of CO_2 retention and subsequent respiratory acidosis.[53] Although $ETco_2$ is standard of care for all patients, careful intraoperative monitoring of CO_2 levels during laparoscopic surgery in these patients is essential. Because of the significant arterial to end-tidal Pco_2 gradient that develops during sustained pneumoperitoneum, and which is compounded in patients with chronic CO_2 retention, $ETco_2$ may underestimate arterial CO_2. Therefore, direct measurement of $Paco_2$ via arterial blood gases or P_Tco_2 may be warrented.[34,42] Recent studies show that P_Tco_2 is an accurate, noninvasive predictor of arterial carbon dioxide levels and can be used as a proxy.[42]

Mild pulmonary dysfunction after laparoscopic procedures has been shown to persist into the immediate postoperative period in patients recovering from laparoscopic surgery. A slight restrictive breathing pattern in the postoperative period has been observed secondary to the residual effects of anesthesia, pain, and diaphragmatic dysfunction induced by stretching or reflex inhibition. In addition, after laparoscopic surgery, patients may still be subjected to an elevated CO_2 load secondary to systemic absorption and subcutaneous tracking of gas during the procedure. Moreover, if surgery is prolonged and exposure to pneumoperitoneum is sustained for the majority of the procedure, CO_2 may be stored in skeletal muscle and bone. It may take hours for this excess CO_2 to be excreted from the patient.[54]

Renal Effects

The effects of pneumoperitoneum on renal physiology primarily manifest as transient increases in creatinine clearance and decreases in urinary output.[23,55,56] Oliguria has been reported but most commonly occurs only during periods of sustained high intraabdominal pressures.[23,55,56] It is proposed that the high intraabdominal pressures created during the pneumoperitoneum cause transient renal injury by reducing renal blood flow and subsequently causing hypoperfusion of the renal cortex. High intraabdominal pressures (15 mmHg or greater) create renal oxidative stress and the generation of tissue oxidases that promote tubular injury.[23] In addition, the neuroendocrine response to pneumoperitoneum, the release of antidiuretic hormone (ADH), and the presence of respiratory acidosis induces a sympathetic response and renal vasoconstriction, which further diminishes renal blood flow.[23,57,58]

Hepatic and Splanchnic Effects

There is conflicting evidence regarding the effects of increased intraabdominal pressure on hepatic and splanchnic blood flow. Several animal studies have demonstrated that abdominal insufflation can cause marked decreases in splanchnic and liver perfusion, as well as intestinal ischemia secondary to the production of oxygen free radicals and bacterial translocation.[59,60] This is further supported by the fact that approximately 50% of patients undergoing laparoscopic cholecystectomy demonstrate elevated liver enzymes.[61,62] Other studies indicate that low-pressure insufflation

of the abdomen either did not disrupt or improved hepatic and splanchnic perfusion, possibly secondary to the local vasodilatory effect of CO_2 on splanchnic vasculature.[63,64]

Immunologic Effects

CO_2 pneumoperitoneum also may have a negative effect on the local immune response by altering the concentrations of certain cytokine levels with the peritoneum. Several studies have demonstrated that CO_2 pneumoperitoneum influences the growth of cultured human cancer cells, and that this effect is pressure dependent.[65,66] Other studies have shown no significant differences in levels of cytokines and other proinflammatory factors between low- and high-pressure insufflation.[67] Proinflammatory cytokines and angiogenic factors have been shown to influence neoangiogenesis, adhesion formation, and normal wound healing processes.

COMPLICATIONS OF LAPAROSCOPIC SURGERY

Although laparoscopy has revolutionized the way surgery is conducted today, it is not devoid of complications. Even though major complications are rare, when they do occur, they are usually associated with significant morbidity. More than 50% of all complications occur during entry into the abdomen and insertion of trocars.[8,68] Entry-related complications involve intestinal, urinary tract, and vascular injuries, as well as carbon dioxide gas embolism.[68] The reported incidence of these injuries is between 0.3% and 1.0% of all laparoscopic procedures.[68,69]

Unfortunately, approximately 30% to 50% of these injuries go undiagnosed intraoperatively, resulting in significant surgical mortality (3.5%-5%).[8] Rates as high as 30% have been reported when major bowel and vascular injuries occur.[70] Delayed diagnosis may occur because initial signs and symptoms may be confused with other conditions such as anaphylaxis, gas embolism, or perioperative cardiac events. Frequently, bleeding may be occult and confined to the retroperitoneal space, which can tamponade significant hemorrhage.

The potential for injury to intraabdominal structures during the creation of the pneumoperitoneum is easily understood when one considers the proximity of anatomic structures to the site of incision and infraumbilical puncture. The major abdominal vessels including inferior vena cava, aorta, and iliac arteries and veins, as well as the bladder, bowel, and uterus, lie in close proximity to the entry points. Factors that increase risk of injury include body habitus, anatomic anomalies, prior surgery, surgical skill, degree of abdominal elevation during trocar placement, patient position, and the volume of gas insufflation.[6,68]

A prompt and coordinated response is required to prevent morbidity associated with vascular injury. Blood on aspiration of the Veress needle, free intraperitoneal blood, or unexplained hypotension and tachycardia should alert the operative team to a potential vascular injury.[69] Retroperitoneal hematomas are often difficult to visualize during laparoscopy and may become apparent only when blood loss is significant. Temporary measures to control bleeding may be possible through the abdominal trocar while resuscitative measures are instituted, but definitive treatment is usually achieved via conversion to an open laparotomy.

Visceral injuries can occur at any time during laparoscopy and are associated with significant morbidity and mortality. Intestinal injuries occur in 0.3% to 0.5% of operative laparoscopies, and less than 50% of these are recognized at the time of surgery. Diagnosis is difficult because presenting symptoms vary significantly depending upon the location of injury and degree of peritoneal contamination. Early recognition and surgical repair is essential to prevent mortality from bowel injuries. Untreated patients may develop peritonitis, sepsis, respiratory distress, and multisystem organ failure.[69] Because of the seriousness of these complications, many practitioners advocate the use of the open (Hasson) entry laparoscopic technique, because it is believed to be associated with a lower incidence of unrecognized vascular and visceral injury.[6]

Injury to the urinary tract occurs in 0.5% to 8.3% of cases secondary to trauma from instrument manipulation, electrocautery, or laser.[71] These injuries are easily recognized by direct visualization of urine leakage from damaged structures. Therefore, urinary bladder catheterization and instillation of methylene blue dye is often employed during these procedures when significant risk of damage to urinary structures is suspected.[68]

To help decrease the incidence of major vascular and visceral injury during laparoscopic surgery, the Royal College of Obstetricians and Gynaecologists (RCOG) has established evidence-based practice guidelines for abdominal entry.[6] Quality randomized controlled trials and systematic reviews consistently demonstrate that placement of the primary trocar under high pressure (25 mmHg) creates the safest distance between the anterior abdominal wall and underlying abdominal contents in order to minimize injury from trocar insertion. In addition, in healthy patients these transitory, high intraperitoneal pressures appear to be well tolerated without significant adverse clinical effects.[9]

Another potentially life-threatening complication of laparoscopic surgery is gas embolism. Gas embolism is defined as the direct entrainment of air and/or other medical gases such as carbon dioxide into the arterial or venous system.[68,71] Significant gas embolism is rare, having a reported incidence of 0.001% to 0.59% and an associated mortality rate of up to 28.5%.[68] Massive and/or fatal gas embolisms have been reported during all types of laparoscopic procedures including laparoscopic cholecystectomy, liver resection, and hysterectomy.[72-74] It can occur any time there are open vessels that have an intravascular pressure that is below intraabdominal pressure or with the erroneous placement of a Veress needle or trocar into the lumen of an intraabdominal vessel.

Recent animal and human studies using transesophageal echocardiography and monitoring of pulmonary artery pressure have shown that the actual incidence of gas embolism during laparoscopic procedures is between 65% and 100%.[71,75,76] The majority of these embolisms, while minor, were still associated with respiratory and hemodynamic changes that usually resolved spontaneously. These studies raise concerns regarding best practices for appropriate monitoring during the perioperative period in patients undergoing laparoscopic procedures. Intravascular insufflation of large volumes of gas can travel to the right side of the heart where they enter the pulmonary circulation and lodge in the pulmonary outflow tract, causing increased pulmonary artery pressure, right ventricular failure, decreased pulmonary venous return with subsequent decreased left ventricular preload, decreased cardiac output, asystole, and cardiovascular collapse.[68]

Signs and symptoms of a significant gas embolism in the anesthetized patient include an acute decrease in end-tidal pressure of carbon dioxide ($P_{ET}CO_2$), and an increase in end-tidal nitrogen, hypotension, or hypoxia that cannot be explained by deep anesthesia or hypovolemia.[71] Dysrhythmias, severe hemodynamic instability, and cardiovascular collapse can occur with large volumes of gas, especially in patients with impaired cardiovascular function and minimal cardiac reserve.[71]

Diagnosis of gas embolism depends upon recognition of the physiologic manifestations of gas emboli and/or visual detection of gas emboli in the right side of the heart and pulmonary outflow tract. Transesophageal echocardiography is the most sensitive diagnostic technique for the detection of gas emboli and can

identify emboli as small as 0.02 mL/kg.[77] However, this technology is rarely used because these volumes of air are well tolerated and usually not associated with hemodynamic changes. Changes in Doppler sounds and increases in pulmonary artery pressures will occur with volumes of 0.5 mL/kg of gas. Unfortunately, when the "classic mill wheel murmur" is audible, gas volumes of 2 mL/kg or more have been entrained, and significant hemodynamic instability is present manifesting in tachycardia, hypotension, cardiac dysrhythmias, cyanosis, and electrocardiogram (ECG) changes indicative of right-sided heart strain.[78]

Management of gas embolism includes halting the insufflation of gas, eliminating nitrous oxide (N_2O) from the anesthetic gases if it is being administered to prevent expansion of the embolism, releasing the pneumoperitoneum, flooding the field with normal saline to halt gas entrainment, placing the patient in left lateral decubitus position (Durant maneuver), aspirating the gas through a central venous catheter if in place, and supporting the hemodynamics with volume and pressors as required.[71] Low central venous pressure (CVP) increases the risk of venous gas embolism; therefore adequate hydration should be provided for the patient undergoing laparoscopy.[79] Box 31-4 lists the signs, symptoms, and treatment of gas embolism.

Another set of serious but rare complications related to the creation of pneumoperitoneum occur as a result of migration of gas into adjacent body cavities and include unilateral or bilateral pneumothorax, pneumomediastinum, and pneumopericardium. Gas may enter the thoracic cavity via congenital defects in the diaphragm, embryonic connections between the thoracic and abdominal cavities that may open under high pressure, or through perforations in the diaphragm or pleura during upper abdominal laparoscopic procedures, most commonly during laparoscopic esophageal surgery.[80,81] A retrospective review of 968 cases revealed an incidence of pneumothorax or pneumomediastinum in 1.9% of patients.[82] Another possible cause of pneumothorax is barotrauma secondary to increased airway pressures and decreased pulmonary compliance as a result of abdominal insufflation.[83] Pneumothorax caused by CO_2 insufflation may rapidly resolve spontaneously without intervention.[84] However, pneumothorax that results from barotrauma, such as a ruptured bleb, requires surgical decompression and chest tube placement.[83]

Mild to severe localized or generalized subcutaneous emphysema is a frequent manifestation of pneumoperitoneum that occurs as a result of gas entry into the subcutaneous tissues. As previously discussed, it can be the result of trocar or Veress needle misplacement in subcutaneous tissue or the result of high intraabdominal pressure and movement of gas through defects in the peritoneum.[38-40] Most cases of subcutaneous emphysema are clinically insignificant; however, it has been associated with the development of severe hypercarbia, decreased chest compliance, and hemodynamic instability.[20,42] Most cases resolve spontaneously.

The ideal gas for the creation and maintenance of pneumoperitoneum would demonstrate several properties, including colorlessness, lack of flammability in the presence of electrocautery, physiologic inertness, and excretion via a pulmonary route.[85] Several gases have been investigated in an attempt to find an alternative to CO_2 that is devoid of hemodynamic and respiratory effects. Both nitrous oxide and air support combustion and could not be used in the presence of electrocautery, which is essential for successful laparoscopy.[54] Inert gases such as helium have been evaluated for use in abdominal insufflation, but helium is not highly insoluble and raises issues about safety in the presence of a significant gas embolism.[86]

To date, carbon dioxide has proven to be closest to an "ideal" gas for abdominal insufflation. CO_2 is readily available and inexpensive, does not support combustion, and is rapidly absorbed from the vascular space and is readily excreted by the respiratory system. However, when used in a pneumoperitoneum, prolonged CO_2 absorption can cause hypercarbia and respiratory acidosis.[80] It is also a known peritoneal and diaphragmatic irritant, which has been implicated as a causative factor in the development of postoperative shoulder pain.[87]

BOX 31-4

Gas Embolism

Signs and Symptoms
- ↓ $P_{ET}CO_2$, ↑ end-tidal nitrogen
- Increased pulmonary artery pressures
- Hypotension
- Dysrhythmias
- Cyanosis
- Hypoxia
- Pulmonary edema
- "Mill wheel" murmur

Treatment
- Discontinue gas insufflation
- Discontinue nitrous oxide
- Administer 100% oxygen
- Release pneumoperitoneum
- Flood surgical field with normal saline
- Position patient in left lateral decubitus position
- Attempt to aspirate gas via central venous catheter
- Supportive measures to maintain hemodynamics

↑, Increased; ↓, decreased; $P_{ET}CO_2$, end-tidal pressure of carbon dioxide.

ANESTHETIC MANAGEMENT

Laparoscopic surgeries have been performed using local, regional, and general anesthetic techniques. The choice of anesthetic technique is dependent upon the specifics of the surgical procedure and patient preference.

Local anesthesia with sedation has been used successfully in the United States for patients undergoing minor gynecologic laparoscopic surgical procedures such as diagnostic laparoscopy or sterilization since 1971.[88] The use of local anesthesia is facilitated by surgical techniques such as the use of single-port techniques, low-pressure pneumoperitoneum, and port and small-diameter laparoscopes.[89] Research indicates that compared with patients who received general anesthetics, patients who received local anesthesia had shorter hospital stays and a reduction in overall hospital and anesthesia costs.[88,89] In addition, they demonstrated a faster recovery, decreased incidence of postoperative nausea and vomiting, and fewer hemodynamic changes. However, use of this anesthetic technique requires a cooperative patient and gentle surgical manipulation. When heavy sedation is required, the combination with pneumoperitoneum can result in hypoventilation and arterial oxygen desaturation.[90]

Regional anesthesia techniques, including spinal and epidural anesthesia, also have been used successfully for laparoscopic procedures including cholecystectomy without significant ventilatory compromise.[91] However, significantly high sensory levels are required for these procedures, which may lead to patient discomfort. In addition, shoulder pain secondary to diaphragmatic irritation from insufflated carbon dioxide is not well managed by means of regional techniques.[92]

General anesthesia is the most common anesthetic technique for the diagnostic and surgical laparoscopy. General anesthesia allows for control of ventilation and facilitates management of patient discomfort associated with the creation of the pneumoperitoneum and changes in intraoperative position such as steep Trendelenburg.

Most often the airway is secured with a cuffed endotracheal tube to facilitate ventilation and prevent aspiration of gastric contents. Minute ventilation is increased by approximately 15% to 35% to offset CO_2 absorption and maintain $P_{ET}CO_2$ between 35 and 45 mmHg. This is most effectively performed using pressure-controlled versus volume-controlled ventilation.[50] Intraoperative recruitment maneuvers, the application of positive end-expiratory pressure (PEEP), and the use of innovative ventilator modes have all been successful in improving lung compliance, oxygenation, and ventilation.[93-95] Studies show that the combination of PEEP 10 cm H_2O and intermittent positive airway pressure (40 cm H_2O) for 40 seconds was most effective in improving end-expiratory lung volumes, lung compliance, and arterial oxygenation in both healthy weight and obese patients than either intervention alone.[93,94]

The use of laryngeal mask airway (LMA) and other supraglottic airway devices in patients receiving general anesthesia for laparoscopic surgery remains controversial. Several authors have expressed concerns that the increased intraabdominal and intrathoracic pressures characteristic of pneumoperitoneum place the patient at increased risk of gastroesophageal reflux and pulmonary aspiration. In addition, the classic LMA does not secure the airway and the low seal pressures preclude the use of high airway inflation pressures without causing gastric distention.[96]

The barrier pressure (BrP) quantifies resistance to gastroesophageal reflux and is defined as the difference between the lower esophageal sphincter pressure and the gastric pressure.[97] To prevent aspiration, the gradient needs to remain positive because this will help prevent the lower esophageal sphincter from opening. A study examining the effect of induction, intubation, anesthesia, and pneumoperitoneum on barrier pressure in nonobese patients undergoing laparoscopy and obese patients undergoing laparoscopic gastric bypass showed that BrP decreased in both groups but at all times remained positive.[97] The obese patients, however, had lower BrP at all points when compared with the nonobese patients, suggesting that they may be at increased risk for aspiration. In addition, Rabey et al.,[98] in a study of general and orthopedic surgery patients, demonstrated reductions in lower esophageal sphincter pressures when an LMA was used as an airway in general anesthesia.

Researchers have conducted studies to evaluate the safety and efficacy of LMAs in a variety of laparoscopic procedures. A meta-analysis by Brimacombe and Berry[99] of 547 LMA publications, which used multiple anesthetic techniques, found the incidence of pulmonary aspiration to be two in 10,000 or 0.02%. Most of these patients demonstrated preexisting risk factors for pulmonary aspiration. A study comparing the ProSeal LMA and Laryngeal Tube Suction demonstrated that both devices were able to provide a secure airway under conditions of elevated intragastric pressure and positive pressure ventilation, without evidence of pulmonary aspiration.[100] In addition, both devices allow for decompression of the stomach so that continuous gastric decompression can be accomplished. The efficacy of the LMA supreme versus the i-gel was also evaluated in approximately 100 patients undergoing laparoscopic surgery in the Trendelenburg position.[101] Again, both devices provided an adequate seal during controlled ventilation and allowed for decompression of the stomach throughout the procedures. Similar findings were demonstrated in a randomized prospective study evaluating the Cobra Perilaryngeal Airway and the LMA classic.[102] There have been reports of aspiration after improper placement and foldover of ProSeal LMA.[103] The authors recommend that placement be guided using a gum elastic bougie and that positioning be confirmed by determining patency of the gastric lumen.

Research suggests that under certain circumstances, the use of the LMA and other supraglottic devices may be appropriate during laparoscopy, but no general consensus exists to date.[104] Many clinicians feel that the risk of airway difficulties is too high to warrant their use. With the development of newer supraglottic devices that allow for decompression of the stomach and adequate high-pressure ventilation, the issue may become clearer. Guidelines for use of the LMA in laparoscopy were developed by Brimacombe and Brain in 1996.[105] They recommend that clinicians who use the LMA during laparoscopy should, among other considerations, be experienced and adhere to the "15" rule, which requires that the surgery not exceed 15 minutes' duration, the tilt of the bed be less than 15 degrees, and the intraabdominal pressure be less than 15 cm H_2O. Box 31-5 lists some LMA guidelines for laryngoscopy.

There is no one specific anesthetic technique that is best for laparoscopic surgery. The choice is dictated by a combination of factors including the surgical procedure, postoperative disposition of the patient (ambulatory or in-patient) and the presence of coexisting disease processes. However, the use of nitrous oxide (N_2O) in laparoscopic surgery has been a source of controversy because of beliefs that N_2O contributes to bowel distention and increases the incidence of postoperative nausea and vomiting (PONV). Based upon the evidence, the jury is still out.

The effect of nitrous on the incidence of PONV has been evaluated in several recent studies. A randomized controlled trial in three groups of patients undergoing gynecologic laparoscopy showed that N_2O increases the incidence and severity of PONV in a dose-dependent manner.[106] Patients who received 70% nitrous oxide had a statistically significant greater incidence of nausea than patients who received no nitrous oxide or 50% nitrous oxide. However, a similar study showed that the elimination of nitrous oxide from a propofol-based anesthetic for ambulatory gynecologic

BOX 31-5

Some Guidelines for Use of the Laryngeal Mask Airway During Laparoscopy

- Ensure that clinician is an experienced LMA user.
- Select patients carefully (e.g., fasted, not obese).
- Use correct size of LMA.
- Use LMA that allows for gastric drainage.
- Make surgeon aware of the use of LMA.
- Use total IV anesthetic technique or volatile agent.
- Adhere to "15" rule: <15 degree tilt; <15 cm H_2O intraabdominal pressure; <15 min duration.
- Avoid inadequate anesthesia during surgery.
- Avoid disturbance of the patient during emergence.

Data from Roth H, et al. The ProSeal laryngeal mask airway and the Laryngeal Tube Suction for ventilation in gynaecological patients undergoing laparoscopic surgery. *Eur J Anaesthesiol.* 2005;22(2):117-122; Maltby JR, et al. LMA-Classic and LMA-ProSeal are effective alternatives to endotracheal intubation for gynecological laparoscopy. *Can J Anaesth.* 2003;50(1):71-77; Jakobsson J. The airway in day surgery. *Minerva Anestesiol.* 2010;76(1):38-44.
IV, Intravenous; *LMA*, laryngeal mask airway.

surgery had no effect on readiness to discharge and did not increase the incidence of adverse postoperative events including PONV.[107]

The effect of N_2O on bowel distention has been examined in two studies. In a randomized controlled trial involving 28 patients undergoing laparoscopic donor nephrectomy, the use of N_2O caused bowel distention in 50% of patients.[108] In 25%, the distention was severe enough to interfere with the progress of the surgery and as a result needed to be discontinued. In contrast, a randomized controlled trial examined the use of N_2O in 50 morbidly obese patients undergoing laparoscopic bariatric surgery.[109] Half of the patients received N_2O as part of the anesthetic and the other half did not. The surgeons, unaware of anesthetic technique, were unable to detect any differences in bowel distention between the groups over a 90-minute time period.

POSTOPERATIVE CONCERNS

Postoperative nausea and vomiting is a major concern for patients undergoing laparoscopic surgical procedures. In fact, patients report that they are more worried that they will experience nausea and vomiting after surgery than they are about experiencing postoperative pain.[110] The incidence of PONV in the laparoscopic population has been reported to be as high as 72% and is known to be associated with significant postoperative complications such as surgical wound dehiscence, aspiration, and unanticipated hospital admission.[111-113] Because the etiology of PONV is multifactorial, multimodal therapy using antiemetics that target different receptors has become standard of care.[113,114] The use of total intravenous anesthesia (TIVA) and a combination of antiemetics has been reported to decrease the incidence of PONV to less than 10%. A randomized controlled trial compared TIVA and multimodal therapy with inhalation anesthesia plus multimodal therapy or propofol anesthesia alone.[114] The study showed that patients who received TIVA and multimodal therapy had a 90% response rate versus 63% and 66% in the other two groups. In addition, multimodal therapy was associated with a greater degree of patient satisfaction.

Although the development of laparoscopic surgical procedures has reduced the overall need for analgesia both intraoperatively and postoperatively, pain still continues to be a concern in the postoperative period. Pain after laparoscopy is comprised of three components; incisional pain (parietal pain), deep intraabdominal pain (visceral pain), and shoulder pain, which is believed to be referred visceral pain.[115] However, the majority of postoperative pain after laparoscopic surgery is typically of a visceral quality on the day of surgery, with shoulder pain predominating on the first postoperative day.[116] The creation of the pneumoperitoneum is associated with distention of the peritoneum and abdominal wall, and in conjunction with visceral dissection and resection activates nociceptors via the enteric nervous system.[86] The enteric nervous system is a complex system that functions to some extent independent of the central nervous system.[86] The peritoneum and viscera convey unpleasant sensations and autonomic reactions to injury via the vagus nerve giving rise to both painful and nonpainful sensations.[117,118] In addition, intraabdominal CO_2 contributes to postoperative pain by decreasing intraperitoneal pH and causing irritation of the phrenic nerve.[119]

Management of postoperative pain in laparoscopy patients is complex and involves a multimodal approach that includes opioids, nonsteroidal antiinflammatory drugs (NSAIDs), corticosteroids, and local anesthetics. The multimodal approach has been found to improve patient satisfaction, decrease opioid requirements, and decrease the incidence of postoperative complications including PONV and unplanned hospital admission.[86,120]

NSAIDs have proven to be of value in managing postoperative laparoscopic pain. Several types of NSAIDs have been used including the cyclooxygenase-2 (COX-2) inhibitors, ketorolac, and acetaminophen, and their efficacy has been repeatedly studied. Although NSAIDs are not potent enough as a sole analgesic for managing laparoscopic pain, they have been shown to act synergistically leading to decreased opioid use. A double-blinded, placebo-controlled, randomized study of 80 American Society of Anesthesiologists (ASA) class I to III patients undergoing outpatient laparoscopy showed that short-term use of celecoxib decreased postoperative pain and postoperative opioid-containing analgesic requirements, while improving the quality of recovery.[121] In addition, multiple NSAIDs are being combined to optimize their effectiveness. A retrospective comparative study examining the efficacy of preemptive administration of pregabalin, acetaminophen, and celecoxib for the management of perioperative pain after robotic-assisted laparoscopic radical prostatectomy showed a decrease in both intraoperative and postoperative opioid use.[122]

Glucocorticoids also have been used successfully for the management of post-laparoscopy pain. In addition to possessing antiemetic properties, glucocorticoids have antiinflammatory and analgesic properties that make them useful in the management of visceral pain. The exact mechanism is not fully understood, but it is known that glucocorticoids reduce prostaglandin synthesis by inhibiting phospholipase enzyme and cyclooxygenase type II. In addition, they modulate the inflammatory response by inhibiting major cytokines including C-reactive protein, tumor necrosis factor, and several interleukins.[123,124] In a randomized controlled trial, the efficacy of dexamethasone administration in decreasing perioperative opioid consumption was evaluated.[120] The study showed that preemptive administration of glucocorticoids decreased total opioid consumption in the first 24 hours after laparoscopic hysterectomy. In addition, it was not associated with an increase in adverse effects.

The effectiveness of peripherally administered local anesthetics in the management of postoperative laparoscopy pain is a complicated question because research evidence remains mixed. A systematic review conducted by Mouton et al.[125] in 1999 evaluated 41 randomized controlled trials that studied pain control using local anesthesia in intraperitoneal and port-site infiltration, as well as mesosalpinx and fallopian-tube blocks.[125] The authors concluded that local infiltration and mesosalpinx and fallopian-tube blockade offered little benefit in the management of postoperative pain. Evaluation of studies of intraperitoneal local anesthesia injection showed that the technique improved overall pain scores but questioned the clinical significance of the treatment effect. In contrast, a recent meta-analysis of five randomized trials evaluated the efficacy of intraperitoneal local anesthetic for pain reduction after laparoscopic gastric procedures.[86] The analysis revealed an overall reduction in abdominal pain intensity, reduced incidence of shoulder pain, and decreased opioid use without adverse effects in patients managed using the block. Other techniques, such as ultrasound-guided rectus sheath block, are also proving to be effective in the management of post-laparoscopy pain by blocking the terminal branches of the lower intercostal nerves in a T8 to L1 dermatomal distribution.[126-128]

THE FUTURE OF LAPAROSCOPIC SURGERY

Minimally invasive surgery has become the norm over the last 20 years, prompting major advances in laparoscopic techniques. Recent innovations in technology include the development of robotic-assisted surgical systems such as the DaVinci Surgical System, which provide for greater surgical precision, decreased

postoperative pain, and shorter lengths of hospital stay.[129,130] (see Chapter 29) In addition, efforts have been made to eliminate the need for pneumoperitoneum through the development of "gasless" laparoscopic systems. The gasless laparoscopy technique creates a working space for the surgeon by inserting a fan-shaped device into the abdomen to lift the abdominal wall away from the viscera, eliminating the need for CO_2 insufflation. Current research shows much promise for this technique. Compared with conventional laparoscopy, gasless laparoscopy was associated with lower intraoperative blood loss, decreased postoperative pain, and less postoperative inflammation.[131-133]

Standard laparoscopic techniques are limited in several ways. They provide only two-dimensional depth perception, and control of standard laparoscopic instruments is counterintuitive. To move an instrument within a patient on the screen in one direction, the operator is required to move his or her hand in the opposite direction.[134] This creates a steeper learning curve for training. Newer technologies allow surgeons to operate laparoscopic equipment far more intuitively and with much greater dexterity than standard laparoscopic techniques.

The development of robotic-assisted laparoscopic surgery has allowed surgeons to overcome some of the limitations imposed by standard laparoscopic technology.[129,130] A surgeon using robotic-assisted technology controls surgical instruments from a control console that may be immediately adjacent to the patient, within the operative suite, or at a site hundreds of miles away from the operating room. An important advantage of robotic technology is the incorporation of three-dimensional (stereoptic) imaging, which permits superior depth perception. The surgeon manipulates the robotic arms from the control console, which then simulate the motion of the human wrist and fingers in the surgical field. These motions are also scaled down so that larger movements by the surgeon are translated into finer movements of the instruments. Robotic-assisted surgery offers the surgeon improved ergonomics, superior dexterity, and the ability to use traditional open surgical skills for laparoscopic operations. Robotic-assisted surgical techniques have been used in all types of procedures—cardiac, general, gynecologic, and urologic surgical specialties.[135]

Anesthetic management of robotic-assisted laparoscopic surgery is similar to standard laparoscopic surgery with a view caveats. Robotic-assisted radical prostatectomy and gynecologic procedures are performed in the steep Trendelenburg position (30-45 degree head-down position); this places the patient at risk for tracheal tube displacement, brachial plexus injury, and posterior ischemic optic neuropathy.[48,136,137] Careful positioning and attention to tube position and fluid management is essential. Another potential issue surrounds the prolonged set-up of robotic equipment and limited patient access during robotic procedures. Because of the potential for limited access to patients undergoing robotic-assisted surgery, especially pediatric patients, careful contingency plans should be made by the surgical team in case an intraoperative crisis call for immediate access to the patient is needed.[138]

SUMMARY

As technology advances, laparoscopic surgical techniques will be employed in increasingly more complicated procedures and patient populations. Providing safe and effective anesthetic care demands that the anesthetist understand the unique challenges of laparoscopic surgery, with particular attention to the physiologic effects of carbon dioxide insufflation and pneumoperitoneum.

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Musculoskeletal System Anatomy, Physiology, Pathophysiology, and Anesthesia Management

CHAPTER 32

◆ *Mary C. Karlet and Terri M. Cahoon*

Somatic musculature is broadly classified into three compartments—skeletal, cardiac, or smooth—based on the muscles' anatomic and functional roles. Force generated by all these muscle types depends on the transient elevation of intracellular calcium (Ca^{2+}) and activation of actin and myosin filaments. Skeletal muscle is under voluntary control and is striated in appearance. Smooth muscle is found in most internal organs (except the heart), is under involuntary autonomic control, and is nonstriated. Cardiac muscle is striated in appearance and under control of an intrinsic pacemaker modulated by the autonomic nervous system.[1] The focus of this chapter is skeletal muscle, its function, and its neurologic control.

Skeletal muscle tissue includes muscles of the tongue and the soft palate, the extrinsic eye muscles, the muscles that move the scalp, all muscles attached to the skeleton, and the muscles in the pharynx and the upper third of the esophagus. Some skeletal muscles, such as those of the lips and the anus, serve as sphincters. Skeletal muscle is innervated by myelinated efferent motor nerve fibers called *alpha (α) motor neurons*. These fast-conducting somatic fibers arise from cell bodies located in the ventral horn of the spinal cord gray matter (Figure 32-1).

The motor nerve axon exits through the spinal cord ventral root and travels uninterrupted to the muscle through a mixed peripheral nerve. Inputs to the ventral horn motor nerve cell body are both excitatory and inhibitory. The inputs include neurons from the brain, neurons from other spinal cord segments, and afferent neurons from various sensory receptors. A motor neuron fires an action potential when the sum of the excitatory and inhibitory inputs depolarizes the nerve cell body to its critical threshold potential. Threshold depolarization of the cell body produces local electrical currents that spread to adjoining regions of the nerve membrane, leading to depolarization and action potential propagation down the axon.

At the muscle, each motor nerve divides into branches that enter the muscle and end on individual muscle cells called *muscle fibers*. A single motor neuron and all the muscle fibers it innervates are collectively called a *motor unit* (Figure 32-2). When a motor nerve fires, all the fibers within a single motor unit contract simultaneously.

Motor units exhibit considerable variability, and each unit usually contains between 100 and 200 muscle fibers. However, the motor unit may contain as few as two muscle fibers for fine, delicate movements or as many as a thousand for coarse movements.[1,2]

The strength of a muscle contraction is determined in large part by the number of motor units stimulated and the frequency of the stimulation. A minimal stimulus applied to a muscle may cause only a few muscle units to contract, with a weak overall response. As the stimulus is increased, more units are recruited, and a greater contraction of the muscle occurs.

OVERVIEW OF NEUROMUSCULAR TRANSMISSION

Skeletal muscles are normally relaxed and do not contract without nervous stimulation. At rest, the electrical potential difference across the muscle membrane is approximately −90 mV (inside negative). There is a high potassium ion (K^+) concentration inside the muscle cell and a high sodium ion (Na^+) concentration outside the cell.

The process of muscle contraction begins when the electrical activity of a *presynaptic* motor neuron communicates across a *junctional cleft*, or *synaptic gap*, to *postsynaptic* skeletal muscle fibers. The specialized conduction area, or *synapse*, where the axon of a motor neuron ends on a skeletal muscle fiber is called the *neuromuscular junction*, or *myoneural junction*. Each skeletal muscle fiber usually has only one neuromuscular junction, a notable exception being extraocular muscles that have multiple innervations per cell. The mediator substance that chemically transduces the axon's electrical message across the synaptic gap to the muscle is the neurotransmitter *acetylcholine* (ACh).[1-3]

Muscle contraction develops when the propagated action potential of the presynaptic motor neuron induces expulsion of the chemical mediator ACh into the junctional cleft. ACh binds to specialized receptors on the postsynaptic muscle membrane. If released from the axon nerve ending in sufficient quantity, ACh-receptor (AChR) occupation induces a transient change in the electrical property of the skeletal muscle membrane, and an action potential and muscle contraction follow.[2]

In the overall process of neuromuscular transmission, an action potential in the motor neuron induces the release of ACh into the junctional cleft, which evokes an action potential in the muscle. As described in greater detail in the following sections, the end result of muscle membrane depolarization is muscle contraction.

Neuromuscular Junction

Motor nerve endings develop in intimate and precise proximity to skeletal muscle fibers. The motor axon terminal is separated from the muscle cell it innervates by a synaptic gap of only 20 to 30 nm.[2] The demyelinated distal portion of the motor axon is essentially surrounded by a terminal Schwann cell that reinforces the connection of nerve and muscle.[4] This anatomic alliance increases the likelihood for prompt receptor activation after transmitter release.[2,4,5]

The synaptic gap is contiguous with the extracellular fluid, which provides a route for drugs or toxins to gain access to the neuromuscular junction. Botulinum toxin, for example, gains access to the junction through the extracellular fluid and produces its depressive neuromuscular effects by inhibiting ACh release from the nerve ending.[2,6,7]

Both sides of the neuromuscular junction, the presynaptic motor axon and the postsynaptic muscle cell, serve specialized functions. As it nears the neuromuscular junction, the motor

nerve axon loses its myelin sheath and divides into many smaller nerve fibers, which terminate as *end-feet*.

The motor nerve end-foot is distinct from the rest of the nerve. It is rich in mitochondria and the materials and support structures necessary for the synthesis, storage, mobilization, and release of the neurotransmitter ACh. Small, clear vesicles or granules are particularly numerous in the part of the nerve ending closest to the junctional gap, approximately 300,000 normally in a single end plate.[2] Each of these vesicles contains a small packet, or *quantum*, of ACh molecules. The ACh vesicles concentrate along the junctional surface of the nerve end-feet in areas called "active zones."[6,8]

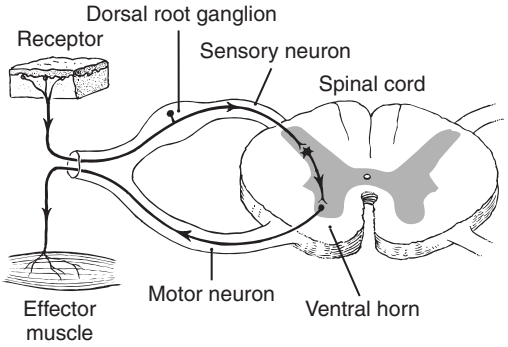

FIGURE **32-1** Spinal reflex arc. Sensory information from the skin is relayed to the motor neuron in the ventral horn of the spinal cord gray matter.

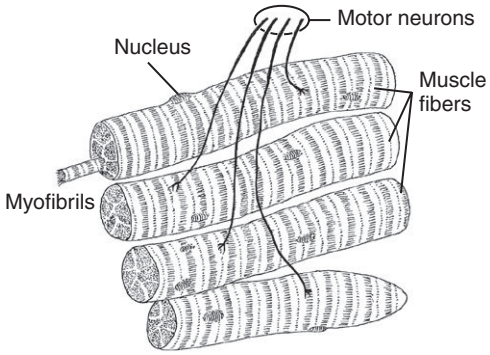

FIGURE **32-2** A motor unit. One motor neuron can synapse with several muscle fibers, which contract as a unit.

At the neuromuscular junction, each motor nerve ending closely approximates with a thickened and highly convoluted portion of the postsynaptic membrane called the *motor end plate*. The motor end plate is physically and functionally demarcated from the surrounding muscle membrane. The many membrane convolutions at the end plate are known as *junctional folds*. Both the primary and secondary folds expand the surface area of the postsynaptic membrane.[2,4] ACh receptors are concentrated near the shoulders of the junctional folds, lying near the ACh release sites. The close approximation of ACh release site and target receptor site ensures little transmitter waste and direct coupling of nerve signal and muscle response.[4,9] Figure 32-3 summarizes the anatomy and dynamic function of the neuromuscular junction.

Acetylcholine Release

Physiologic transmission of the nerve message to the muscle begins with a Ca^{2+}-dependent mechanism for ACh release from the nerve terminal. When a nerve impulse arrives at a motor nerve ending, the action potential causes a transient increase in Ca^{2+} conductance across the nerve membrane by activating voltage-dependent Ca^{2+} channels. Both "fast" and "slow" Ca^{2+} channels appear to open, but it is primarily the fast ("N-type" and "P/Q-type") Ca^{2+} channels that are involved in depolarization-induced transmitter release.[6,9] Calcium enters the nerve terminal, flowing down its electrochemical gradient. The influx of Ca^{2+} causes ACh vesicles to fuse with the nerve plasma membrane and then expel their content into the synaptic cleft.[4,6,10] The amount of ACh released is influenced by the amount of Ca^{2+} that enters the nerve terminal during nerve stimulation. The more Ca^{2+} that enters the nerve terminal, the greater the amount of ACh released.

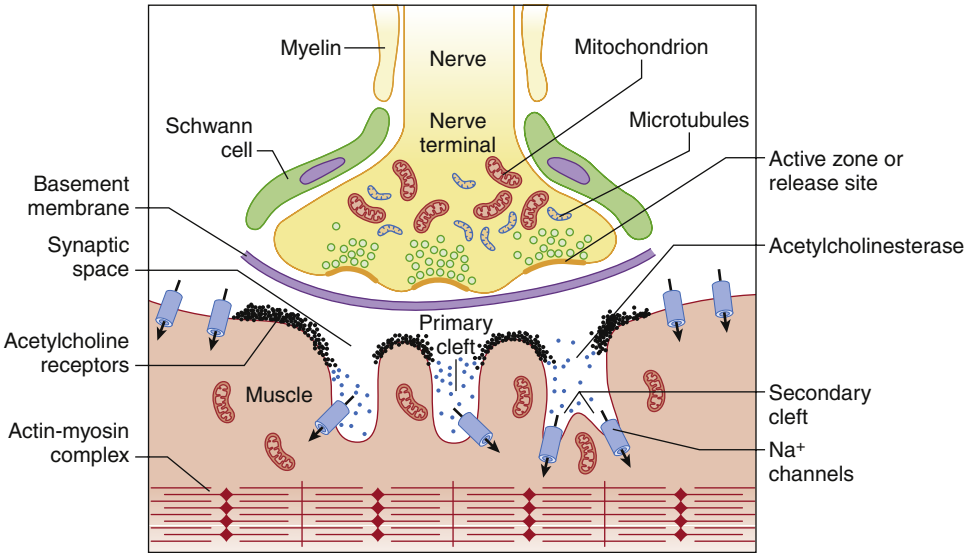

FIGURE **32-3** Structure of the adult neuromuscular junction showing the motor neuron, muscle fiber, and Schwann cell. The nerve terminal, covered by a Schwann cell, has vesicles positioned near the active zones on the membrane toward the synapse. The synaptic cleft is between the nerve and the muscle. The muscle surface has folds with dense areas on the shoulders of each fold containing acetylcholine receptors. The acetylcholinesterase are present in the synaptic clefts. (From Miller RD et al, eds. *Miller's Anesthesia*. 7th ed. Philadelphia: Churchill Livingstone; 2010.)

About 150 to 200 ACh vesicles, or quanta, are released with each nerve impulse. Each quantum in turn contains about 10,000 molecules of the neurotransmitter.[2,11] This amount of ACh and the normal abundance of postjunctional receptors at each neuromuscular junction readily ensure muscle activation. A considerable safety margin exists in the synaptic transmission. With each nerve impulse, excess ACh is released, and excess ACh receptors are available for occupation.[9,11-13]

Small concentrations of other divalent cations can compete with and limit Ca^{2+} influx into the nerve ending, decreasing ACh release and impairing neuromuscular transmission. When administered intravenously, magnesium sulfate, for example, can interfere with Ca^{2+} influx and produce muscle weakness by inhibiting ACh release.[3,12]

Certain antibiotics, particularly the aminoglycosides, inhibit ACh release from the nerve terminal and can enhance neuromuscular blockade when administered concomitant with clinical dosages of neuromuscular blocking agents.[3,11,12]

Calcium channel–blocking drugs used for the treatment of dysrhythmias and hypertension block Ca^{2+} conductance through so-called "slow" ("L-type") channels. Their primary action is on the slow Ca^{2+} channels of the heart and blood vessels, but they can inhibit prejunctional Ca^{2+} influx. The large safety margin inherent in normal neuromuscular transmission obscures any clinically detectable effect these drugs may have on neuromuscular transmission. However, with disorders associated with impaired neuromuscular transmission, such as myasthenic syndrome, the Ca^{2+} channel blocker's prejunctional attenuation of ACh release may be unmasked, and neuromuscular transmission may be further weakened.[10,12,14]

Acetylcholine Synthesis

Neurons that release the neurotransmitter ACh are called *cholinergic neurons*. Active cholinergic motor neurons replenish their ACh stores by continually resynthesizing the neurotransmitter. Many enzymes and other proteins needed by the nerve ending to synthesize, store, and release ACh are made in the motor nerve cell body and are transported distally to the nerve ending by a process called *axonal transport*.

In the axoplasm of the motor nerve ending, the enzyme *choline acetyltransferase* (CAT) catalyzes the reaction of two substrates, *acetyl coenzyme A* (acetyl CoA) and *choline*, to form ACh, as seen in the following equation.

$$\text{Choline} + \text{Acetyl CoA} \rightarrow \text{Ach} + \text{CoA}$$

Choline is obtained locally by a Na^+-linked uptake into the cholinergic nerve ending. Acetyl CoA is synthesized from pyruvate in neuronal mitochondria. Mitochondria and other metabolic machinery used to synthesize ACh are abundant in the nerve ending (Figure 32-4).

About 80% of the newly synthesized ACh is stored within synaptic vesicles in the nerve terminal, positioned for release. Each nerve ending contains more than 300,000 of these vesicles. The remainder of the ACh is stored in a nonvesicular axoplasmic reserve.[2,4]

The ACh vesicles are released through exocytosis in response to action potential stimulation, but only a small fraction of the available vesicles is used to send each signal.[2,4]

Postjunctional End Plate

There is a distinction between the postjunctional cation channels of the muscle end plate and other cation channels of nerve and muscle membranes. Motor end-plate cation channels are *ligand-gated*, that is, they are opened or closed by the action of a chemical. Cation channels of nerve axons, on the other hand, are *voltage-gated* by electrical changes in the membrane.[5]

The binding of ACh molecules to postsynaptic receptor proteins causes a transient increase in conductance in ligand (ACh)-gated cation channels at the postjunctional motor endplate. The cation flow at the end plate produces a net inward Na^+ current and a net outward K^+ current. The previously polarized end-plate membrane (resting membrane potential of approximately −90 mV) becomes transiently "depolarized." The resulting postjunctional membrane voltage change is called the *end-plate potential* (EPP).[5] The EPP does not begin until 0.5 millisecond after the arrival of the action potential at the presynaptic nerve ending. This *synaptic delay* arises from the relatively slow liberation and diffusion of ACh across the junctional cleft.[2,5]

EPPs vary in strength according to the quantity of ACh released. The more ACh released, the greater the postsynaptic end-plate voltage change. In other words, EPPs do not adhere to the "all-or-none" principle. EPPs can be summed, and their magnitude depends on the strength of the summed stimuli of ACh molecules.

Perijunctional Area

The postjunctional end-plate membrane does not fire action potentials. After it is depolarized by ACh-receptor occupation, the current sink created by the local EPP depolarizes the *adjacent* muscle membrane. If the depolarizing input is great enough and reaches threshold potential, action potentials are fired from either side of the end plate in both directions along the muscle fiber (Figure 32-5).[5]

The transition zone where the potential developed at the end plate is converted to an action potential is called the *perijunctional area*. A demarcation exists between the chemically sensitive AChR channels of the end plate and the chemically insensitive but electrically sensitive Na^+ channels in the perijunctional area of the muscle membrane. The membrane in the perijunctional area is rich in Na^+ channels, and this feature enhances its capacity to respond to an EPP and transform it to an action potential.

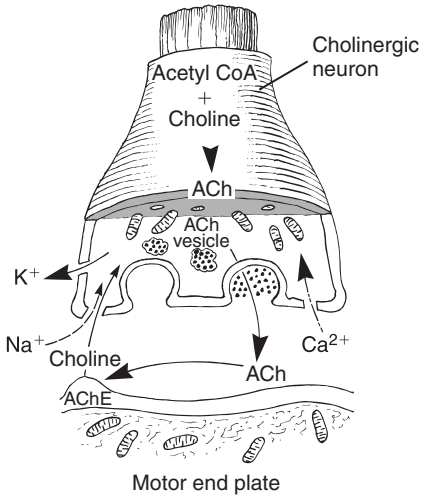

FIGURE 32-4 Acetylcholine (ACh) synthesis from choline and acetyl coenzyme A (acetyl CoA) in the motor nerve ending. Calcium ion entry into the nerve ending causes the ACh vesicles to release their contents. Acetylcholinesterase (AChE) on the postjunctional membrane destroys ACh. Choline is recycled into the nerve ending by a sodium ion–linked transport mechanism.

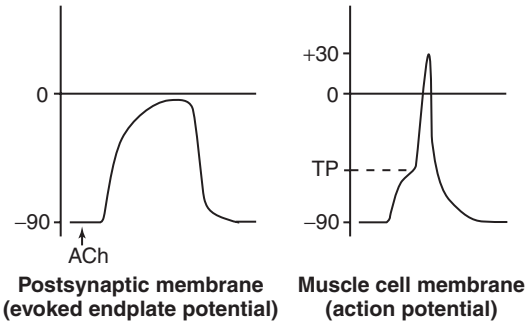

FIGURE **32-5** Depiction of the depolarization characteristics (the endplate potential) at the postsynaptic membrane in response to acetylcholine (ACh) and the depolarization and action-potential response at the adjacent, electrically excitable muscle membrane. *TP*, Threshold potential.

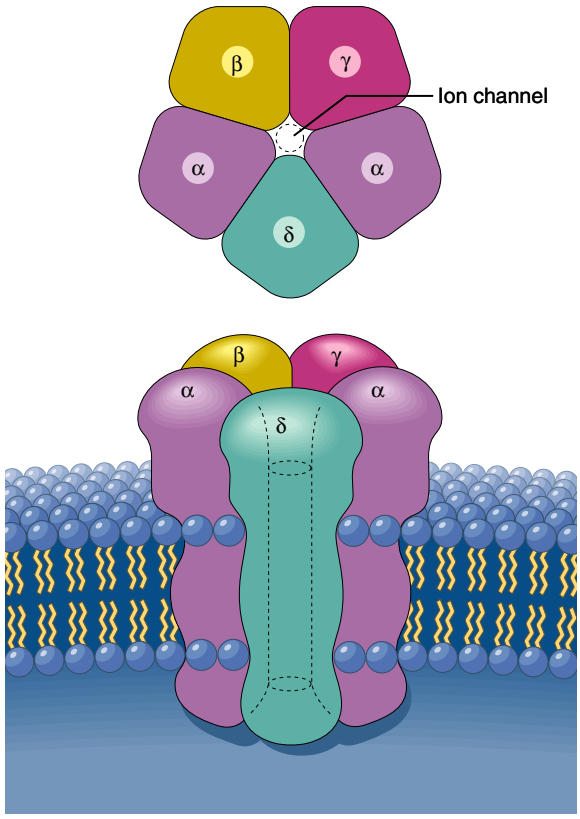

FIGURE **32-6** The fetal acetylcholine (ACh) receptor. (From Taylor P. Are neuromuscular blocking agents more efficacious in pairs? *Anesthesiology*. 1985;63:1-3.)

With a typical motor neuron's action potential, the EPP produced at the muscle end plate is usually sufficient to create an action potential at the muscle membrane, and muscle contraction is regularly produced.

Acetylcholine Receptor

Postjunctional neuromuscular ACh receptors have been extensively purified and studied in detail.[4,15] An estimated 50 million tightly packed nicotinic AChR sites are at each neuromuscular junction.

In fetal muscle, the ACh nicotinic receptor is a protein composed of five polypeptide subunits: two identical alpha (α) subunits, a beta (β) subunit, a gamma (γ) subunit, and a delta (δ) subunit. Figure 32-6 shows the receptor subunits organized in a pentagonal array around a central ion channel. Without ACh occupation, the central channel is closed; when open, small cations (Na^+ and K^+) are allowed to pass through the channel down their electrochemical gradients.[5]

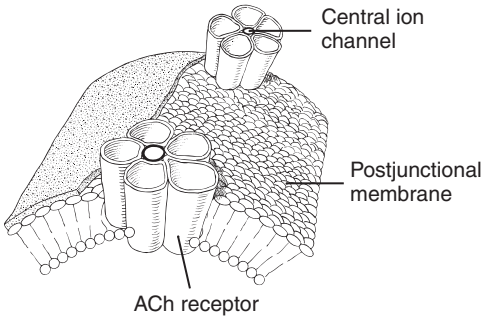

FIGURE **32-7** Two acetylcholine (ACh) receptors embedded in the postjunctional membrane.

In adults, the AChR protein structure is similar, except that the fetal γ subunit is replaced by an epsilon (ε) subunit.[3,16] The change produces an adult cholinergic postjunctional receptor that has an increased cation conductance and a shortened open time.

As noted earlier, the ACh receptors are located at the crests of the motor end-plate junctional folds, which directly approximate with nerve terminal release sites. In active adults, only the end-plate region of the muscle contains ACh receptors. As little as 200 μm away from the end plate, the muscle membrane becomes practically devoid of receptors.

The ACh receptors are synthesized in the muscle cells and then incorporated into the end-plate membrane as integral membrane proteins. The extracellular or junctional face of the receptor protrudes from the surface of the end-plate membrane, whereas the cytoplasmic surface of the receptor is more flush to the plasma membrane surface (Figure 32-7).

Activation of the postjunctional AChR and opening of the cation channel requires simultaneous ACh occupation at each of the two α-receptor subunits. The binding of two ACh molecules causes a conformational change in the α polypeptides, and the protein conformational change causes the central ion channel to open.[2] If only one α subunit site is occupied by the agonist, the channel remains closed. As described earlier, the open channel increases the conductance to positively charged ions, particularly Na^+, an effect that produces the net depolarizing potential, the EPP. When even one ACh molecule leaves an α subunit, the channel snaps shut and the current stops.

The α subunits are the sites of competition between the cholinergic agonist ACh and receptor antagonists, such as nondepolarizing neuromuscular blocking agents. The outcome of the competition, neuromuscular transmission or neuromuscular blockade, depends on the concentration of ACh and the relative concentration and binding properties of the antagonist involved.[3,12] Nondepolarizing muscle relaxants produce neuromuscular blockade, in part because they bind to one or both α subunit sites and, in so doing, prevent ACh from binding to both sites and opening the channel.

Prejunctional Receptors

Cholinergic receptors are also present at the prejunctional motor nerve ending. It is postulated that in addition to mediating nerve transmission at postjunctional receptor sites, ACh also acts on prejunctional receptors to enhance transmitter mobilization and release. Prejunctional cholinergic receptor occupation may transform the ACh pool from a reserve store to a readily releasable store so that transmitter output can keep pace with transmitter demand.[10]

All the nondepolarizing muscle relaxants used in anesthesia practice compete with ACh for postjunctional cholinergic receptor sites to produce neuromuscular blockade. Receptor antagonist effects at prejunctional receptors may augment nondepolarizing blockade by diminishing ACh output as well. Herein also lies an explanation for the *fade* that is observed with neuromuscular blockade monitoring of nondepolarizing muscle relaxers. Fade of tetanic and train-of-four stimulation may reflect the blockade of prejunctional ACh receptors by the muscle relaxant and failure of ACh release to keep pace with rapid stimulation.[12]

Acetylcholinesterase

As noted earlier, the combination of ACh with its muscle end-plate receptor causes a transitory depolarization of the end plate. The EPP is short lived because soon after binding, ACh is rapidly destroyed by hydrolysis, and its depolarizing action halts.[5] Paradoxically, the rapid destruction and removal of ACh from the junctional cleft is critical for continued muscle contractile response. The ACh molecule must be off the muscle end-plate receptor for the perijunctional muscle membrane to repolarize, or "reset," in anticipation of further activation.

The hydrolysis of ACh to choline and acetate is rapid and efficient. Most ACh is destroyed within a few milliseconds after it is released into the junctional cleft.[2] The enzyme *acetylcholinesterase* (AChE), also known as *true* or *tissue cholinesterase*, catalyzes the hydrolysis.

$$\text{Acetylcholine} \xrightarrow{\text{Acetylcholinesterase}} \text{Choline + Acetate}$$

Much of the choline by-product released by hydrolysis is efficiently drawn back within the prejunctional nerve terminal for use in the synthesis of new ACh. Acetylcholinesterase is present in high concentrations on the external surface of the postjunctional muscle membranes. The enzyme resembles a balloon-like structure and is loosely connected to the muscle end-plate membrane by thin stalks of collagen.

Without AChE, the concentration of ACh would become extremely high in the junctional cleft. Under these circumstances, ACh would maintain the muscle end plate in a state of persistent depolarization as ligand-gated cation channels remained open, yet the muscle itself would be paralyzed.[12] The reason for this seemingly illogical behavior (ACh-receptor occupation, end-plate depolarization, yet no muscle contraction) is that in the face of persistent end-plate depolarization, the Na^+ channels of the perijunctional muscle membrane do not reactivate or reset; these voltage-gated ion channels remain closed, impeding further muscle membrane depolarization. Thus, even with persistent end-plate depolarization, muscle contraction is prevented, and clinical weakness follows. A cyclic muscle membrane depolarization/repolarization sequence is necessary for normal muscle contraction to occur.

The mechanism of depolarizing muscle relaxants can, at least in part, be explained by a similar mechanism. Depolarizing muscle relaxants, such as succinylcholine, activate the muscle end plate in a manner similar to that of ACh, but they have a more protracted end-plate depolarizing response because they are less rapidly metabolized. AChR occupation by a depolarizing muscle relaxant causes a prolonged depolarization of the end plate, prohibits activation of perijunctional channels, and produces a depolarizing block.[3,17]

Reversal of a nondepolarizing neuromuscular block may be accomplished by the use of cholinesterase inhibitors. Anticholinesterase agents inhibit the breakdown of ACh and, in so doing, increase the amount of ACh at the neuromuscular junction. The abundance of ACh in the synaptic gap changes the agonist-antagonist ratio and enables the agonist (ACh) to bind to the ACh receptor with greater frequency than the antagonist (nondepolarizing muscle relaxant). Hence, a higher ACh concentration can overcome the receptor occupation by the muscle relaxant, and neuromuscular transmission can be restored (see Chapter 12).

Various other esterases, in addition to AChE, are present throughout the body. One that is found in the plasma is *pseudocholinesterase*, or *nonspecific cholinesterase*. Like AChE, pseudocholinesterase is capable of hydrolyzing ACh, but it also has properties separate from those of AChE. One distinction particularly relevant to anesthesia practice is the ability of pseudocholinesterase to metabolize ester local anesthetics and the depolarizing muscle relaxant succinylcholine.

Extrajunctional Receptors

In utero, before muscle innervation occurs, the muscle cells of a fetus synthesize *extrajunctional receptors*. These fetal receptors (γAChR) as well as receptors made up of five $\alpha 7$ subunits are inserted over the entire length of the muscle cell. As the fetal neuromuscular junction develops, increasing motor nerve activity appears to have a trophic effect in restricting the ACh receptors specifically to the neuromuscular junction.[12] By the age of 2 years, the nerve-muscle contact is fully mature and active, and the extrajunctional receptors disappear from the peripheral part of the muscle. If neural activity is reduced or abolished and the neural trophic influence is lost, the muscle resorts to fetal-like synthesis of γAChR and $\alpha 7$ receptors.[6,7,12,18]

Several situations, including stroke, spinal cord transection, thermal trauma, direct muscle damage, and prolonged immobility, have been associated with the accelerated spread of both γAChR and $\alpha 7$ receptors from the end-plate region to large areas of the skeletal muscle membrane.[6,7,18,19] These so-called *denervation injuries* result in an abnormal excitability of the muscle and an increase in muscle sensitivity to ACh, a condition that is called *denervation hypersensitivity*.[1,20] The extrajunctional receptors may develop within 48 hours after diminution of nerve activity. Eventually, the number of aberrant receptors per muscle fiber may increase 5- to 32-fold.[20] These receptors disappear and muscle sensitivity returns to normal if neural input is reestablished. Extrajunctional and end-plate cholinergic receptors are similar in many ways, but an important distinction pertinent to anesthesia practice is their differing response to receptor agonists and antagonists.

Clinically, extrajunctional receptors demonstrate a resistance to nondepolarizing muscle relaxants. Hence, larger doses of nondepolarizing relaxants may be necessary to induce neuromuscular blockade—for example, in an immobilized limb or in parts of the body affected by a stroke.[3,4,7,12] Monitoring a nondepolarizing neuromuscular block with a peripheral nerve stimulator in a paretic limb may result in an underestimation of the magnitude of neuromuscular blockade in nonparetic muscles.

Conversely, extrajunctional receptors are more easily activated by agonists (e.g., ACh, succinylcholine) than junctional receptors. Moreover, each extrajunctional channel stays open about four times longer than junctional receptors, allowing more ions to flow (primarily Na^+ into the muscle cell and K^+ out) in response to agonist-induced depolarization.[3]

The clinical significance of denervation injuries and the proliferation of extrajunctional receptors becomes evident with the administration of succinylcholine, which can produce alarmingly high levels of plasma K^+ in these patients.[12,21] Succinylcholine-induced hyperkalemia reflects the extensive proliferation of extrajunctional receptors along the entire muscle membrane and their

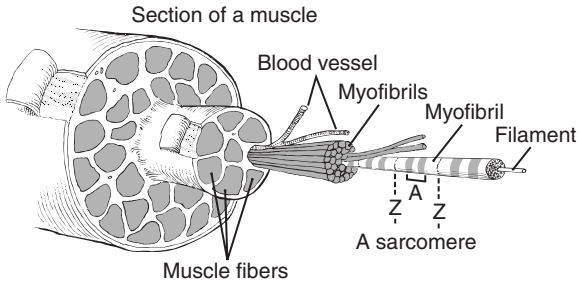

FIGURE **32-8** The structural arrangement and organization at each level of the muscle assembly. The skeletal muscle is composed of muscle fibers that contain long, cylindrical myofibrils. Each myofibril is made up of precisely arranged thick and thin filaments that form repeating dark and light bands called *sarcomeres*.

prolonged and exaggerated depolarization response to agonists. Succinylcholine stimulates the aberrant cholinergic receptors and triggers a protracted opening of the cation channels, allowing excess Na^+ movement into the cell and excess K^+ movement out, down their respective gradients.

Dangerous levels of succinylcholine-induced hyperkalemia have been observed within 4 days of denervation injury with doses of succinylcholine as low as 20 mg.[21] The pronounced release of K^+ in response to succinylcholine cannot be circumvented by the prior administration of nonparalyzing doses of nondepolarizing muscle relaxants.

MUSCLE PHYSIOLOGY

Skeletal muscle constitutes the greatest mass of somatic musculature. Skeletal muscle is composed of bundles of multinucleated, long, cylindrical cells. Muscle fibers typically extend the entire length of a muscle.[2] Because their length is much greater than their width, these cells are called *muscle fibers*. Each muscle fiber is a single cell surrounded by an electrically polarized cell membrane called the *sarcolemma*. The sarcolemma separates the extracellular space from the *myoplasm*, the muscle-fiber intracellular space. Dystrophin is a large protein that is located on the intracellular side of the sarcolemma and serves to stabilize the muscle membrane during contraction.[1]

Individual skeletal muscle cells are parallel to the muscle body and have no anatomic or functional bridges between them. The parallel arrangement helps maximize shortening capacity and velocity. The cells function independently so that the force of contraction of the total muscle is equal to the sum of individual fibers. This contrasts with smooth and cardiac muscle, in which the muscle cells are interdependent and are mechanically coupled to adjacent cells.[1,2]

Bundles of cylindrical filaments called *myofibrils* run along the axis of the muscle fiber. Each skeletal muscle fiber contains several hundred to several thousand myofibrils. The myofibrils are composed of contractile proteins that impart a striking, repetitive, light-and-dark banding pattern along the entire fiber length. The repeating unit, called a *sarcomere*, is the basic contractile unit of skeletal muscle. The alternating light-and-dark banding pattern is responsible for the classification called *striated muscle*. Cardiac muscle is also classified as striated muscle because it too has the repetitive pattern of light and dark bands.[1,2] The arrangement of the muscle fibers, myofibrils, and sarcomeres is shown in Figure 32-8.

Most skeletal muscles bridge two skeletal attachment points and are recruited to generate force and movement in voluntary actions ranging from chewing to walking. A muscle contraction that involves shortening of the muscle length to perform work

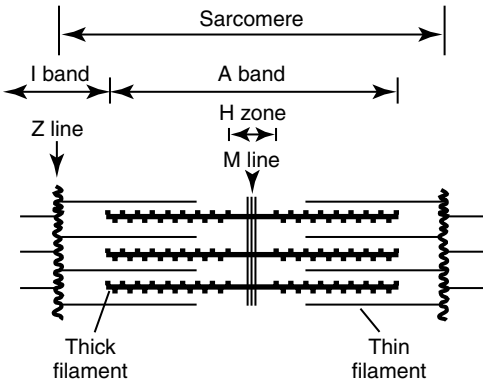

FIGURE **32-9** Longitudinal diagram of a sarcomere showing the arrangement of the thick filaments (myosin) and the thin filaments (primarily actin).

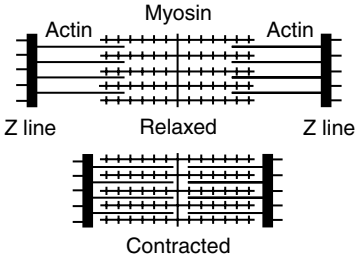

FIGURE **32-10** Actin filament sliding over myosin filament during muscle contraction.

is an *isotonic contraction*. A muscle contraction that produces increased tension but no appreciable decrease in length is an *isometric contraction*.

Structure of the Contractile Apparatus

The repeating, striated arrangement of the myofibril arises from the contractile filaments that compose the sarcomere: the *thick filaments* and the *thin filaments*.

The thick filaments, which are composed primarily of the protein myosin, are in the central region of the sarcomere in a dark-colored area termed the *A band*. A densely staining *M line* in the middle of the A band contains proteins that link the thick filaments. The thin filaments are about half the diameter of the thick filaments and are composed of the proteins actin, troponin, and tropomyosin. The less dense areas of the sarcomere, which contain only thin filaments, are referred to as *I bands*. Thin filaments, connected to *Z lines* or *Z disks*, partially interdigitate with the thick filaments in the relaxed muscle. With muscle contraction, force is generated by interaction and further overlap of thick and thin filaments. Two adjacent Z lines delimit each repeating sarcomere unit. The diagram of the sarcomere units in Figure 32-9 may merit careful study.

Cross sections of the myofibril reveal that each thick filament is surrounded by a hexagonal arrangement of thin filaments. The myosin and actin filaments are arranged to slide over one another, overlap, and create shortening of the sarcomere and the muscle during contraction[2] (Figure 32-10).

Thin Filament

The three major proteins that compose the thin filament—actin, tropomyosin, and troponin—each play a different role in the contractile process. Each thin filament includes two beadlike chains of polymerized *actin* twisted into a helix. *Tropomyosin* molecules are

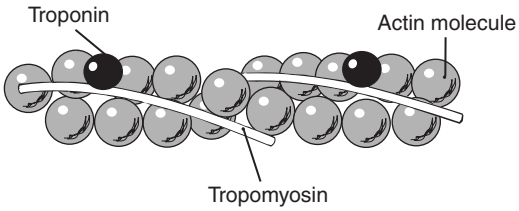

FIGURE **32-11** A thin filament. Globular actin molecules polymerize into a two-stranded, twisted filament. Rod-shaped tropomyosin molecules occupy the grooves between the two actin chains. The regulatory protein troponin binds to the tropomyosin component.

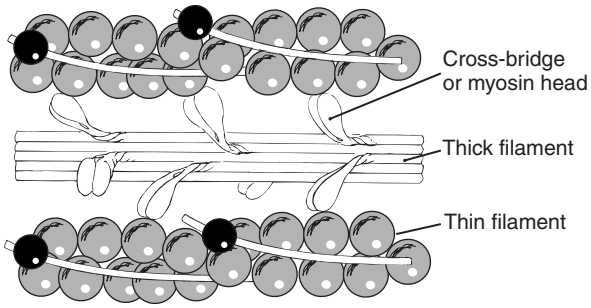

FIGURE **32-12** The tail regions of many myosin molecules intertwine to form a thick filament. The myosin heads, or cross-bridges, project out laterally toward the actin in the surrounding thin filaments.

located along the groove between the two actin chains. Each rod-shaped tropomyosin molecule covers about six or seven individual actin proteins. The most important protein in the regulation of the contractile process is *troponin*.[1] As depicted in Figure 32-11, troponin is attached intermittently to tropomyosin molecules.

Thick Filament

Myosin, the primary protein component of the thick filament, is a very large protein containing three pairs of polypeptides: one pair of heavy chains and two pairs of light chains. The six different polypeptides assemble to form the myosin protein. Each myosin protein contains a long tail with two globular heads.

The tail regions of several hundred myosin molecules aggregate to form one thick filament. The globular heads project out laterally from the thick filament at regular intervals toward the thin filaments surrounding it. In the relaxed muscle, the myosin heads are oriented toward but not attached to the thin filaments. The thick filament's globular projections are termed *cross-bridges* because they can link the thick and thin filaments. The cross-bridges in each half of the sarcomere are oriented in opposite directions away from the midpoint of the filament, which is important for their functional role in sarcomere shortening and muscle contraction.[1] The cross-bridge components are arranged as shown in Figure 32-12.

The myosin head and tail have a hingelike attachment, permitting a certain degree of movement. When muscle contraction is activated and myosin and actin link, the ability of the myosin head to swivel enables the attached actin filaments to slide over the thick myosin filaments (Figure 32-13).

Cross-Bridge Interaction and Cycling

Sliding Filament Theory

Physiologic contraction of striated muscle occurs when muscle fibers are depolarized to a threshold for action-potential formation. The depolarizing wave initiated by AChR occupation at the motor end plate is carried along the muscle membrane surface from one Na^+ channel to the next. Action potential depolarization of the

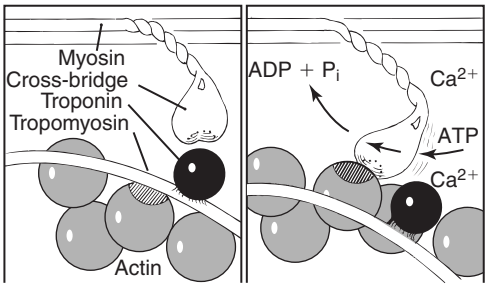

FIGURE **32-13** Formation of the actomyosin complex. Hydrolysis of adenosine triphosphate (ATP) leads to tipping of the myosin heads. *ADP,* Adenosine diphosphate; P_i, high-energy phosphate.

sarcolemma spreads rapidly to the muscle cell's interior through a reticular network of intracellular tubules that are contiguous with the cell membrane.

This network, composed of *transverse tubules*, or *T tubules*, forms a grid around the intracellular myofibrils and closely associates with the intracellular sarcoplasmic reticular membranes. The T tubules rapidly transmit the action potential from the sarcolemma to the myoplasm.

The *sarcoplasmic reticulum* is an irregular, closed membrane structure that weaves throughout the myoplasm of the muscle cell and contains large amounts of Ca^{2+}. The sarcoplasmic reticular membrane is active in sequestering Ca^{2+} by way of numerous high-affinity Ca^{2+} active-transport carriers in its membrane. These pumps maintain a high sarcoplasmic reticular store of Ca^{2+} and a very low resting myoplasmic Ca^{2+} concentration.[1,9]

The transit of an action potential along the sarcolemma and into the T-tubule system is detected by intracellular voltage sensors that trigger Ca^{2+} efflux from the sarcoplasmic reticular stores. The major Ca^{2+} release channels located on the sarcoplasmic reticulum are called *ryanodine receptors*. These channels are commonly called "receptors" because they bind the alkaloid ryanodine.[1] In response to action potential stimulation, the myoplasmic Ca^{2+} concentration rises several-fold from a resting value of less than 0.1 mmol. The overall effect is the discharge of Ca^{2+} from the sarcoplasmic reticulum into the myoplasm by the transit of an action potential into the muscle cell.[9]

The Ca^{2+} released into the myoplasm binds to troponin, which acts as a switch that changes the conformation of the tropomyosin to which it is bound. The conformational change in the rod-shaped tropomyosin exposes myosin binding sites on the underlying actin. The myosin heads react by binding to the exposed thin filament sites, forming a reversible complex with actin—the *actomyosin complex*. The process of myosin-actin binding in response to elevated myoplasmic Ca^{2+} is termed *cross-bridge formation*.

The myosin filaments' heads contain not only an actin-binding site but also a catalytic adenosine triphosphatase (ATPase) site that hydrolyzes the breakdown of ATP to adenosine diphosphate (ADP) and phosphate. ATP is essential for the sliding of the filaments and for muscle contraction. The energy yielded by the ATP hydrolysis is harnessed to tilt the myosin heads, in a "cocked" spring position. When the myosin heads bind to the actin site, the heads use the energy stored in the myosin heads to drag the actin filaments towards the center of the sarcomere. The pull of the actin filaments accentuates the overlap of the thick and thin filaments, causing shortening of the sarcomere and culminating in muscle contraction (Figure 32-14). Cross-bridge cycling and the associated movement of actin is called the *sliding filament theory*.

The actomyosin complex is stable and can be broken only by a renewed binding of ATP to each myosin head. With the binding

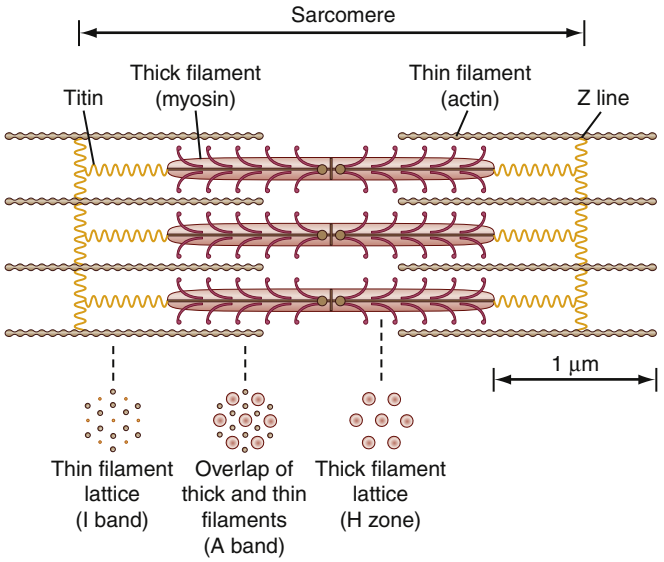

FIGURE **32-14** Organization of the proteins within a single sarcomere. The cross-sectional arrangement of the proteins is also illustrated. (From Koeppen BM, Stanton BA. *Berne & Levy Physiology*. 6th ed. Philadelphia: Mosby; 2010.)

of ATP, the actomyosin cross-bridge dissociates, and the myosin heads are repositioned for another round of cross-bridge formation. If the intracellular Ca^{2+} concentration is still sufficiently high, which mainly depends on the frequency of incoming action potentials, the cycle begins again: myosin links to actin, swivels, detaches, and reconnects at the next actin site.

A single sliding cycle or myosin "power stroke" shortens the length of the sarcomere by about 1%, causing the entire muscle fiber, which consists of a serial arrangement of sarcomeres, to also shorten by 1%. The sliding cycle has to be repeated about 50 times for full shortening of the muscle. The cycle continues until it is interrupted by the active removal of Ca^{2+} from the myoplasm or until the ATP is exhausted. Active Ca^{2+} removal from the cytoplasm back into the sarcoplasmic reticulum causes troponin, tropomyosin, and actin to return to a configuration that prohibits myosin-actin binding, and the muscle relaxes.

The overall process by which depolarization of the muscle fiber causes Ca^{2+} release from the sarcoplasmic reticulum into the myoplasm to cause cross-bridge cycling and muscle contraction is called *excitation-contraction coupling*.[9]

Box 32-1 summarizes the excitation-contraction coupling events. Box 32-2 summarizes the events leading to skeletal muscle relaxation.

Grading Contractile Force

Two major mechanisms grade skeletal muscle contractile force. One determining factor of muscle force is the number of motor units activated or recruited. With increasing voluntary effort, more and more motor units are recruited, and an increasing muscle force develops.

The other mechanism by which skeletal muscle tension is graded is by varying the frequency of the action potential discharge to the muscle. A single action potential invariably liberates sufficient Ca^{2+} ions to activate skeletal muscle contraction. However, the Ca^{2+} ions are rapidly transported back into the sarcoplasmic reticulum before the muscle has time to develop maximal tension. The brief contraction that results from transit of a single action potential is called a *twitch*.[2]

BOX 32-1

Steps of Neurohumoral Transmission and Excitation-Contraction Coupling

An action potential reaches the motor nerve ending when:

1. Ca^{2+} enters the nerve ending; ACh is released into the synaptic cleft.
2. ACh binds to a postsynaptic cholinergic receptor at the motor end plate.
3. The motor end-plate membrane depolarizes (the EPP).
4. An action potential is generated at the perijunctional muscle membrane.
5. The action potential spreads along the muscle membrane and inward to the transverse tubules.
6. Depolarization of the T tubules causes Ca^{2+} release from the sarcoplasmic reticulum.
7. Ca^{2+} triggers actomyosin complex cross-bridge formation; the sarcomere shortens; the muscle contracts.

ACh, Acetylcholine; *EPP*, end-plate potential; *T*, transverse.

BOX 32-2

Steps of Skeletal Muscle Relaxation

1. ACh is hydrolyzed by AChE in the synaptic cleft.
2. The end plate and muscle membrane repolarize to their resting potentials.
3. Ca^{2+} is actively pumped back into the sarcoplasmic reticulum.
4. Myoplasmic Ca^{2+} concentration returns to a normal low level.
5. The muscle relaxes.

ACh, Acetylcholine; *AChE*, acetylcholinesterase; *Ca^{2+}*, calcium ion.

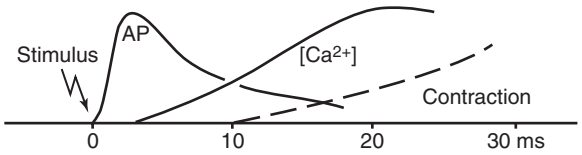

FIGURE **32-15** The electrical, ionic, and mechanical responses of a skeletal muscle to a single maximal stimulus. *AP*, Action potential.

Unlike cardiac muscle, skeletal muscle does not have a refractory period. Because of this property, rapidly repeated electrical impulses can cause summation of contractions and greatly increase the muscle tension. Repetitive action potentials maintain a high Ca^{2+} concentration in the myoplasm. The greater the myoplasmic Ca^{2+} concentration, the more cross-bridge sites are exposed, and the stronger the force of the contraction. Maximal and sustained muscle tension without relaxation—produced by the fusion and summation of successive twitch responses—is called *tetanus*.[9]

Figure 32-15 shows the time course and relationship between a single action potential, the myoplasmic Ca^{2+} rise, and the resulting twitch response. The action potential lasts about 2 to 4 milliseconds. The twitch begins about 2 milliseconds after the start of the muscle membrane depolarization. The duration of the twitch varies with the type of muscle stimulated.

Slow Versus Fast Muscle

Skeletal muscle fibers are classified as type I ("slow fibers") or type II ("fast fibers"), based on different myosin isoenzymes that distinguish the two types. The two fiber types differ in their metabolic

demands, their myosin ATPase activity, and their cross-bridge cycling rates. Muscles usually contain a mixture of both types of fibers, but one type often predominates.[1,22,23]

Slow (type I) muscle fibers are adapted for sustained movements, such as maintaining posture, and are resistant to fatigue. They have slow twitch durations, depend on oxidative metabolism for energy, have extensive blood supplies, and have rich concentrations of mitochondria.[1,22,23] An example of a type I muscle is the soleus muscle of the leg, an important muscle used for maintaining posture and walking. Type I muscle is called "red" muscle because its high myoglobin content imparts a dark, rubrous color.

Fast (type II) muscle fibers usually predominate in "white" muscle and are primarily concerned with rapid or powerful movement. They have short twitch durations, depend on glycolytic pathways for energy, and are easily fatigued.[1,23] Muscles specialized for fine, skilled movement, such as extraocular muscles, and some muscles of the hand are in this category.

The diaphragm is engaged in continuous rhythmic activity and so the muscle fibers must be resistant to fatigue. Infants have a greater tendency toward respiratory failure in part because at birth only 25% of their diaphragm is composed of type I fatigue-resistant fibers, compared with 55% in the adult. Before 27 weeks' gestational age, type I slow fibers make up less than 10% of the total diaphragm muscle content.[22]

Energy Sources for Skeletal Muscle

Muscle contraction requires a continual supply of energy at a rate proportionate to its energy consumption. The energy consumed by skeletal muscle is used for (1) cross-bridge cycling during muscle contraction, (2) sarcoplasmic reticular resequestration of Ca^{2+} during muscle relaxation, (3) rephosphorylation of creatine to replenish creatine phosphate energy stores, (4) activation of the Na^+/K^+ pump to restore proper membrane polarization, and (5) resynthesis of muscle glycogen.[2]

The amount of ATP present in the muscles is sufficient to sustain maximal muscle power for only about 3 seconds. For this reason, actively contracting muscles must continually form new ATP. There are three metabolic systems that provide a continuous supply of ATP in muscle cells: (1) the phosphocreatine-creatine system, (2) the glycogen-lactic acid system, and (3) the aerobic system.[23]

Phosphocreatine—Creatine System

The energy-rich phosphate bonds in muscle *phosphocreatine* (also called *creatine phosphate*) supply a limited amount of energy to produce ATP in skeletal muscle. The hydrolysis of creatine phosphate to creatine and phosphate is an extremely rapid reaction that releases large amounts of energy for the conversion of ADP to ATP. Creatine phosphate provides a stored source of energy that is used for short bursts of muscle power or for use at the very beginning of muscle contraction while other, more sustainable, energy-regenerating systems are being turned on.[2]

Glycogen—Lactic Acid System

Skeletal muscle stores glucose as energy-rich glycogen. With brief, intense muscle exertion, muscles meet their energy demands from the breakdown of glycogen to glucose (*glycogenolysis*) and the metabolism of glucose to pyruvate and lactate (*glycolysis*). Glycolysis occurs without the consumption of oxygen in the cytoplasm of the muscle cell. The energy released from the breakdown of glucose to pyruvate or lactate is used to convert ADP to ATP for short to moderate periods of muscle contraction.[23]

Aerobic System

When oxygen is plentiful, the skeletal muscle takes up products of the glycolytic pathway and other substrates, such as amino acids, fatty acids, or ketone bodies, and efficiently oxidizes them to CO_2 and water in the muscle fiber mitochondria. This energy-yielding process is called *oxidative metabolism*. The oxidation of products of the glycolytic pathway and free fatty acids is a slow process, but it is usually sufficient to meet the continual but more modest energy demands of the most frequently used skeletal muscle. The aerobic system is the primary source of energy for muscle cells during prolonged exercise and for steady-state requirements.[23]

MUSCULOSKELETAL PATHOPHYSIOLOGY AND ANESTHESIA

Musculoskeletal diseases have a wide variety of causes, ranging from autoimmune destruction of tissue, to genetically determined defects in muscle membrane proteins, to pharmacologically induced alterations in Ca^{2+} metabolism. Musculoskeletal defects may reside in the neuromuscular junction, the muscle infrastructure, or the skeletal support structures.

Myasthenia Gravis

Myasthenia gravis (MG), a chronic disease of the neuromuscular junction, is manifested by increasing skeletal muscle weakness, fatigability on effort, and at least partial restoration of function after rest.

Incidence

Myasthenia gravis is the most prevalent neuromuscular disorder. With variability depending on country and time of study, a recent incidence rate ranged from 3 to 30 people in every 1,000,000 with myasthenia gravis.[24] In individuals younger than 50 years, the ratio of women to men with the disease is 3 to 2; however, in those older than 50 years, the disease is equally distributed between the sexes. Myasthenia gravis can begin spontaneously at any age, but it occurs most often in women between the ages of 30 and 40 years and in men between the ages of 50 and 60 years.[11,25] The onset may be abrupt or insidious, and the course is fluctuating, marked by periods of exacerbation and remission.[26] Spontaneous remissions that do occur sometimes persist for years.

Pathophysiology

Electron microscopic examination of the neuromuscular junction of the patient with myasthenia gravis shows a decrease in the number of functional postsynaptic ACh receptors (Figure 32-16). The AChR lesion appears to be caused by immune-mediated destruction, blockage, or inactivation. The prejunctional ACh pool is normal.[11]

Myasthenia gravis is an autoimmune disease with two distinct forms. In the most prevalent form, circulating antibodies react with myoneural AChR proteins, leading to varying degrees of dysfunction. Anti-AChR antibodies (AChR-Ab) are found in the sera of 80% to 85% of patients with myasthenia gravis, but the antibody level does not necessarily correlate with the severity of the disease.[27-30]

A subset of AChR-Ab-seronegative myasthenia gravis patients have muscle-specific kinase (MuSK) antibodies. MuSK-MG patients have more bulbar muscle involvement and are at increased risk for aspiration. Up to 50% of these patients are likely to experience myasthenia crisis requiring mechanical ventilation.[27-31] Serum concentration of MuSK-MG correlates with severity of symptoms.[27] Evidence from case series have demonstrated increased prevalence in people living closer to the equator.[28,32]

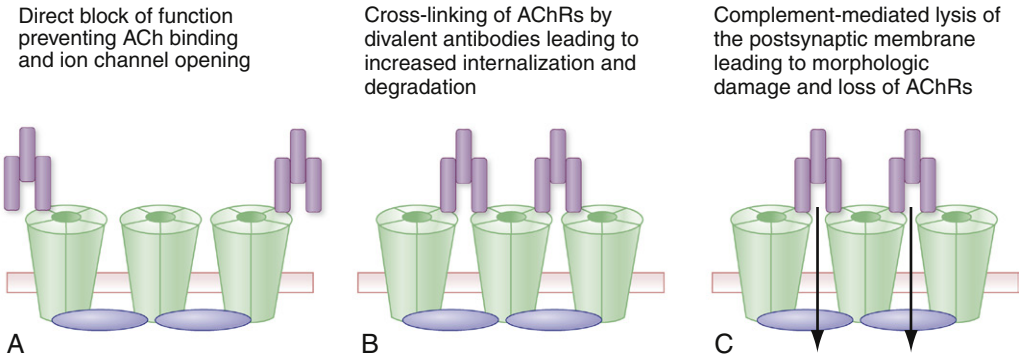

FIGURE **32-16** Mechanisms of loss of the acetylcholine receptor (AChR) at the neuromuscular junction. Antibodies can act **(A)** by directly blocking ACh binding or ion channel function; **(B)** by cross-linking the AChRs in the membrane, thereby leading to increased internalization and degradation; or **(C)** by complement-dependent lysis of the AChR-containing postsynaptic membrane. In myasthenia gravis, complement-dependent lysis is likely to be the most important mechanism overall. Interestingly, there is no evidence of complement-dependent mechanisms in either the Lambert-Eaton myasthenic syndrome or acquired neuromyotonia, in which cross-linking of the respective ion channels with increased internalization seems to be the main mechanism. (From Goldman L, Schafer AI. *Goldman's Cecil Medicine*. 24th ed. Philadelphia: Saunders; 2012.)

The initiating stimulus for the production of IgE antibodies against AChR or MuSK is unclear. The antibodies are T cell–dependent. The thymus gland seems to play a central role in the pathogenesis.[11,28,29] The thymus produces autoantibodies that cross-react to antigens in the neuromuscular junction.[28,33,34] The thymus is hyperplastic in approximately 65% and abnormal in about 75%. Thymomas, thymic tumors, are present in an additional 10%. Thymectomy is a viable treatment option for such patients.[11,28] Thymectomy improves symptoms, but is not curative, suggesting that antibodies are also produced elsewhere.[34]

Pregnancy exacerbates the symptoms of myasthenia gravis in 33% of pregnant women with the disease; however, other patients with the disease experience remission or no change in symptoms during pregnancy.[35] Anti-AChR antibodies that pass across the placenta may produce transitory symptoms of weakness in less than 20% of infants born to mothers with myasthenia gravis. Neonatal MG signs of weakness (e.g., difficulty with swallowing, sucking and breathing, ptosis, facial weakness) in the affected infant are usually present within the first few hours after birth. Spontaneous remission usually occurs within 2 to 4 weeks.[34,36] Neonatal MG has been linked to both AChR and MuSK antibodies.[28]

Clinical Manifestations

The clinical hallmarks of myasthenia gravis include generalized muscle weakness, which improves with rest, and an inability to sustain or repeat muscular contractions. Enhanced and repetitive effort produces enhanced weakness. The severity of myasthenia gravis can range from mild (slight ptosis only) to severe (respiratory failure). Environmental, physical, and emotional factors seem to affect the disease process, although unpredictably.[11]

Mouth, eyes, pharynx, proximal limb, and shoulder girdle musculature are most often affected. Visual symptoms (ptosis and diplopia) from extraocular muscle weakness occur in more than 50% of patients with myasthenia gravis.[28,37] The disease is restricted to the extraocular muscles in 20% of patients. Sensation and cognition are not affected by the disease process.[38]

Thymus gland abnormalities are detectable in about 75% of patients with myasthenia gravis.[11,37] Other autoimmune disorders, such as thyroid disease, collagen vascular diseases, polymyositis, and rheumatoid arthritis, occur more often in patients with myasthenia gravis.[36-38]

Myocarditis may complicate myasthenia gravis, especially in patients with thymomas. Microscopic lesions of myasthenic cardiac muscles are similar to skeletal muscle lesions, indicating a common pathogenesis. The myocardial inflammation produces dysrhythmias, particularly atrial fibrillation and atrioventricular block.[39]

Treatment

Therapy for patients with myasthenia gravis is directed toward improving neuromuscular transmission and includes cholinesterase inhibitors, corticosteroids and other immunosuppressants, plasmapheresis, intravenous immunoglobulin, and thymectomy.[40-42]

Treatment with cholinesterase inhibitors can dramatically reduce the symptoms of myasthenia gravis by inhibiting the hydrolysis of ACh and therefore increasing the neurotransmitter's concentration at the neuromuscular junction. Increasing the synaptic concentration of ACh enhances the possibility of postsynaptic AChR occupation, which is critical for the production of a threshold-reaching EPP for muscle contraction. Anticholinesterase treatment is particularly successful in patients with milder disease.[11,37,42] The most commonly used anticholinesterase agent in the United States is oral pyridostigmine.[42] An oral dose of 60 mg pyridostigmine lasts 3 to 6 hours and is equivalent to an intramuscular or intravenous dose of 2 mg pyridostigmine or 1 mg neostigmine.[36] The dosage is patient dependent with the average dose of 600 mg daily. Timing of administration should correlate to periods of highest activity.[34]

Titration of the anticholinesterase dose is challenging. Underdosing does not sufficiently retard the muscle weakness and can result in *myasthenic crisis*, a severe exacerbation of myasthenic symptoms resulting in respiratory distress. Overmedicating with a cholinesterase inhibitor can produce a surplus of ACh at the myoneural junction, causing a depolarizing-like block and augmenting skeletal muscle weakness. This situation is called *cholinergic crisis*. Muscarinic side effects (e.g., abdominal cramping, diarrhea, salivation, bradycardia, respiratory distress, and miosis) predominate in a cholinergic crisis.

Corticosteroid therapy produces an 80% remission rate in patients with myasthenia gravis, in part by reducing AChR antibody levels.[42] Glucocorticoid therapy is often used in combination with other agents. Use is limited by the side effects (e.g., osteoporosis, gastrointestinal bleeding, suppression of endogenous

cortisol release, cataracts, increased susceptibility to acute infections, hypertension, and glucose intolerance) observed with long-term administration.

In patients with more debilitating, widespread disease, immunosuppressive drugs such as azathioprine (Imuran) and cyclosporine may induce remission by interfering with the production of AChR antibodies. Side effects of azathioprine include severe hemopoietic depression and liver dysfunction. Cyclosporine side effects include hypertension and nephrotoxicity.[11,37,42,43]

Excision of the thymus gland is recommended for adults with generalized disease and for patients with thymomas, thymus gland hyperplasia, or drug-resistant myasthenia gravis.[11,38,42] Thymectomy effectively arrests or reverses the myasthenic process by removing a major source of antibody production. Clinical improvement of myasthenic symptoms is seen in 85% of patients within weeks to months after surgery; almost 35% of these patients go into remission requiring no medications.[11] Early evidence is suggestive that MuSK-MG patients respond less well to thymectomy.[11,42]

Plasmapheresis (plasma exchange) arrests severe refractive myasthenia gravis by reducing the concentration of circulating antibodies. It is used primarily as a short-term treatment because the improvement that it produces in symptoms is generally short lived.[44] Intravenous immunoglobulin also may be used for short-term control of symptoms prior to surgery.[11,37,42,44]

Anesthetic Implications

Several days before the operation and again immediately prior to surgery, the surgical candidate with myasthenia gravis should be evaluated for disease control and, if applicable, for stabilization of anticholinesterase dose.

The use of anticholinesterase medication in the immediate preoperative period is controversial.[12,37,40,41,45,46] Some experts feel that an awareness of drug mechanisms can enable anticholinesterase therapy to be safely continued into the preoperative period, especially in patients who depend on this therapy for their well-being. Others recommend discontinuing or tapering anticholinesterase medication before surgery to avoid complicating the anesthetic management. Patients with mild myasthenia gravis can usually tolerate the temporary disruption in treatment.[41,46]

The presence of cholinesterase inhibitors may potentiate vagal responses and beclouds both the intraoperative administration of muscle relaxants and the differential diagnosis and treatment of postoperative muscle weakness.

Emotional stress and surgery may precipitate or worsen skeletal muscle weakness. Pharyngeal and laryngeal muscle weakness, difficulty in eliminating oral secretions, and the risk of pulmonary aspiration should be considered in the anesthesia plan of care.[36] Swallowing and respiratory muscle dysfunction account for much of the morbidity and potential mortality in patients with myasthenia gravis.[41,47]

Regional and local anesthesia with careful monitoring are the preferred anesthetic techniques when appropriate. If general anesthesia is indicated, the respiratory depressant effects of sedatives, narcotics, and volatile anesthetic agents, compounded by the presence of an already weakened respiratory system, must be carefully considered.[40,41.48,49]

In many patients, the relaxant effects of a volatile anesthetic in combination with the patient's preexisting skeletal muscle weakness are sufficient to facilitate intubation of the trachea.[46,48,50] Enhanced muscle relaxation may be seen with the administration of all the potent volatile anesthetics.[40,41]

Small doses of succinylcholine may be used to facilitate tracheal intubation, but the response may be unpredictable.[36] Untreated patients with myasthenia gravis appear to be two to three times more resistant to succinylcholine. Normal dosages of succinylcholine may not effectively depolarize the end plate because of the deficiency of viable AChRs. For rapid-sequence induction, the dose of succinylcholine should be increased to 1.5 to 2 mg/kg.[12,40,41] On the other hand, patients treated with cholinesterase inhibitors exhibit a normal or prolonged response to succinylcholine. Cholinesterase inhibitors block the effects of plasma cholinesterase, as well as those of true cholinesterase; hence, succinylcholine and other medications metabolized by plasma cholinesterase (e.g., ester local anesthetics) may have a delayed hydrolysis and a prolonged duration of action.[12,46] The ester hydrolysis of atracurium and cisatracurium is independent of plasma cholinesterase activity.

The deficient number of functioning AChRs in patients with myasthenia gravis produces an extraordinary sensitivity to nondepolarizing muscle relaxants. Small doses of nondepolarizing agents can produce a profound block with a prolonged effect, even in patients being treated with cholinergic drugs.[37,40,41] One study showed that myasthenia gravis patients with a preanesthetic train-of-four ratio of less than 0.9 had a significantly lower ED_{95} (effective dose, 95%) of atracurium than myasthenia patients with no fade or nonmyasthenic patients.[50] Some patients require no medication at all for surgical muscle relaxation.[48,49,51]

Generally, muscle relaxant requirements are widely variable in patients with myasthenia gravis, a characteristic that makes neuromuscular blockade monitoring an essential and integral part of the anesthetic management. The orbicularis oculi muscle may overestimate the degree of muscle relaxation in patients with myasthenia gravis.[52] This site may be the most ideal site to monitor neuromuscular blockade to avoid the possibility of undetected residual muscle weakness. When needed, the use of smaller doses (half to two thirds the normal dose) of shorter-acting nondepolarizing relaxants is the prudent choice.[36,37,40,41,53]

Reversal of neuromuscular blockade with an AChE inhibitor should be performed cautiously in patients with myasthenia gravis. Overtreatment with an anticholinesterase agent can precipitate a cholinergic crisis and aggravate rather than reverse the muscle weakness. In many circumstances, the neuromuscular block can be titrated to allow complete spontaneous recovery, avoiding the use of reversal.

Case reports have reported effective use of sugammadex for reversal of neuromuscular blockade in myasthenia gravis patients.[54,55] In both cases a rapid and complete recovery from rocuronium was achieved without the use of anticholinesterase agents.

Complete, sustained return of muscle strength must be demonstrated before extubation and resumption of spontaneous ventilation. The patient should be informed that postoperative tracheal intubation and ventilatory support may be required. Skeletal muscle strength may appear to be adequate shortly after surgery but may deteriorate a few hours later. A higher likelihood for postoperative ventilation can be predicted for patients undergoing transsternal thymectomy, duration of the disease longer than 6 years, a daily pyridostigmine dose greater than 750 mg, the presence of chronic obstructive pulmonary disease, and a preoperative vital capacity less than 2.9 L.[46] Postoperative ventilation related to myasthenia crisis can be predicted for patients after transsternal thymectomy by the preoperative bulbar symptoms, history of preoperative crisis, preoperative serum AChR antibody greater than 100 nmol/L and intraoperative blood loss greater than 1000 mL, severity of preoperative muscle weakness, and major postoperative complications.[56,57]

Lambert-Eaton Myasthenic Syndrome

Incidence

Lambert-Eaton myasthenic syndrome (LEMS) is a rare autoimmune disease that classically occurs in patients with malignant disease, particularly small-cell carcinoma of the bronchi. One third to one half of patients, however, have no evidence of carcinoma.[10,58,59] Most patients with myasthenic syndrome are men between the ages of 50 and 70 years.

Pathophysiology

The predominant defect associated with LEMS appears to be an autoantibody-mediated derangement in presynaptic P/Q-type voltage-gated Ca^{2+} channels (VGCC) leading to a reduction in Ca^{2+}-mediated exocytosis of ACh at neuromuscular and autonomic nerve terminals.[10,58,60,61] The decreased release of ACh quanta from the cholinergic nerve endings produces a reduced postjunctional response. Unlike in myasthenia gravis, the number and quality of postjunctional AChRs remain unaltered, and the end-plate sensitivity is normal. The neuromuscular junction abnormality of LEMS is similar in location to that of Mg^{2+} intoxication or botulism poisoning, in which the release of presynaptic ACh is attenuated.

Clinical Manifestations and Treatment

Muscle weakness, fatigue, hyporeflexia, and proximal limb muscle aches are the dominant features of LEMS. The diaphragm and other respiratory muscles are also involved. Autonomic nervous system dysfunction is often present and is manifested as impaired gastric motility, orthostatic hypotension, and urinary retention.

Patients with LEMS experience a brief increase in muscle strength with voluntary contraction, distinguishing it from myasthenia gravis. Tetanic stimulation results in a progressive augmentation in muscle strength as the frequency of the stimulation is increased. Posttetanic potentiation is also enhanced.

There is no cure for LEMS. Treatment is aimed at improving muscle strength and reversing autonomic deficits.[11,36,40,60] 3,4-Diaminopyridine improves muscle strength in some patients by promoting presynaptic Ca^{2+} influx and increasing the number of ACh quanta that are liberated by a single nerve action potential. Plasmapheresis, corticosteroids, intravenous immunoglobulin, and immunosuppressive drugs provide improvement for some patients with LEMS. Unlike the effective use in myasthenia gravis, anticholinesterase drugs do not provide improvement for patients with LEMS.[36]

Anesthetic Implications

An index of suspicion for LEMS should be maintained in surgical patients with a history of muscle weakness and suspected or diagnosed carcinoma of the lung. Patients with LEMS are extremely sensitive to the relaxant effects of both depolarizing and nondepolarizing muscle relaxants.[12,36,37] Inhalational anesthetics alone may provide adequate relaxation, but if muscle relaxants are required, their dosages should be reduced and the neuromuscular blockade closely monitored.[37,62] Neuromuscular reversal with an anticholinesterase agent may be used. Prolonged ventilatory assistance may be required postoperatively.

Duchenne Muscular Dystrophy

Muscular dystrophy is a heterogeneous set of diseases that includes fascioscapulohumeral dystrophy, limb-girdle dystrophy, Becker muscular dystrophy (BMD), Duchenne muscular dystrophy, and others. *Duchenne muscular dystrophy* is the most common of these and has the most severe clinical course.[63]

Incidence

Duchenne muscular dystrophy (DMD), described by G.B. Duchenne in 1861, is an inherited, sex-linked, recessive disease that presents in early childhood at between 3 and 5 years of age. It is clinically evident in males and has an incidence of approximately 1 in 3500 live-born males.[64] Females are generally unaffected but are carriers of the disorder. Mental retardation of varying degrees occurs in about 30% of patients with DMD.[64] There is no cure for the disease. Corticosteroid therapy improves muscle strength, reduces the risk of scoliosis, and may slow disease progression in some patients.[65-67] Death often occurs in early adulthood and is usually caused by progressive cardiomyopathy or pneumonia.[63-65]

Pathophysiology

Patients with DMD experience an infiltration of fibrous and fatty tissue into the muscle, followed by a progressive and painless degeneration and necrosis of muscle fibers. The disease affects skeletal muscle, cardiac muscle, and smooth muscle. Muscle weakness ends with muscle destruction.

In 1987 the abnormal gene responsible for DMD was identified. This gene is located on the X chromosome and is errant in coding for the vital muscle protein *dystrophin*. Dystrophin is normally bound to a complex of glycoproteins as a transmembrane structural component of the muscle fiber sarcolemma.[68] Patients with DMD have an absence or a severe deficiency of the dystrophin protein, which alters sarcolemma integrity and stability.[67,69] The protein is present in low amounts or is structurally altered in Becker muscular dystrophy, a similar but rarer disorder that follows a milder and less progressive course than the Duchenne type.[68,69]

In the early stages of DMD, increased permeability of the sarcolemma and skeletal muscle necrosis are mirrored by elevated serum levels of the enzyme creatine kinase (CK). Serum CK levels are often 20 to 100 times normal levels (normal level, 40 to 150 units/L), but as muscle is lost to the destructive process, CK levels decrease.[64]

Clinical Manifestations

Duchenne muscular dystrophy is characterized by an unremitting weakness and a steady deterioration of the proximal muscle groups of the pelvis and shoulders. The child exhibits a clumsy, waddling gait and falls frequently. Weakness of the pelvic girdle leads to the classic finding of *Gowers sign*, in which patients use their hands to climb up their legs to arise from the floor. A steady deterioration of muscle strength forces most of these boys to be wheelchair bound by the age of 12 years.[64]

Skeletal muscle atrophy is usually preceded by fat and fibrous tissue infiltration, resulting in pseudohypertrophy. The infiltrative process is most apparent in the calf muscles, which become particularly enlarged.

Degeneration of respiratory muscles (diaphragm, intercostal, accessory muscles) occurs and leads to a restrictive type of ventilatory impairment. Unopposed action by healthy, nondystrophic axial muscles predisposes these patients to kyphoscoliosis, which further decreases the pulmonary reserve. Decreasing muscle strength also results in ineffective cough, impaired swallowing, and inability to mobilize secretions.[70,71]

More progressive forms of the disease affect not only skeletal muscle but also smooth muscle of the alimentary tract and cardiac muscle. Alimentary tract involvement can lead to intestinal hypomotility, delayed gastric emptying, and gastric dilation.[72,73]

Myocardial involvement occurs in almost all patients with progressive disease and includes cardiomyopathy, ventricular dysrhythmias, and mitral regurgitation.[46,64,65,74] Preclinical cardiac

involvement can be detected in up to 62% of boys between the ages of 6 and 10 years. Cardiomyopathy can be evident at 10 years of age and is present in nearly all patients over the age of 20 years.[75,76] In a study by Duboc et al.,[77] left ventricular ejection fraction was shown to be depressed in 25% of the patients with DMD before the age of 13 years. Angiotensin-converting enzyme inhibitors and β-adrenergic blockers may be used to slow the deterioration of cardiac function.[65,76-78] Typical electrocardiographic (ECG) changes include tall R waves in the right precordial leads and deep Q waves in the left precordial leads.[64]

Although often severe, compromised cardiac and respiratory conditions may be masked by the limited activity imposed by the patient's skeletal myopathy. Added stress, such as that produced by surgery and anesthesia, may suddenly increase cardiorespiratory demand and uncover the weakened cardiac and respiratory states.[79,80]

Anesthetic Implications

Patients with DMD are susceptible to untoward anesthesia-related complications. When possible, local or regional anesthesia should be considered.[80,81] For the patient on chronic corticosteroid treatment, consideration needs to be given to steroid coverage over the period of surgery.

Generalized muscle weakness, especially in the advanced stages of DMD, makes these patients exquisitely sensitive to the respiratory depressant properties of opioids, sedatives, and general anesthetic agents. Preoperative sedation should be omitted or minimal, and the smallest possible amounts of anesthetic agents should be used.

Preoperative and postoperative respiratory therapy can help maximize the patient's pulmonary condition.[46,80] In patients with more advanced disease, arterial blood gas determinations and preoperative pulmonary function studies may elucidate the extent of respiratory involvement and the amount of respiratory reserve. A preoperative forced vital capacity (FVC) less than 50% of predicted places the patient at increased risk for respiratory complications when undergoing general anesthesia or procedural sedation. Patients with a FVC greater than 35% of predicted have a high risk for pulmonary complications.[80] In one series, aggressive preoperative chest physiotherapy and incorporation of postoperative noninvasive positive pressure ventilation (NPPV) enabled patients with preoperative FVC levels of 30% and below to successfully undergo corrective spinal surgery.[82] Extubation directly to NPPV should be considered for DMD patients with baseline FVC less than 50% of predicted and is strongly recommended for patients with a FVC less than 30% of predicted.[80,83] Assiduous attention to respiratory function must be continued into the postoperative period. Delayed pulmonary insufficiency, as late as 36 hours after surgery, has been reported.[46,72]

The effects of nondepolarizing muscle relaxants must be scrupulously monitored. There is enhanced muscle relaxant sensitivity, and recovery may be prolonged three to six times the normal duration in patients with DMD.[84] If surgical muscle relaxation is required, a short-acting nondepolarizing muscle relaxant that is carefully titrated with the use of a nerve stimulator is recommended.

Cardiomyopathy and decreased cardiac reserve makes these patients sensitive to the myocardial depressant effects of general anesthetic agents, sedatives, and narcotics.[85,86] A preoperative consultation with a cardiologist is advised before anesthesia.[80] Echocardiography is recommended for operative patients to evaluate left ventricular (LV) function, but it cannot exclude the development of congestive heart failure (CHF) during surgery.[46,65,79,87] A carefully titrated intravenous "balanced" technique may help provide a smoother cardiovascular course. Ketamine has been used successfully for anesthesia during diagnostic muscle biopsy in patients with DMD. Judicious administration of intravenous fluids is warranted. The sudden occurrence of hypotension and tachycardia during anesthesia may herald heart failure.[79]

The potential for delayed gastric emptying, plus the presence of weak laryngeal reflexes, dictates that the anesthesia plan of care include measures for guarding against aspiration of stomach contents. Gastrokinetic agents and the prophylactic use of a nasogastric tube are recommended for patients with gastrointestinal dysmotility.[73,80]

Succinylcholine is contraindicated in patients with DMD.[65] The altered sarcolemma can lead to rhabdomyolysis and myoglobin efflux with succinylcholine administration. The resultant massive breakdown of the diseased muscle fibers produces a profound hyperkalemia that requires extensive and tenacious treatment with hyperventilation, calcium chloride, sodium bicarbonate, and glucose and insulin. Ventricular fibrillation and intractable cardiac arrest have been associated with succinylcholine administration to patients with diagnosed and undiagnosed muscular dystrophy.[88,89]

Rhabdomyolysis, hyperkalemia, hyperthermia, unexplained tachycardia, and cardiac arrest also have been reported after the administration of potent inhalation anesthetics to DMD patients without the use of succinylcholine.[85,86,90-92] These "malignant hyperthermia-like" reactions may be due to the destabilizing effect of inhalational agents on an already unstable and frail muscle membrane.[93] The term associated with DMD rhabdomyolysis in response to succinylcholine and/or potent inhalational agents is "anesthesia-induced rhabdomyolysis" (AIR).[86]

Although only a small proportion of DMD patients develop AIR in response to succinylcholine and inhalational anesthetics, given the availabilities of safe anesthesia alternatives, the anesthetist should consider a "trigger-free" total intravenous anesthesia (TIVA) or regional anesthetic for patients with DMD.[65,80,83,92-94] In addition to the strict contraindication of succinylcholine, this includes when feasible avoiding potent volatile inhalational agents or using them for the absolute shortest period possible.[83,93]

Despite the increased risk for "MH-like events" in patients with DMD, malignant hyperthermia (MH) and DMD are genetically distinct diseases. Current evidence indicates that DMD and BMD are not among the myopathies that are genetically associated with malignant hyperthermia and that patients with DMD and BMD do not have an increased risk of MH.[80,93,94]

Malignant Hyperthermia

Epidemiology/Incidence

Malignant hyperthermia (MH) is an uncommon, life-threatening, hypermetabolic disorder of skeletal muscle, triggered in susceptible individuals by potent inhalation agents, including sevoflurane, desflurane, and isoflurane and the depolarizing muscle relaxant succinylcholine.[95,96] A review of MH cases in New York State by Brady et al.[97] reported an estimated prevalence of MH in males 2.5 to 4.5 times the rate for females.[97] The exact incidence of MH is unknown, but the rate of occurrence has been estimated to be between 1:5000 to 1:50,000 general anesthetics.[95,96] The highest incidence of MH is in young people, with a mean age of 18.3 years.[95] High-incidence areas in the United States include Wisconsin, Nebraska, West Virginia, and Michigan.[98]

Susceptibility to MH is inherited as an autosomal-dominant pattern.[95,96] If a parent is identified as MH-susceptible (MHS), then each of the parent's siblings have a 50% chance of also being MHS.[95,96] MH has been associated with at least 23 genetic

mutations, and in many cases, the genetic defects have not been established.[98]

The first formal case report of MH was of an Australian family, described by Denborough et al.[99] over 40 years ago in the journal *Lancet*.[99] Since that time, a great deal has been learned about the biochemical and physiologic components of the disease. Nonetheless, many questions remain regarding the pathophysiology, diagnosis, and significance of some clinical manifestations.

Pathophysiology

Although the cause(s) of MH are not yet known with certainty, it is generally agreed that MH is an inherited disorder of skeletal muscle. In susceptible patients, a defect in calcium regulation is expressed by exposure to specific anesthetic triggers, the volatile inhalational anesthetic agents or succinylcholine. An uncontrolled rise in myoplasmic calcium results. The ryanodine receptor (RYR1) is the major calcium release channel of the sarcoplasmic reticulum, and much attention has been focused on RYR1 as the site of the MH defect.[1,96,100] The channel is called a "receptor" because it binds the plant alkaloid ryanodine. The calcium release defect involves skeletal muscle, and there is no evidence for a primary defect in cardiac or smooth muscle cells.

Malignant hyperthermia is initiated in MHS patients when specific anesthetic-triggering agents induce enhanced calcium release from the sarcoplasmic reticulum in myocytes. The enhanced intracellular calcium results in muscle contraction. Energy-dependent reuptake mechanisms attempt to remove excess calcium from the myoplasm, increasing muscle metabolism two- to three-fold. The accelerated cellular processes increase oxygen consumption, augment carbon dioxide and heat production, deplete ATP stores, and generate lactic acid.[95] Acidosis, hyperthermia, and ATP depletion cause sarcolemma destruction, producing a marked egress of potassium, myoglobin, and creatine kinase to the extracellular fluid.[98] Skeletal muscle constitutes 40% to 50% of our body mass, so relatively small changes in muscle metabolism may produce the dramatic systemic biochemical changes observed with MH.

Clinical Manifestations

Not all cases of MH are fulminant, but rather there is a spectrum or continuum of severity, ranging from an insidious onset with mild complications to an explosive response with pronounced rigidity, temperature rise, arrhythmias, and death.[95,96,101]

Although MH may present in several ways, a typical MH episode begins while the patient is under general anesthesia (GA) with a volatile anesthetic. Succinylcholine may or may not precede the MH episode.[95] The onset of MH symptoms may occur immediately after induction of anesthesia or several hours into the surgery.[101] Succinylcholine appears to accelerate the onset and increase the severity of the MH episode.[95,96] Desflurane and sevoflurane have been associated with more delayed onset of MH, as long as 6 hours after induction of anesthesia.[101-104] Although an uncommon event, MH can occur in the recovery room, usually within 1 hour after general anesthesia.[105]

The clinical features of MH are not uniform and the time course between onset of initial signs and fulminant MH is variable. Overall clinical manifestations of MH reflect increased intracellular muscle Ca^{2+} concentration and greatly increased body metabolism (Box 32-3). The most sensitive and an early indicator of MH is an unanticipated increase in end-tidal carbon dioxide ($ETCO_2$) levels out of proportion to minute ventilation.[96,106] The increased $ETCO_2$ may be abrupt or it may rise gradually over the course of the anesthetic. Common signs of MH include tachycardia, tachypnea, skin mottling, cyanosis, and total body or jaw muscle rigidity. Muscle rigidity is clinically apparent in 75% of cases. Hyperthermia, which may climb at a rate of 1° to 2° C every 5 minutes and averages 39.3° C (102.7° F), is often a late but confirming sign of MH.[95,106,107]

BOX 32-3

Clinical Events and Laboratory Findings During Malignant Hyperthermia

Clinical Events During MH

- Unexplained, sudden rise in end-tidal CO_2 (greater than 55 mmHg)
- Unexplained tachycardia, tachypnea, labile blood pressure, or arrhythmias
- Masseter muscle or generalized muscle rigidity
- Unanticipated respiratory or metabolic acidosis
- Rising patient temperature
- Cola-colored urine (myoglobinuria)
- Mottled, cyanotic skin
- Decreased Sa_{O_2}

Laboratory Findings Consistent with MH

- Arterial blood gases: Pa_{CO_2} greater than 60 mmHg, base excess more negative than −8 mEq/L, pH less than 7.25
- Serum potassium greater than 6 mEq/L
- Creatine kinase greater than 20,000 units/L
- Serum myoglobin greater than 170 mcg/L
- Urine myoglobin greater than 60 mcg/L

MH, Malignant hyperthermia; Pa_{CO_2}, partial pressure of carbon dioxide in alveolar gas; Sa_{O_2}, % of oxygen saturation.

The combination of acidosis, hyperkalemia, and hyperthermia leads to cardiac irritability, a labile blood pressure, and arrhythmias that can rapidly progress to cardiac arrest. Laboratory findings mirror the muscle breakdown and include myoglobinuria and increased serum potassium and CK. Myoglobin appears in the plasma within minutes of the hypermetabolic muscle response. Arterial and venous blood gas analysis reveals decreased oxygen tension and mixed metabolic and respiratory acidosis. Late complications may include cerebral edema, myoglobinuric renal failure, consumptive coagulopathy, hepatic dysfunction, and pulmonary edema.[95,107]

The variable time course and nonspecific clinical features and laboratory findings can make the diagnosis of MH difficult. Insufficient anesthetic depth, hypoxia, neuroleptic malignant syndrome, propofol infusion syndrome, thyrotoxicosis, pheochromocytoma, and sepsis can share several characteristics with MH, making the clinical picture ambiguous and the differential diagnosis challenging to even the most experienced practitioner[95,108,109] (Box 32-4). The average time between the onset of the first adverse sign indicating MH and the administration of dantrolene is 35 minutes.[107] Surgical procedures performed of necessity in a darkened operating room can further compromise the practitioner's diagnostic acumen.

Preoperative Assessment and Prevention

Patients who are MH susceptible are usually phenotypically normal, otherwise healthy, and completely unaware of their risk until exposed to a triggering anesthetic.[95,110] Furthermore, not everyone who has the MH gene develops an MH episode upon each exposure to triggering anesthetics. An MH-susceptible patient may be anesthetized multiple times before experiencing an MH

BOX **32-4**

Manifestations That Mimic Malignant Hyperthermia—Signs and Symptoms

Tachycardia
- Hypoxia
- Hypercarbia
- Hypovolemia
- Insufficient anesthetic depth
- Anticholinergics, sympathomimetics, cocaine, amphetamine
- Pheochromocytoma

Hyperpyrexia
- Heatstroke
- Blood transfusion reaction
- Infection
- Drug reaction
- Neuroleptic malignant syndrome
- Serotonin syndrome
- Hypermetabolic states (sepsis, thyroid storm, pheochromocytoma)
- Iatrogenic overheating

Tachypnea, Hypercapnia
- Congestive heart failure, pulmonary edema
- Hypermetabolic states
- Intraperitoneal carbon dioxide insufflation
- Airway obstruction, pneumothorax
- Excess dead space, low minute volume

Masseter Muscle Rigidity
- Insufficient neuromuscular blockade
- Temporomandibular joint syndrome
- Neuroleptic malignant syndrome
- Myotonia

event. Although MH susceptibility cannot be ruled out by history alone, every surgical patient should be questioned about:
- Family history of unexpected intraoperative complications or deaths
- Family or personal history of MH, muscle rigidity/stiffness, and/or high fever under anesthesia
- Personal history of dark or cola-colored urine after surgery or exercise
- Personal history or family history of high temperature or death during exercise

Because MH is an inherited disorder, all members of a family in which MH has occurred must be considered MHS unless proven otherwise.[98] Moreover, the absence of a positive family history does not preclude MH susceptibility.

Patients with a variety of neuromuscular disorders may exhibit one or more clinical features of MH in the perioperative period. There are a limited number of relatively rare disease entities that have a strong clinical and/or genetic link to MH susceptibility. These include *central core disease*, *King Denborough syndrome*, and *multiminicore disease*.[98,111-113] There is no risk for MH over the general population in patients with Duchenne or Becker muscular dystrophy, neuroleptic malignant syndrome, myotonia congenita, and myotonic dystrophy.[96,106,112]

All patients given general anesthesia for more than 20 to 30 minutes should have core temperature monitoring.[95,96] Pulmonary artery, distal esophageal, nasopharyngeal, and tympanic membrane temperature monitors are the gold standards for core temperature measurement. Intermediate temperature monitoring sites include mouth, axilla, rectum, and bladder. Skin temperature may not accurately reflect core temperature during an MH event.[98]

Weglinski et al.[114] reported that 50% of patients with unexplained CK elevation test positive for MH on biopsy. However, as a screening test for MH, CK levels are imprecise and nonspecific.

Heat stroke and strenuous exercise have been implicated as causal factors of MH in some patients. It is unclear whether these factors cause, exacerbate, or have no effect on MH triggering in humans.[106,115,116] It may be advisable to provide a trigger-free anesthetic to patients with unexplained exertional heat illness or exertional rhabdomyolysis until definitive MH testing can be performed.[115]

Management

Enhanced patient monitoring, earlier diagnosis and treatment, and the introduction of dantrolene are responsible for the dramatic decrease in mortality from nearly 80% 30 years ago to less than 5% today.[95,106,107] In a review of the North American MH Registry from 1987 to 2006, cardiac arrest and patient death occurred more often in patients with muscular builds and was associated with the development of disseminated intravascular coagulation.[107]

In 1979, dantrolene sodium was introduced as a treatment for MH. Since that time, dantrolene has been the cornerstone of treatment and has contributed greatly to the dramatic decline in death and disability associated with MH. Dantrolene is a unique muscle relaxant that does not work at the neuromuscular junction as do standard neuromuscular blocking drugs. Rather, it works by reducing calcium efflux from the sarcoplasmic reticulum, counteracting the abnormal intracellular calcium levels accompanying MH.[96,117,118] At clinical concentrations, dantrolene does not render the muscle totally flaccid and without tone, but it may cause significant muscle weakness and respiratory insufficiency, especially in patients with preexisting muscle disease.

Dantrolene administration with calcium channel blockers may induce life-threatening myocardial depression and hyperkalemia.[96,118] Dantrolene may cause significant muscle weakness in patients with preexisting muscle disease.[98]

Once MH is recognized, it is critical to discontinue the inhalation agent, hyperventilate with 100% O_2, administer dantrolene, cool the patient, and treat symptoms.[96] The Malignant Hyperthermia Association of the United States (MHAUS) provides an "Emergency Therapy for MH" poster that should be posted in every surgical site. The following treatment sequence is recommended for an acute MH episode:
- Discontinue the volatile anesthetic and succinylcholine.
- Call for help and alert the surgeon to conclude the procedure promptly.
- Hyperventilate with 100% oxygen at high flows (at least 10 L/min) to improve tissue oxygenation and eliminate CO_2.
- Administer 2.5 mg/kg dantrolene IV bolus and repeat as necessary every 5 to 10 minutes until symptoms abate. Occasionally, a total dose greater than 10 mg/kg may be needed, but if greater than 20 mg/kg is given without reversal of symptoms, the diagnosis should be reassessed. The alkaline solution is highly irritating to vessels and should be administered through the largest vein possible.[98,118]
- Monitor core temperature. If fever is present, initiate cooling by lavage (orogastric, bladder, open cavities), administration of chilled intravenous normal saline, and surface cooling (e.g., hypothermia blanket; ice packs to the groin, axilla, and neck). Stop cooling measures at 38° C to avoid hypothermia.
- Dysrhythmias will usually respond to treatment of acidosis or hyperkalemia. Treat persistent or life-threatening arrhythmias

with standard antiarrhythmic agents. Do not administer calcium channel blockers with dantrolene.
- Determine arterial blood gases, serum electrolytes, and blood glucose every 15 minutes until the syndrome stabilizes. Correct severe metabolic acidosis with sodium bicarbonate, 1 to 2 mEq/kg, guided by pH and base deficit. Coagulation profile, CK, blood and urine myoglobin, and liver enzyme levels should be established.
- Treat hyperkalemia with hyperventilation, bicarbonate, and intravenous insulin and glucose.
- Maintain urine output greater than 2 mL/kg/hr with hydration, furosemide (0.5 to 1.0 mg/kg), and mannitol as needed. Large losses of intravascular volume should be anticipated. Evaluate need for invasive hemodynamic monitoring.[95,96]

Each 20-mg vial of dantrolene must be reconstituted with 60 mL of sterile water for injection United States Pharmacopeia (USP) (with no bacteriostatic agent). The initial dantrolene dose of 2.5 mg/kg equates to 9 vials of dantrolene for a 70-kg patient. The poor water solubility of dantrolene makes it very time consuming to mix and administer the requisite doses. Although a newer dantrolene formulation is reportedly easier to reconstitute, during an MH emergency, the full-time efforts of additional medical personnel should be enlisted to assist with the labor-intensive preparation. A warmed diluent fluid stored at 37° to 39° C may expedite dantrolene preparation.[98,119,120]

Documentation of an MH episode should include patient responses, personnel involved, medications, interventions, and patient outcomes.

Anesthesia for the Malignant Hyperthermia–Susceptible Patient

Patients known or suspected of having MH should be assessed well before their date of surgery so that anesthesia records and MH testing center reports (if available) can be collected to corroborate the history.

Standard intraoperative monitoring for the MHS surgical patient includes blood pressure, ECG, pulse oximetry, capnography, and continuous measurement of core body temperature. A cooling water mattress should be placed under the MHS patient at the start of the procedure. Dantrolene pretreatment for the MHS surgical patient is not routine.[118]

If the surgical site permits, a regional or local anesthetic technique is preferable for the MHS patient. Local anesthetics (both amide and ester) are nontriggering drugs. Preoperative administration of anxiolytics followed by a nontriggering general anesthetic also can be administered safely in concert with close monitoring of appropriate vital functions. The list of "nontriggering" anesthetic agents is comprehensive enough to meet most anesthetic requirements (Box 32-5). All potent volatile inhalation agents and succinylcholine are MH triggers and should not be administered to the MHS patient. Nitrous oxide is not a MH trigger.

Not all drugs have been thoroughly screened as potential MH triggers, but it is clear that the vast majority of prescription and nonprescription drugs are safe, including antibiotics, antihypertensive agents, and drugs used in the treatment of gastrointestinal disorders. Keys to successful perioperative outcome for the MHS patient include the following[96]:
- Preoperative care in a relaxed and quiet environment with premedication anxiolysis as appropriate
- Avoidance of MH-triggering medications
- Preparation of an anesthesia machine by changing the carbon dioxide absorbent and removing or inactivating vaporizers. The anesthesia machine and ventilators should be flushed with oxygen set at 10 L/min. Newer anesthesia machines may require up to 150 minutes for the anesthesia machine to be "cleaned" of volatile agents with oxygen flush. Older anesthesia machines require only 20 minutes for adequate preparation.[96,121-123] An activated charcoal filter placed in the inspiratory limb of the circuit may speed the removal of potent inhalational anesthetics from the anesthesia workstation.[124]
- An MH kit or cart in the OR
- Assiduous perioperative observation for signs of MH, including continuous intraoperative monitoring of the patient's $ETCO_2$, arterial oxygen saturation, and core temperature
- A full appreciation of a preestablished treatment protocol by all perioperative medical personnel
- Ready availability of ice and the ability to crush it
- Ready availability of at least 3000 mL of cold intravenous solution

Surgery in an ambulatory surgical center can be safely performed for the MHS patient with appropriate planning and if proper safety precautions are regarded.[124-126] A preoperative evaluation and consultation with the surgeon will help determine the best location to perform the needed surgery. Appropriate monitoring, including end-tidal CO_2 and core temperature, must be in place and an adequate supply of dantrolene available.[96,127] A "trigger-free" anesthetic must be administered. Yentis et al.[128] reviewed the medical records of 303 children labeled as MHS who underwent surgery with nontriggering anesthetics between 1981 and 1990. None of the children developed MH, and on the basis of their retrospective analysis, the authors concluded that admission to the hospital solely on the basis of the MHS label is not warranted.[128]

For the MHS patient who has undergone an uneventful surgical course, close observation and monitoring should continue for at least 2.5 hours in the postanesthesia care unit (PACU). Malignant hyperthermia can first manifest in the recovery room after uneventful surgery and anesthesia. The MHS patient may be discharged on the day of surgery if the anesthetic has been uneventful.[98]

All locations where general anesthesia is administered should contain a fully stocked MH cart with drugs and supplies, including 36 vials of dantrolene and preservative-free sterile water for injection. Dantrolene has a shelf life of 30 months. Each minute

BOX 32-5

Malignant Hyperthermia: Triggering and Nontriggering Agents

Triggering Agents
- All volatile inhalation anesthetics (desflurane, isoflurane, sevoflurane)
- Succinylcholine

Nontriggering Agents
- Local anesthetics
- Opioids
- Nitrous oxide
- Barbiturates, propofol, ketamine, etomidate
- Benzodiazepines
- Nondepolarizing skeletal muscle relaxants (vecuronium, atracurium, cisatracurium, pancuronium, rocuronium)
- Digoxin, tricyclic antidepressants, magnesium
- Anticholinesterase agents
- Anticholinergic agents

is critical in an MH emergency, so a dantrolene supply should not be shared with a nearby facility. Dantrolene should be kept in or very close to the operating room so it is available immediately if MH occurs.[96]

Diagnostic Testing

The most accurate and commonly accepted test available for determining MH susceptibility is the caffeine halothane contracture test (CHCT). This test involves taking a biopsy of skeletal muscle from the patient and measuring its contractile response to caffeine, halothane, or both. Normal muscle contracts in response to caffeine or halothane, but this is augmented in the patient with MH. The test is available at four medical centers in North America.[96] Because it must be completed within hours after muscle biopsy, the patient must travel to the testing site. Patients who have survived an unequivocal episode of MH are considered MHS. The CHCT is indicated for family members of an MHS patient or for patients who have had a previous suspicious but undiagnosed reaction to anesthesia.

An alternative to the caffeine halothane contracture test for confirmation of MH susceptibility is genetic testing and DNA-based mutation analysis.[129,130] Intensive investigations have focused on identifying the gene or genes responsible for MH. Most of the focus has been on searching for mutations in genes that encode the ryanodine receptor (RYR1), the dihydropyridine receptor, and associated proteins on chromosome 19. Currently, only about 25% of the people at risk for MH are reliably detected by genetic testing.[130,131] For other MHS patients, the molecular genetic basis for the disease may be more heterogeneous, involving mutations at various sites on different chromosomes.[100,132,133]

Postoperative Care

The patient who has experienced an acute MH episode should be admitted to and monitored in an intensive care unit (ICU) for at least 36 hours. For surgery performed outside a hospital setting, a transfer protocol to a hospital must be available. Intravenous dantrolene should be continued for a minimum of 24 hours, at approximately 1 mg/kg every 4 to 6 hours as a bolus dose or continuous infusion.[98] Recrudescence of an intraoperative episode may occur in 20% to 25% of cases.[95,134,135] In a review by Burkman et al.[135] of 63 cases of recrudescence after a MH reaction, the mean time from the initial reaction to recrudescence was 13 hours. Patients who experience recrudescence are more likely to have a muscular body type and to have had greater than 150 minutes transpire from induction to MH reaction.[98,135,136]

Masseter Muscle Rigidity

Masseter muscle rigidity (MMR), or trismus, is a sustained and forceful contracture of the masseter muscle. The contracture may be severe enough to make opening the jaw impossible ("jaws of steel"). A mild increase in masseter muscle tone or incomplete jaw relaxation after succinylcholine administration is fairly common and may be a normal response. However, if the patient experiences severe jaw tightness that interferes with jaw opening or generalized muscle rigidity after succinylcholine administration, the clinician should assume this is an MH event and immediately begin MH treatment.[95,96]

Clinical signs of MH appear in about 20% of cases of MMR.[98] Because MMR after succinylcholine administration may be a harbinger of MH, many authorities recommend discontinuing the anesthetic after MMR and postponing elective surgery until the patient is evaluated for MH.[95,96] For emergency procedures, the anesthesia may be cautiously continued with nontriggering agents, while assiduously monitoring for rhabdomyolysis and signs and symptoms of MH.[96]

Because of the likelihood of MH and/or rhabdomyolysis, the surgical patient should remain in the hospital and be observed for at least 24 hours in an ICU after marked jaw rigidity.[98] Myoglobinuria may be apparent following MMR, and inducing a brisk urine output is important to lessen the risk of myoglobinuric renal damage. Patients who have experienced MMR should be counseled concerning the possibility that they are MHS and should be referred to a well-informed primary or specialty care physician or genetic counselor for further investigation.

Information Resources

A clinical grading scale may be used to retrospectively determine whether a patient who responded abnormally to anesthesia is likely to have had an MH episode.[137] The Malignant Hyperthermia Association of the United States (MHAUS) provides educational and technical information to patients and healthcare providers. Information is available via fax-on-demand (1-800-440-9990) or on the World Wide Web at http://www.mhaus.org. An MH hotline may be accessed for MH emergencies 24 hours a day at 1-800-MH-HYPER (1-800-644-9737). Healthcare providers are encouraged to report MH episodes to the North American MH Registry of MHAUS.

Myotonic Dystrophy

The myotonia are a group of hereditary skeletal muscle diseases that include myotonic dystrophy, myotonia congenita, myotonia fluctuans, and paramyotonia congenita. A symptom common to all myotonias is the inability of skeletal muscles to relax after chemical or physical stimulation.

Myotonic dystrophy (dystrophia myotonica) is composed of at least two clinical disorders, type 1 (DM1) and type 2 (DM2), with overlapping phenotypes and distinct genetic defects. *Myotonic dystrophy, type 1*, also known as *Steinert's disease*, is the most severe and the most common, accounting for 98% of all cases of myotonic dystrophy.[138] DM1 and DM2 are characterized by skeletal muscles that are hypoplastic, dystrophic, and weak yet prone to persistent contraction. Although muscles are primarily affected, myotonic dystrophy is distinguished from nondystrophic myotonias by being a multisystem disease.[64,139]

Incidence

Myotonic dystrophy is inherited as an autosomal dominant trait. In most cases, an affected person has one affected parent. The onset of symptoms can occur at any age, but usually occurs in the second to third decade of life. A slow, progressive deterioration of skeletal, cardiac, and smooth muscle occurs, resulting in death due to skeletal muscle wasting and cardiac conduction defects.[140] Particularly with DM1, the severity of clinical symptoms increases with transmission to subsequent generations (*genetic anticipation*).[141] An estimated 1 to 4 in 20,000 people worldwide have myotonic dystrophy, with an equal occurrence in males and females.[76,138] Myotonic dystrophy is the most common and severe inherited muscular dystrophy that begins in adulthood.[138]

Pathophysiology and Treatment

Myotonia is a condition of muscle membrane excitability that results in self-sustaining muscle contraction. Skeletal muscle chloride and sodium channel dysfunction is implicated in aspects of myotonia.[76,140] Therapeutic agents used to treat the myotonic contractures include phenytoin, procainamide, tocainide, and mexiletine. These agents delay the return of membrane excitation

by blocking rapid Na^+ influx into muscle cells. Regional anesthesia and nondepolarizing muscle relaxants do not prevent or relieve the recalcitrant contraction.[46] No treatment is available for the muscle weakness that develops with myotonic dystrophy.

Clinical Manifestations

A wide variety of symptoms are characteristic of myotonic dystrophy. Facial weakness ("expressionless facies"), ptosis, and sternocleidomastoid muscle and distal limb weakness are prominent features.[64] Frontal balding, cataracts, and testicular atrophy in males form a frequently recognized triad of characteristics. Endocrine abnormalities, such as insulin resistance, occur with a greater frequency in this patient group than in the general population.[64]

Myotonia occurs in most symptomatic patients and may be worsened by pressure, touch, cold, or shivering.[46,64] Insidious muscle atrophy, particularly of the face, neck, pharynx, and distal limbs, causes severe muscle debility in the later stages of the disease.[64] Myotonic symptoms usually precede the atrophy and weakness.

Cardiac disturbances occur in most patients with myotonic dystrophy, often manifesting as conduction defects and arrhythmias.[64] Conduction defects were present in over 50% of the patients in one series.[142] First-degree atrioventricular block is the most common finding, but greater degrees of heart block are also seen.[64,143] Arrhythmias include sinus bradycardia, atrial flutter or fibrillation, and ventricular extrasystole.[64,142-144] Complete heart block and sudden cardiac death can occur.[64,143] Structural cardiac abnormalities increase with age, and include left ventricular systolic dysfunction, mitral valve prolapse, and regional wall motion abnormality.[145]

Weakening of the thoracic muscles, including the diaphragm and intercostal muscles, reduces the respiratory reserve and the vital capacity. A restrictive type of ventilatory impairment develops with progression of the disease. Central sleep apnea and hypersomnolence cause hypoventilation and decreased ventilatory response to carbon dioxide.

Anesthetic Implications

Any drug that has the potential to depolarize skeletal muscle may produce an exaggerated contraction in patients with myotonic dystrophy. Succinylcholine is avoided, because administration can produce an intense generalized myotonic contracture for several minutes, making ventilation and intubation difficult or impossible. Agents associated with myoclonus such as etomidate have the potential to produce similar effects.[46]

Nondepolarizing muscle relaxants may be used in these patients, as long as the degree of muscle wasting and weakness is appreciated.[140] The dose of the nondepolarizer should be reduced according to the degree of muscle impairment, and the neuromuscular block should be monitored closely with a peripheral nerve stimulator.

Reversal of neuromuscular blockade with anticholinesterase agents may theoretically precipitate skeletal muscle contraction by producing an ACh-induced depolarizing block.[36,46] Shorter-acting nondepolarizing muscle relaxants have the obvious advantage of being less likely to require reversal. The anesthetist should be mindful that peripheral nerve stimulation may induce an exaggerated muscle contraction and be misinterpreted as sustained tetanus.

An abnormal swallowing mechanism resulting from palatal, pharyngeal, and esophageal muscle involvement and gastrointestinal hypomotility renders myotonic dystrophy patients vulnerable to pulmonary aspiration of gastric contents.[46,146]

Hypothermia and shivering should be avoided by raising the room temperature, warming inhaled gases and intravenous fluids, and active warming with thermal warming devices.

Underestimating the severity of respiratory compromise is not uncommon in these patients. Pulmonary function results may serve as useful baselines in the patient with advanced disease. The respiratory depressant effects of barbiturates, opioids, and volatile anesthetics may compromise already weakened respiratory musculature and lead to unexpected decompensation.[46,147] In the patient with a history of hypersomnolence, even small doses of short-acting anesthetic agents may be associated with an exaggerated and prolonged anesthetic effect.[46] Speedy[148] reported on a typical case in which a 31-year-old man with myotonic dystrophy remained unconscious and unable to maintain a patent airway for 4 hours after receiving an anesthetic that consisted of 50 mg of propofol, 0.5% isoflurane, and 50% nitrous oxide in oxygen. Completely uneventful responses to general anesthesia in myotonic patients have also been reported. Regional anesthesia may be a prudent choice for anesthesia when appropriate.[46]

Diligent monitoring of cardiovascular parameters should be maintained intraoperatively and postoperatively. Cardiac function that was clinically normal preoperatively may become unacceptably depressed when general anesthetic agents are administered. The patient should be questioned preoperatively about syncope, and the ECG should be examined closely for advanced conduction blocks. It may be wise to assume that even asymptomatic patients have some degree of cardiac involvement. Transthoracic pacing should be readily available.[46]

Pregnancy may exacerbate the symptoms of myotonic dystrophy. Uterine atony, postpartum hemorrhage, and retained placenta have accompanied delivery in patients with myotonic dystrophy. Increased progesterone levels are linked to the deleterious effects.[149]

The risk of MH in patients with myotonic dystrophy is no greater than in the general population.[140] Although succinylcholine is avoided due to the risk of sustained muscle contraction, halogenated inhalational agents can be safely used in patients with myotonia dystrophy.[93]

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory polyarthropathy with myriad degrees of systemic involvement. The disease is multifactorial, and the clinical picture varies widely in severity, extent of involvement, and symptoms. The capricious course of the disease may be persistent and debilitating or relapsing and remitting.[150] With each successive exacerbation, new joints may become involved.

Incidence

Rheumatoid arthritis is the most common form of inflammatory arthritis, affecting 0.8% of the U.S. population. The onset of RA can occur at any age, but most cases are diagnosed in patients between the ages of 25 and 55 years. RA is two to three times more likely to develop in women than in men. The life expectancy of patients with RA may be reduced by 3 to 7 years.[36,150,151] Because RA patients are living longer due to improved treatments and understanding of the pathophysiology and more elderly patients are being diagnosed, the age of greatest prevalence of RA is increasing. One third of patients with RA are older than 60 years.[150-152]

Etiology

The exact cause of RA remains elusive, but heredity may contribute up to 50% of the risk for a person's susceptibility.[150,151]

Impaired immunity, stress, and other environmental factors may precipitate or aggravate the disease.[36,150]

A viral or a bacterial infection that alters the immune system in a genetically susceptible host may play a role in the etiology.[150] The invading microbe may produce a protein similar to those in the body's own tissue, particularly joint tissue *(molecular mimicry)*. To destroy the antigen, the immune system may mount an autoimmune response and mistakenly direct its attack against its own tissue. Circulating autoantibodies called *rheumatoid factors* are detectable in up to 90% of patients with RA.[36,150,151] Another antibody found in 34% of RA patients is one that attacks citrullinated proteins (CCP). This anti-CCP antibody found in inflamed joints may be useful as a biomarker for RA because it can be detected in the blood prior to onset of RA symptoms.[150,153]

Clinical Manifestations

Joint Involvement. Inflammation and destruction of synovial tissues are responsible for most of the symptoms and chronic disability associated with RA. One contributor to the inflammatory process is the overproduction of pro-inflammatory cytokines, tumor necrosis factor (TNF), caused by interactions between T and B lymphocytes, synovial-like fibroblasts, osteoclasts, and macrophages.[151,154] Joint involvement progresses in three main stages: (1) inflammation of the joint synovial membrane and infiltration by polymorphonuclear leukocytes; (2) rapid division and growth of cells in the joint (synovial proliferation and pannus formation); and (3) liberation of osteolytic enzymes, proteases, and collagenases, which damage small blood vessels, cartilage, ligaments, tendons, and bones. Collapse of normal cortical and medullary architecture leads to erosion and dislocation of bone that is contiguous with the inflammatory cell mass.[150,153]

The onset of symptoms is most often insidious, evolving over a period of weeks to months.[36,150] The most common sites of onset are the hands, wrists, and feet. There is often symmetric joint involvement. Swelling, warmth, and pain in the affected joints are caused by the inflammatory process. Morning stiffness, weight loss, and fatigue are noted early in the disease course.

Dissolution of bone and disuse atrophy of bone (osteoporosis) are found in all seriously affected areas. Pain, inflammation, and erosion of bone and tissue may permanently limit the joint's full range of motion. Later stages of the disease are characterized by severe pain, joint instability, loss of physical function, and crippling deformities.[150,154]

Nerve entrapment may occur at any site where peripheral nerves pass near the inflamed joint. Carpal tunnel syndrome is a common peripheral neuropathy.

Synovitis in the temporomandibular joint may limit jaw motion. An estimated 45% to 75% of patients with RA have involvement of the temporomandibular joint.[153] As the disease progresses, flexion contractures and soft-tissue swelling may lead to a marked limitation in the patient's ability to open the jaw.

Although the thoracic and lumbar spine are usually spared, involvement of the cervical spine may be extensive and can lead to limited movement or deformity of the neck and to severe laryngeal deviation.[36,150,155] The most common site of cervical spine synovitis is C1-C2 (Figure 32-17). Atlantoaxial (C1-C2) instability results from erosion and collapse of bone and from destruction of supporting cervical ligaments. Symptoms occur when excessive motion between C1 and C2 exerts pressure on the spinal cord (Figure 32-18). Additionally, separation of the atlanto-odontoid articulation may allow the odontoid process of the axis to impinge on the spinal cord, leading to neurologic damage. The atlantoaxial subluxation, which contributes to 66% of cervical spine disorders related to RA, may also exert pressure and impair blood flow through the vertebral arteries[156] (Figure 32-19).

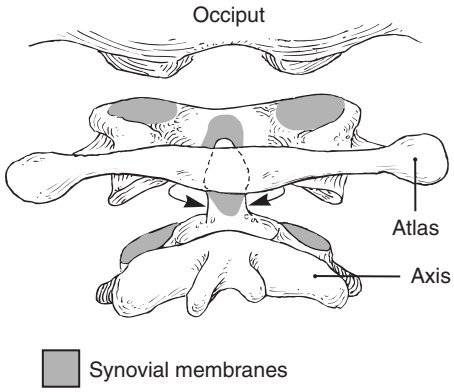

FIGURE **32-17** The relationship between the occiput, the atlas (C1), and the axis (C2). The atlas supports the head and rotates about the odontoid process of the axis. The occipitoatlantoaxial articulations are lined by synovial membranes and are firmly supported by surrounding ligaments (not shown).

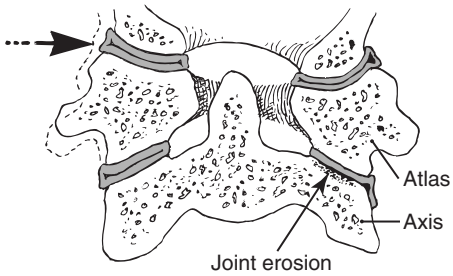

FIGURE **32-18** Erosion and collapse of C1 and C2 articular surfaces can lead to a shifting of the atlas over the axis. If the subluxation is pronounced, spinal cord compression may occur.

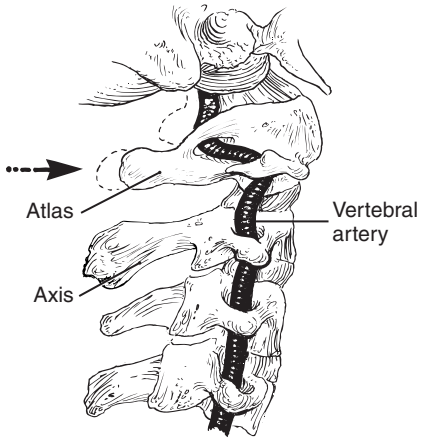

FIGURE **32-19** Vertebral artery compression may result from atlantoaxial subluxation.

Arthritis extends to the cricoarytenoid joint of the larynx in 26% to 86% of patients with severe RA.[157] The joint may become swollen, inflamed, and fixed in a position that obstructs airflow. Vocal cord nodules and polyps also may be present. Symptoms of cricoarytenoid arthritis include tenderness over the larynx, hoarseness, pain on swallowing, with radiation to the ear, and dyspnea or stridor. Patients with no overt clinical symptoms also may have significant laryngeal disease.

Systemic Involvement. Although the effects of RA are most clearly seen in joints, the disease is systemic. The immune-mediated destructive process affects a wide variety of organs, including the heart, lungs, muscle, vasculature, and eyes. The occurrence of extraarticular manifestations is usually associated with more active, erosive articular disease.

Firm, painless subcutaneous nodules occur in approximately 30% to 40% of patients with RA.[150] The nodules usually occur over pressure points, such as the occiput, the sacrum, the ulna, or the Achilles tendon, and may be associated with pressure ulcerations. Rheumatoid nodules also can occur in most visceral organs, including the lungs and the heart. Dural nodules can cause spinal cord compression and neurologic complications.

Pericarditis and pericardial effusion may accompany severe progressive RA and impair cardiac performance. Mitral regurgitation may occur related to cardiac valve fibrosis, and aortitis may cause aortic regurgitation.[36] Although rare, rheumatoid nodules have been isolated from the cardiac conduction system and may be associated with conduction defects.[36,150,151]

Pulmonary involvement manifests as pleural effusion, pneumonitis, pulmonary nodules, or interstitial fibrosis.[36,150,151,158] Decreased lung volume, diffusion capacity, and vital capacity may result from the lung alterations. Decreased arterial oxygenation may result from increased ventilation-perfusion mismatch.[158]

Rheumatoid myositis, which is characterized by muscle weakness and eventual muscle necrosis and atrophy, may accompany RA. Inflamed, painful, and underused joints contribute to the skeletal muscle atrophy.

Lacrimal duct and salivary gland destruction may result in dryness of the eyes and the mouth (Sjögren syndrome) in about 10% of patients with rheumatoid arthritis.[36,150]

Treatment

There is no cure for rheumatoid arthritis, and all treatment interventions are palliative. Medical therapy is directed toward relief of pain, nonspecific suppression of the inflammatory process, immunosuppression, prevention and correction of deformity, and control of systemic involvement.

Most patients, including those with mild to moderate disease, obtain some relief of symptoms with rest, joint immobilization, and use of nonsteroidal antiinflammatory drugs (NSAIDs). NSAIDs relieve joint pain, stiffness, heat, and swelling, in part by blocking cyclooxygenase and inhibiting prostaglandin, thromboxane, and prostacyclin synthesis. Despite their potent antiinflammatory properties, they do not alter the underlying disease process.[36,150,151]

Corticosteroids are potent antiinflammatory drugs that suppress many symptoms of RA. Long-term side effects (e.g., osteoporosis, predisposition to infection, suppression of endogenous cortisol release, cataracts, gastrointestinal bleeding, hypertension, and hyperglycemia), however, limit their use to isolated flares of the disease or to adjunctive rather than primary treatment.

Disease-modifying antirheumatic drugs (DMARDs), the primary treatment for RA, can slow the progressive damage and arrest the underlying disease process.[151] The antimetabolite methotrexate (Rheumatrex) is widely used as an effective DMARD for patients with aggressive RA. It stimulates adenosine release, which has an antiinflammatory effect. Bone marrow suppression, oral ulcerations, pneumonitis, and hepatic damage are potential side effects of methotrexate.[151] Gold salts, sulfasalazine, antimalarial drugs, and penicillamine are effective DMARDs used when more conservative, less toxic measures fail to retard symptoms.

Biologic DMARDs have been used to attach cytokines and cell-surface molecules. Agents such as the anticytokines etanercept (Enbrel), adalimumab (Humira), and infliximab (Remicade) work by interfering with the proinflammatory cytokine, tumor necrosis factor.[151,152] TNF inhibitors cause significant improvement in functional ability and alteration in disease progression. Notably, due to the immunosuppressive effect, these drugs increase the risk of developing serious infection, such as tuberculosis, especially when combined with corticosteroids. Increased risk includes bacterial to fungal to viral infections.[159-161]

Biologic agents such as interleukin-1 receptor antagonists offer the potential for more effective treatment of RA.[150,162] Leflunomide (Arava) is a DMARD that inhibits the proliferation of T lymphocytes and slows disease progression. The major side effect of leflunomide is liver-enzyme elevation and liver disease.[150] Agents target other pathogenetic molecules. Rituximab (Rituxan) is an anti-CD20 monoclonal antibody and works to deplete B cells. Abatacept (Orencia) alters T-cell activation. Tocilizumab (Actemra) is an interleukin-6 receptor antagonist. These are effective in some patients who do not respond to methotrexate treatment alone.[150,162]

Immunosuppressive drugs such as cyclophosphamide (Cytoxan) and cyclosporine (Sandimmune) and antimetabolites such as azathioprine (Imuran) are agents generally reserved for more refractory cases.[150]

Surgical interventions for relief of pain or correction or prevention of deformities include total joint replacement, synovectomy, and tenolysis.

Anesthetic Management

Overall, no individual anesthetic agent or mode of anesthesia is substantially safer than another for the patient with RA. Preoperative examination of an individual patient's disease course and medication history are likely to reveal specific features that affect the anesthesia or surgical course.

NSAID ingestion may result in platelet dysfunction. Mild anemia, a common finding in patients with RA, may be secondary either to the disease process or to drug therapy. Long-term NSAID therapy may exert harmful effects on the liver or kidney and exacerbate allergic rhinitis or asthma; these effects may influence the choice of anesthesia.

Patients receiving long-term corticosteroid therapy may develop hypophyseal-pituitary axis suppression, which may require perioperative steroid supplementation. Long-term administration of corticosteroids may increase the patient's susceptibility to infection by inhibiting normal host defense mechanisms. The tumor necrosis factor inhibitors are also associated with serious infections, mandating close attention to sterile techniques.

A thorough preoperative assessment of the airway is essential. Particular attention should be directed to the temporomandibular joints, cervical spine, and cricoarytenoid joints.

Range of motion of the temporomandibular joint must be assessed before anesthesia is induced. Patients with severe temporomandibular joint involvement may be unable to open their mouths more than 1 to 2 cm. In such cases, the use of a flexible fiberoptic bronchoscope or other optically guided instruments for tracheal intubation are of proven value.[36] Awake intubation with the aid of a intubating laryngeal mask airway using a superior laryngeal nerve block is an alternative.[157]

A thorough neurologic assessment and a radiographic evaluation of the cervical spine should be performed, especially for patients with advanced disease.[163] Atlantoaxial subluxation is radiographically confirmed as the distance from the anterior arch of the atlas to the odontoid process exceeding 3 mm.[36] Some patients with significant radiographic evidence of atlantoaxial or subaxial instability may be entirely asymptomatic.[150,163,164]

Neck pain is an early symptom of cervical spine instability. Paresthesias into the shoulders and arms, muscle weakness, paresis, and bowel or bladder dysfunction are some of the clinical manifestations of spinal cord compression secondary to atlantoaxial or subaxial subluxation. Compression on the vertebral arteries (see Figure 32-19), with interruption of vertebral artery blood flow, may cause symptoms including nausea, vomiting, dysarthria, dysphagia, blurred vision, or transient loss of consciousness. However, absence of preoperative symptoms does not guarantee cervical spine stability and safety.[156]

Altered cervical spine anatomy or laryngeal deviation can make intubation of the trachea an extreme challenge. Flexion deformity as well as cervical stiffness may interfere with positioning of the patient and the ability to perform direct laryngoscopy. Deviation of the larynx often can be detected preoperatively by palpating the location of the larynx in relation to the sternal notch. Anterior subluxation is enhanced by cervical flexion.[156] Flexion, extension, and rotation of the neck must be avoided in the presence of cervical instability. Such circumstances dictate alternative airway management such as fiberoptic-guided intubation of the trachea in the awake patient.

Hoarseness in a patient with RA should alert the anesthetist to possible cricoarytenoid joint involvement. Narrowing of the glottic opening may call for a smaller endotracheal tube. Laryngoscopy can assess normal cord motion and glottic patency. The vocal cords may be edematous and erythematous.[36] The patient should be observed closely for signs of airway obstruction after extubation.

Generalized demineralization of bone may increase the risk of fractures in patients with RA. Glucocorticoid therapy may aggravate the osteopenia. Proper patient positioning and padding of pressure points prevent nerve palsies, skin ulcerations, and further structural damage to the joints.

The spread of sensory spinal anesthesia is higher in RA patients. Epidural nodules and synovitis in the thoracolumbar spine may cause narrowing of the subarachnoid space and decrease the cerebrospinal fluid (CSF). The reduced dilution of the local anesthetic may contribute to the sensory effect averaging 1.5 dermatomes higher in a RA patient. The clinician should weigh the benefit of decreasing the dose of local anesthetic administered to a RA patient for a subarachnoid block with the risk of a insufficient block leading to conversion to general anesthesia.[165]

SUMMARY

Understanding the pathophysiologic characteristics, clinical presentation, and supporting laboratory studies of patients with musculoskeletal abnormalities is essential for safe and effective anesthetic management. A thorough preoperative assessment of this patient helps determine the extent of muscle, respiratory, and cardiac reserve and aids in anesthetic selection and planning for postoperative care.

Management of cases involving musculoskeletal pathology must take into account preoperative drug therapy for the disease and the potential effect this drug therapy may have on anesthetic agents and muscle relaxants. An anesthetic agent's margin of safety is often reduced in such patients; therefore fixed dosage regimens should be avoided.

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CHAPTER 33

The Endocrine System and Anesthesia

◆ *Mary C. Karlet and David N. Fort*

GENERAL PRINCIPLES OF ENDOCRINE PHYSIOLOGY

Body homeostasis is controlled by two major regulating systems: the nervous system and the endocrine or hormonal system.[1,2] Both of these systems communicate, integrate, and organize the body's response to a changing internal or external environment.[1,3]

Organs that secrete hormones are called *endocrine glands*; collectively, these glands make up the *endocrine system*. The purpose of the endocrine system is regulation of behavior, growth, metabolism, fluid and electrolyte status, development, and reproduction. To accomplish these complex processes, multiple hormones interact to produce precise biochemical and physiologic responses.

Endocrine glands secrete their hormone products directly into the surrounding extracellular fluid. This distinguishes them from *exocrine glands*, such as salivary or sweat glands, whose products are discharged through ducts. Important endocrine glands include the pituitary gland, thyroid gland, parathyroid glands, adrenal glands, pancreas, ovaries and testes, and placenta.

Hormones

Endocrine function is mediated by hormones. Hormones are the signaling molecules or chemical messengers that transport information from one set of cells (endocrine cells) to another (target cells). Hormones are released from endocrine glands into body fluids in minute quantities but exert powerful control over most metabolic functions.[1,4]

Transmission of a hormonal signal through the bloodstream to a distant target cell (e.g., pituitary gland to the adrenal gland) is called an *endocrine function*. If a hormone signal acts on a neighboring cell of a different type (e.g., pancreas α cells to pancreas β cells), the interaction is termed a *paracrine function*. If the secreted hormone acts on the producer cell itself or on neighboring identical cells, the interaction is called an *autocrine function*.[1,2]

Types of Hormones

Hormones can be classified into three major categories: (1) proteins or peptides, (2) amines or amino acid derivatives, and (3) steroids.

Peptide or Protein Hormones. Most hormones have a peptide or protein structure. This group of hormones includes insulin, growth hormone, vasopressin (antidiuretic hormone), angiotensin, prolactin, erythropoietin, calcitonin, somatostatin, adrenocorticotropic hormone, oxytocin, glucagon, and parathyroid hormone. Peptide hormones are synthesized in endocrine cells as prehormones and prohormones. They are processed by the cell and stored in secretory granules within the endocrine gland.[1,2] The proper stimulus to secretion causes exocytosis of the peptide or protein hormone into the extracellular fluid.

Protein hormones, such as insulin, erythropoietin, and growth hormone, can now be synthesized for therapeutic purposes by recombinant deoxyribonucleic acid (DNA) techniques.

Amine- or Amino Acid–Derivative Hormones. Several hormones are amino acid or amine compound derivatives. Serotonin, important for its central nervous system effects, is synthesized from the naturally occurring amino acid tryptophan.[2] Thyroid hormones and catecholamine hormones (dopamine, epinephrine, and norepinephrine) are derived from the amino acid tyrosine. Thyroid hormones and catecholamine hormones are stored in the thyroid gland and adrenal medulla, respectively, and are released by the appropriate stimulation.[1]

Steroid Hormones. All steroid hormones are lipid soluble derived from cholesterol or have a chemical structure similar to that of cholesterol.[4] Common steroid hormones include hormones of the adrenal cortex (e.g., cortisol, aldosterone) and reproductive hormones (e.g., estrogen, progesterone, testosterone). Active metabolites of vitamin D are also steroid hormones.[1] In contrast to most other hormones, steroid hormones are not stored in discrete secretory granules but are compartmentalized within the endocrine cell and released into the extracellular fluid by simple diffusion through the cell membrane.[1,2]

Circulating steroid and thyroid hormones are bound to *transport proteins*, whereas circulating catecholamine hormones and most protein hormones are not bound to carriers. Plasma protein binding protects hormones from metabolism and renal clearance.[2] The circulating half-life of steroid and thyroid hormones is therefore typically longer than that of peptide and catecholamine hormones. For example, the thyroid hormone thyroxine, which is 99.95% protein bound, has a plasma half-life of 6 days, whereas insulin, which has essentially no plasma protein binding, has a half-life of about 7 minutes.[1]

The major sites of hormone degradation and elimination are the liver and the kidneys. Some hormone degradation also occurs at target-cell sites.[1,2,4]

Hormone Receptors

Binding to a specific target-cell receptor is the primary event that initiates a hormone response.[2] The hormone receptor displays high specificity and affinity for the proper hormone ligand, and the location of the receptor directs the hormone to the specific target organ or target-cell site.[3] Some hormones, such as insulin and growth hormone, act on widespread target sites; others, such as thyroid-stimulating hormone, act on one target tissue.[1] After binding, the hormone-receptor complex induces a cascade of intracellular events that produce specific physiologic responses in the target cell.[2]

Hormone Receptor Activation. Hormone receptors are located either on the surface of cells or inside cells.[4] Receptors for protein, peptide, and catecholamine hormones are located in or on the surface of the target-cell membrane. Hormone binding to a cell membrane receptor triggers a response by activating

enzyme systems in or near the plasma membrane bilayer. The activated enzymes generate intracellular signals, called *second messengers*, which carry the hormone's message within the intracellular space.

Several different second-messenger systems operate in response to cell membrane receptor-hormone binding. Probably the most widely described second-messenger system is the *cyclic adenosine monophosphate (cAMP) system*. This hormone transduction mechanism is initiated when receptor occupation activates the plasma membrane enzyme *adenyl cyclase*. The membrane-bound adenyl cyclase then catalyzes the intracellular conversion of adenosine triphosphate (ATP) to cAMP; cAMP in turn becomes the hormone's intracellular messenger, activating intracellular enzymes, modifying cell-membrane permeability or transport, and altering cellular gene expression.[1] The enzyme phosphodiesterase catalyzes the hydrolysis of cAMP and terminates its intracellular actions. Hormones that use cAMP as their second messenger include thyroid-stimulating hormone, vasopressin, parathyroid hormone, glucagon, some catecholamines, corticotropin, follicle-stimulating hormone, and luteinizing hormone.

Other intracellular second messengers include calcium, diacylglycerol, inositol triphosphate, and cyclic guanosine monophosphate. The primary intracellular messenger has not been identified for many hormones.

In contrast to peptide and catecholamine hormones, thyroid and steroid hormones produce the desired target-cell response chiefly by interacting with specific intracellular hormone receptors.[1] Thyroid and steroid hormones are small lipophilic molecules that enter target cells by simple diffusion or by special transport mechanisms. Once within the cell, these hormones occupy specific intracellular receptors.[2] In combination with their receptors, the hormones interact with DNA in the cell nucleus to enhance or suppress gene transcription or translation.[1,2]

Thyroid and steroid hormones enable the cell to alter gene expression, protein formation, and cell activity in response to environmental and developmental stimuli.[2] Every hormone has a specific onset and duration of action.[4] Hormones that act by binding to cell membrane receptors (peptide, protein, and catecholamine hormones) usually generate a hormonal effect in seconds to minutes. Hormones that bind to intracellular receptors and activate the transcription processes of specific genes (thyroid and steroid hormones) may require several hours or even days to generate a hormonal response.[1,4]

Hormone Receptor Regulation. Receptors are dynamic molecules that are constantly being destroyed and replaced. The receptor for insulin, for example, has a normal half-life of only about 7 hours.[2] Hormone receptor destruction may be part of a normal endocrine response or part of an acquired or genetic disease state.

In many instances, the hormone receptor number is inversely related to the concentration of the circulating hormone. A sustained elevation of the plasma level of a given hormone may cause the target site to decrease the number of receptors per cell. This *down-regulation* of receptor number serves to decrease the responsiveness of a target cell to hormone excess.[1] The insulin resistance observed in obesity and type 2 diabetes mellitus may be partly explained by down-regulation of the insulin receptors in response to chronically high levels of circulating insulin.[2]

Conversely, a low circulating hormone concentration may cause the target gland to increase the number of hormone receptors per cell.[2] This *up-regulation* of hormone receptor number amplifies the cell's sensitivity to hormone stimulation.[1,2]

The number of receptors in a target cell usually changes from day to day.[4] Regulation of receptor turnover, and thus hormone receptor number, is a mechanism by which hormone activity can be precisely modulated.[1]

Regulation of Hormone Secretion. The synthesis and secretion of hormones by endocrine glands are regulated by three general control mechanisms: neural controls, biorhythms, and feedback mechanisms.

Neural control can evoke or suppress hormone secretion. Pain, emotion, smell, touch, injury, stress, sight, and taste can alter hormone release through neural mechanisms.[5] Glucagon, cortisol, antidiuretic hormone, and catecholamines, for example, are all stimulated by the stress response to anesthesia, surgery, and trauma.

The secretion of many hormones is governed by genetically encoded or acquired *biorhythms*. These intrinsic hormonal oscillations may be circadian (e.g., the daily variability in glucocorticoid secretion), weekly (e.g., the menstrual cycle), or seasonal (e.g., thyroxine production).[3,5] The biorhythms also may vary at different stages of development and life (e.g., growth hormone secretion).[6]

Feedback control is another sophisticated mechanism through which a hormonal response is controlled. Many endocrine disorders arise from the breakdown of feedback loops.[2] *Negative feedback* acts to limit or terminate the production and secretion of a given hormone once the appropriate response has occurred. Negative feedback of a target-cell product to the hormone producer (the endocrine gland) limits or prevents hormone excess. When concentrations of the product are low, feedback inhibition to the endocrine gland is lessened and hormone secretion enhanced.

Virtually all hormones are controlled by some type of *negative feedback* mechanism.[3,6] For example, parathyroid hormone is controlled by calcium, insulin and glucagon are controlled by glucose, and vasopressin is controlled by serum osmolarity.[5] The negative feedback mechanism is a very important factor in the regulation of hormones of the hypothalamus and pituitary gland. Hypothalamic hormones stimulate the release of pituitary hormones from the pituitary gland. The pituitary hormones in turn may stimulate an output of product from peripheral target cells. Product from peripheral target tissues may then initiate feedback to the pituitary gland or the hypothalamus to inhibit pituitary or hypothalamic hormone synthesis and discharge.[2,5]

Positive feedback is a less common hormone-regulating mechanism in which a given hormone response initiates signals amplifying hormone release. The surge in luteinizing hormone (LH) that precedes ovulation is stimulated by LH; this is an example of positive feedback.[2]

PITUITARY GLAND

Relationship Between Pituitary Gland and Hypothalamus

The *pituitary gland*, or *hypophysis*, is known as the "master endocrine gland."[7] It secretes hormones that have far-reaching effects on various homeostatic, developmental, metabolic, and reproductive functions of the body. The pituitary is a small endocrine gland (only 500 mg in weight and about the size of a pea) centrally located at the base of the brain. It is enclosed within a bony cavity of the sphenoid bone called the *sella turcica*.[5,6] The pituitary gland is connected to the overlying hypothalamus by the *hypophyseal stalk (pituitary stalk)*. The hypothalamus is located below the thalamus, behind the optic chiasm and between the optic tracts. The pituitary, hypothalamus, and some of the surrounding structures are shown in Figure 33-1.

The brain, via the hypothalamus, is an important regulator of pituitary gland secretion. The hypothalamus collects and

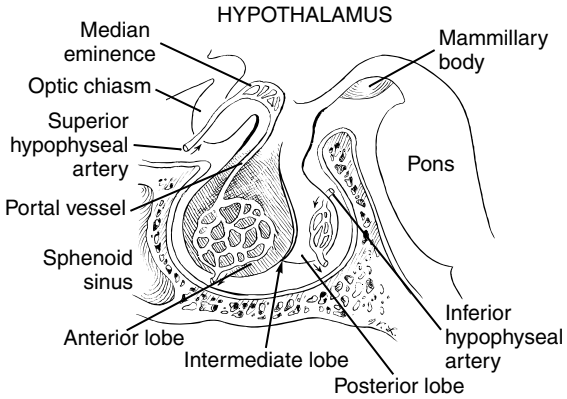

FIGURE **33-1** The pituitary gland is located at the base of the brain, enclosed within a cavity of the sphenoid bone called the *sella turcica*. It is connected to the overlying hypothalamus by the pituitary stalk.

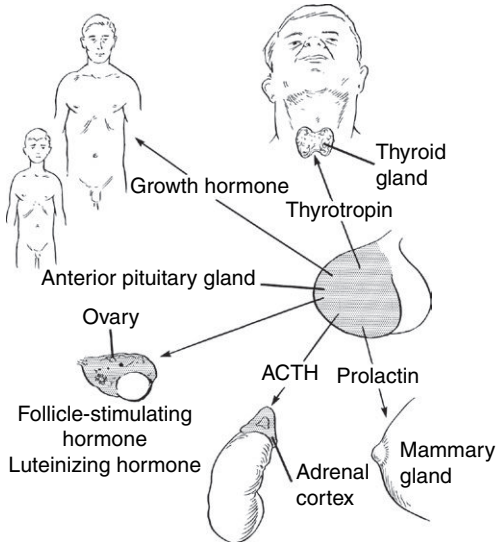

FIGURE **33-2** Major target sites for anterior pituitary hormones. *ACTH,* Adrenocorticotropic hormone.

integrates information (e.g., pain, emotions, energy needs, water balance, olfactory sensations, electrolyte concentrations) from almost all parts of the body and uses this information to control the secretion of vital pituitary hormones.[5,6] Pituitary hormone secretion also is regulated by feedback control from peripheral target-organ hormones or other target-organ products.[6] The pituitary gland and hypothalamus have virtually no blood-brain barrier, allowing feedback products to exert potent effects.[8,9]

Functionally and histologically, the pituitary gland is divided into two distinct portions: the *anterior lobe (adenohypophysis)* and the *posterior lobe (neurohypophysis)*.[5,6] The anterior pituitary lobe is embryologically derived from an upward invagination of pharyngeal epithelial cells. The posterior pituitary lobe develops from a downward outpouching of ectoderm from the brain. Blood supply to the pituitary is from the superior and inferior hypophyseal arteries.[5,7]

Anterior Pituitary Lobe

The anterior pituitary lobe, which constitutes about 80% of the pituitary gland by weight, secretes six primary hormones.[6] Target sites for the anterior pituitary hormones are shown in Figure 33-2.

1. *Growth hormone (GH, somatotropin)* promotes skeletal development and body growth and regulates protein and carbohydrate metabolism.
2. *Adrenocorticotropic hormone (ACTH)* regulates the growth of the adrenal cortex and the release of cortisol and androgenic hormones from the adrenal gland. ACTH possesses mild melanocyte-stimulating properties, resulting in skin pigmentation at high levels.
3. *Thyroid-stimulating hormone (thyrotropin* or *TSH)* controls the growth and metabolism of the thyroid gland and the secretion of thyroid hormones, which regulate the rates of most chemical reactions in the body.[5,6]
4. *Follicle-stimulating hormone (FSH)* stimulates ovarian follicle development in females and spermatogenesis in males.
5. *Luteinizing hormone (LH)* induces ovulation and corpus luteum development in females and stimulates the testes to produce testosterone in males.
6. *Prolactin* promotes mammary gland development and milk production (lactogenesis) by the breasts. Prolactin also exerts an effect on reproductive function by inhibiting the synthesis and secretion of LH and FSH. Prolactin synthesis is markedly increased during pregnancy.[5]

Several other less important or less well-defined hormones also are secreted from the anterior pituitary lobe.[6]

Anterior pituitary hormones are synthesized and secreted by five distinct endocrine cell types within the gland: *somatotrophs* synthesize GH; *gonadotrophs* synthesize the two gonadotropic hormones, LH and FSH; *thyrotrophs* synthesize TSH; *corticotrophs* synthesize ACTH; and *lactotrophs (mammotrophs)* synthesize prolactin. About 40% to 50% of the anterior pituitary cells are somatotrophs and about 20% are corticotrophs.[5]

Control of Anterior Pituitary Hormone Secretion

Synthesis of anterior pituitary hormones is controlled by signals from the hypothalamus. Neurosecretory cells in various hypothalamic nuclei respond to input from the body by synthesizing specific neurohormones that have corresponding anterior pituitary target-cell types.[6]

Hypothalamic neurohormones are released into a capillary bed of the hypothalamus in an area called the *median eminence*. The hypothalamic hormones travel from the capillary plexus of the median eminence, down the pituitary stalk, in a specialized vascular system called the *hypothalamic-hypophyseal portal vessels*. At the anterior pituitary lobe, the hypothalamic hormones are released in high concentrations into capillary sinuses located among the glandular cells.[6] The hypothalamic hormones then locate and bind to their specific target-cell type.

Specific hypothalamic hormones have either an inhibitory or a stimulatory effect on their corresponding anterior pituitary target cells. Synthesis and release of most anterior pituitary hormones depend on a positive stimulatory signal from a given hypothalamic hormone. Some anterior pituitary cells are subject to both inhibitory and stimulatory control by more than one hypothalamic neurohormone.[5]

Synthesis of prolactin from anterior pituitary lactotroph cells is unique in that it is tonically restrained by an inhibitory hormonal signal (dopamine) from the hypothalamus. In essence, dopamine serves as a "physiologic brake" for lactotroph growth and prolactin synthesis. The inhibitory effect of dopamine agonists, such as bromocriptine, is exploited therapeutically for suppressing pathologic production of prolactin from pituitary tumors.[5,7] Table 33-1 outlines the major hypothalamic releasing or inhibiting hormones and their corresponding anterior pituitary target sites.

TABLE 33-1 Hypothalamic Hormones and Corresponding Anterior Pituitary Hormones

Hypothalamic Releasing/ Inhibiting Hormones	Anterior Pituitary Target-Cell Type	Anterior Pituitary Hormone Produced	Hormone Target Site	Primary Peripheral Hormone Involved in Negative Feedback
Thyrotropin-releasing hormone	Thyrotroph	Thyroid-stimulating hormone (TSH, thyrotropin)	Thyroid gland	Triiodothyronine
Corticotropin-releasing hormone	Corticotroph	Adrenocorticotropic hormone (ACTH, corticotropin)	Zona fasciculata and zona reticularis of adrenal cortex	Cortisol
Gonadotropin-releasing hormone	Gonadotroph	Follicle-stimulating hormone Luteinizing hormone	Gonads (testes, ovaries)	Estrogen, progesterone, testosterone
Prolactin-releasing factor	Lactotroph (mammotroph)	Prolactin	Breasts	None
Prolactin-inhibitory factor (dopamine, PIF)	Lactotroph			None
Growth hormone–releasing hormone	Somatotroph	Growth hormone	All tissues	Growth hormone, insulin growth factor-1
Growth hormone–inhibitory factor (somatostatin)	Somatotroph	Growth hormone	All tissues	Growth hormone, insulin growth factor-1

Anterior Pituitary Disorders

Disorders involving the anterior pituitary system may be due to a defect at the peripheral endocrine gland (primary disorder), the pituitary gland (secondary disorder), or the hypothalamus (tertiary disorder).[5] Pituitary tumors account for 15% of all intracranial tumors.[10] Most pituitary tumors, both functional and nonfunctional, are benign adenomas. Pituitary carcinoma is exceedingly rare.[7,10]

Hyposecretion. Anterior pituitary hyposecretion may occur when large nonfunctional pituitary tumors (e.g., chromophobe adenoma, craniopharyngioma, Rathke's pouch cysts) compress and destroy normal anterior pituitary cells. Postpartum shock (Sheehan syndrome), irradiation, trauma, infiltrative disorders (e.g., sarcoidosis, amyloidosis) and hypophysectomy are other causes of pituitary hormone deficiency states. Generalized pituitary hypofunction *(panhypopituitarism)* is more common than reduced output of a single anterior pituitary hormone.[7,11]

Important effects of panhypopituitarism include a decrease in thyroid function due to reduction in levels of TSH, depression of glucocorticoid production by the adrenal cortex due to the lowering of ACTH levels, and suppression of sexual development and reproductive function due to deficient gonadotropic hormone secretion.[6] In addition, large pituitary tumors (macroadenomas greater than 1 cm) may extend into or compress the surrounding brain tissue, producing diplopia, visual loss, facial numbness, facial pain, or seizures.[12]

Surgical intervention may be implemented to control bleeding or for decompression or removal of the pituitary tumor. Surgical patients with hypopituitary disorders may require thyroid hormone replacement and glucocorticoid coverage in the perioperative period.[13] Because of the possibility of diabetes insipidus after removal of the tumor, vasopressin should also be available.

Hypersecretion. Most pituitary tumors are benign hypersecreting pituitary adenomas.[12] The three most common hypersecreting pituitary tumors are those that produce prolactin, ACTH, or GH. Tumors that secrete gonadotropin and thyrotropin hormones are rare. Pituitary tumors also may be inherited as part of multiple endocrine neoplasia (MEN) type 1.[10,14]

Preparation of the patient awaiting pituitary surgery is guided in part by the results of preoperative endocrine tests. Hypersecreting pituitary tumors may become so large that they compress and destroy normal anterior pituitary cells, producing a deficiency in some anterior pituitary hormones.

Prolactin-secreting tumors commonly produce symptoms of galactorrhea, amenorrhea, and infertility in women and decreased libido and impotence in men.[7] The dopamine agonist bromocriptine is used to control prolactin levels, decrease tumor size, and restore normal gonadal function. Patients who have a suboptimal response to medical therapy benefit from microsurgical removal of the pituitary tumor.[7]

Specific anesthetic management implications for patients with excess ACTH (Cushing disease) and excess GH (acromegaly) are described in this chapter.

Growth Hormone

Growth hormone (somatotropin) is synthesized and secreted by somatotroph cells of the anterior pituitary lobe and is under dual control by the hypothalamus.[6] Growth hormone–releasing hormone stimulates GH release, and growth hormone–inhibiting hormone *(somatostatin)* is a powerful inhibitor of GH release. Pulsatile fluctuations of the hypothalamic releasing and inhibiting hormones regulate somatotroph activity throughout the day.[5]

The GH secretion rate is generally increased in childhood, followed by a further increase in adolescence, a plateau in adulthood, and declining values in old age. The normal physical decline associated with aging may in part be due to the age-related decline in GH production.[5,6] In addition, GH secretion is stimulated by stress (including anesthesia and surgery), hypoglycemia, exercise, and deep sleep.[5]

Unlike the other anterior pituitary hormones, GH does not exert its principal effects through a specific target gland but functions through all or almost all tissues of the body; it promotes the growth and development of most tissues capable of growing.[6] A major target of GH is the liver, where it stimulates the production of insulin-like growth factor type 1 (IGF-1), a hormone that mediates many of GH's effects.[6,10] Skeletal muscle, the heart, skin, and visceral organs undergo hypertrophy and hyperplasia in response to GH and IGF-1.[10,15]

The most obvious effect of GH is on the skeletal frame. It produces linear bone growth by stimulating the epiphyseal cartilage or

growth plate at the ends of long bones.[5,6] Throughout childhood, under the influence of GH, bones elongate at the epiphyseal plate, and the skeletal frame enlarges. After puberty, the growth plates unite with the shaft of the bone, bone lengthening stops, and GH has no further capacity to increase bone length.[6]

GH and IGF-1 support growth by increasing amino acid transport into cells and enhancing protein synthesis in the cell. GH also decreases the catabolism of existing proteins by stimulating lipolysis and mobilizing free fatty acids for energy use, a protein-sparing effect.[6] In addition to its growth-promoting activities, GH is said to be a "diabetogenic hormone." It increases blood glucose levels by decreasing the sensitivity of cells to insulin and inhibiting glucose uptake into cells.[6]

As is true of other anterior pituitary hormones, GH secretion is subject to negative feedback control. The primary negative feedback controller of the pituitary somatotrope is IGF-1. GH itself, as well as IGF-1, exert negative feedback control on the hypothalamus. GH release is also inhibited by hyperglycemia and increased plasma free fatty acids.[5]

Hyposecretion. Deficient GH production in childhood can result in insufficient bone maturation and short stature, a condition known as *dwarfism*. Mild obesity, decreased lean body mass, and hypoglycemia are common in GH-deficient dwarfs. Puberty usually is delayed. Symptoms of GH deficiency may be the result of hypothalamic dysfunction, pituitary disease, failure to generate normal insulin growth factor hormones, or GH-receptor defects.[6,7]

The biosynthesis of human GH by recombinant DNA techniques has enhanced the outlook for patients with GH deficiency. Treatment of these patients with GH leads to a positive nitrogen balance, accretion of lean body mass, and an improvement in metabolic homeostasis.[7]

Hypersecretion. Hypersecretion of GH, usually caused by a growth hormone–secreting pituitary adenoma (99% of cases), can produce a highly distinctive syndrome in adults called *acromegaly*. Acromegaly is produced by sustained hypersecretion of GH after adolescence. The condition occurs with equal frequency in both sexes.[12] If hypersecretion of GH occurs before puberty—that is, before closure of the growth plates—the individual grows very tall (8 to 9 feet), a rare condition known as *gigantism*.

Because growth plates close with adolescence, the excessive production of GH associated with acromegaly does not induce bone lengthening but rather enhances the growth of periosteal bone by the stimulatory effects of GH on bone osteoblasts (bone forming cells). Periosteal growth causes new bone to be deposited on the surface of existing bone.[6] The unrestrained bone growth in patients with acromegaly produces bones that are massive in size and thickness. Bones of the hands and feet *(acral)* become particularly large. Overgrowth of vertebrae may cause kyphoscoliosis and osteoarthritis.

Soft-tissue changes are also prominent with GH hypersecretion. The patient develops coarsened facial features *(acromegalic facies)* that include a large, bulbous nose, supraorbital ridge overgrowth, dental malocclusion, and a prominent prognathic mandible.[10,16] The changes in appearance are insidious, and many patients do not seek treatment until the diagnosis is obvious and the disease course advanced.[10,16,17]

Overgrowth of internal organs is less apparent clinically but no less serious. The liver, heart, spleen, and kidneys become enlarged. Pulmonary function tests are consistent with increased lung volumes and extrathoracic obstruction, but gas exchange is usually not grossly abnormal.[17] Exercise tolerance may be limited due to increased body mass and skeletal muscle weakness.[7]

BOX 33-1

Common Features of Acromegaly

- Skeletal overgrowth (enlarged hands and feet, prominent prognathic mandible)
- Soft-tissue overgrowth (enlarged lips, tongue, and epiglottis; distortion of facial features)
- Visceromegaly
- Osteoarthritis
- Glucose intolerance
- Peripheral neuropathy
- Skeletal muscle weakness
- Extrasellar tumor extension (headache, visual field defects)

Cardiomyopathy and hypertension in patients with acromegaly can lead to symptomatic cardiac disease (e.g., diastolic dysfunction, congestive heart failure, arrhythmias).[13,17,18] Bi-ventricular concentric hypertrophy manifests early in the disease course.[7,10]

The insulin-antagonistic effect of GH produces glucose intolerance in most patients and frank diabetes in up to 25% of patients with acromegaly.[7]

Clinical manifestations resulting from the local effects of the expanding tumor may include headaches (55%), papilledema, and visual field defects (19%), which are caused by compression of the optic nerves and chiasm. Significant increases in intracranial pressure are uncommon. Compression or destruction of normal pituitary tissue by the tumor may eventually lead to panhypopituitarism.[7] Common features of acromegaly are summarized in Box 33-1.

Life expectancy in patients with acromegaly is decreased on average by about 10 years.[10] Most patients die of cardiovascular causes. Hormonal control has a definite impact on survival. Lowering serum GH to less than 2.5 mcg/L results in reduction of the mortality rate to levels comparable with the general population.[19,20]

Treatment for acromegaly is aimed at restoring normal GH levels. The preferred initial therapy for active acromegaly is microsurgical removal of the pituitary tumor, with preservation of the gland.[12] Surgery achieves biochemical cure (normalization of IGF-1 and a glucose-suppressed GH of less than 2 mcg/L) in about 70% to 90% of microadenomas (less than 1 cm). Cure rates for macroadenomas by surgery are much lower (about 50%).[7,10,21]

Surgical approach to the pituitary tumor most often is via the endonasal transsphenoidal route, and this route is generally well tolerated by most patients.[8,10,13] A transcranial approach may be used for very large tumors with suprasellar extension.[13]

For transsphenoidal pituitary surgery, the head of the bed is typically elevated 15 degrees to improve venous drainage.[13,22] The anesthetist should consider monitoring for venous air embolism, especially if cavernous sinus invasion by the tumor is suspected and the patient is positioned in a steep head-up tilt.[12] Infrequently, the approach and exposure of the tumor are associated with significant blood loss. The use of submucosal injection of epinephrine-containing solutions or topical vasoconstrictors to assist in hemostasis may result in large blood pressure increases.[23] An anesthetic technique that incorporates muscle relaxation and allows for smooth extubation and rapid neurologic assessment is desirable.[12] Nitrous oxide should be omitted from the anesthetic plan if air is injected surgically to aid with tumor visualization. Preparing the patient preoperatively for awakening with nasal

packing is a consideration for some cases. Surgical complications are not common, but may include epistaxis, transient diabetes insipidus, cranial nerve damage, symptomatic hyponatremia, and cerebral spinal fluid leaks.[22]

Surgical ablation is usually successful in rapidly reducing tumor size, inhibiting GH secretion, and alleviating some symptoms.[7,24]

Administration of octreotide or lanreotide (long-acting somatostatin analogs), pegvisomant (a GH-receptor antagonist), and gland irradiation are adjunctive treatments for tumor regression or treatment options for patients who are not surgical candidates.[10,18,21]

Anesthetic Implications of Acromegaly. Preanesthetic assessment of patients with acromegaly should include a careful examination of the airway. Facial deformities and the large nose may hamper adequate fitting of an anesthesia mask. Endotracheal intubation may be a challenge because of the patient's large and thick tongue (macroglossia), prognathism, enlarged thyroid gland, obstructive teeth, hypertrophy and distortion of the epiglottis, and general soft-tissue overgrowth in the upper airway.[8,13,17,25-27] Subglottic narrowing and vocal-cord enlargement may dictate the use of a smaller-diameter endotracheal tube. Nasotracheal intubation should be approached cautiously because of possible turbinate enlargement.[11] The occurrence of Mallampati III and IV grades is higher in patients with acromegaly, and the incidence of difficult intubations may be four to five times higher than patients without acromegaly.[24,26] Preoperative dyspnea, stridor, or hoarseness should alert the anesthetist to airway involvement.[11] Indirect laryngoscopy, computed tomography (CT) scan of the neck, and neck radiography may be performed for thorough assessment. If difficulties in maintaining an adequate airway are anticipated, optically guided intubation or fiberoptic-guided intubation in an awake patient is of proven value.[12,13,17] Equipment for tracheostomy should be available if airway changes are advanced.[12] The endotracheal tube should remain in place until the patient is fully awake and has total return of reflexes.

More than 60% of patients with acromegaly have a history of sleep apnea associated with upper airway obstruction.[13,17] Sleep apnea and the predisposition to airway obstruction in these patients makes assiduous perioperative monitoring of the patient's respiratory status an absolute precaution.[12,18]

The frequent occurrence of cardiac arrhythmias, coronary artery disease, and hypertension in acromegalic patients warrants a thorough preanesthetic cardiac evaluation. Hyperglycemia may complicate the perioperative period, mandating careful perioperative monitoring of blood glucose and electrolyte levels.[17,18]

If preoperative assessment reveals impairment of the adrenal or thyroid axis, stress-level glucocorticoid therapy and thyroid replacement should be implemented in the perioperative period.

Entrapment neuropathies, such as carpal tunnel syndrome, are common in patients with acromegaly.[7] If arterial access is required, an Allen test should be performed before placement of a radial artery catheter; hypertrophy of the carpal ligament may cause inadequate ulnar artery flow. Alternatively, catheterization of other arterial sites should be considered.[11]

Posterior Pituitary Lobe

The posterior pituitary lobe secretes two important peptide hormones: *antidiuretic hormone (arginine vasopressin* or *ADH)* and *oxytocin*. Oxytocin and ADH are structurally very similar, but they have quite different actions. ADH controls water excretion and reabsorption in the kidney and is a major regulator of serum

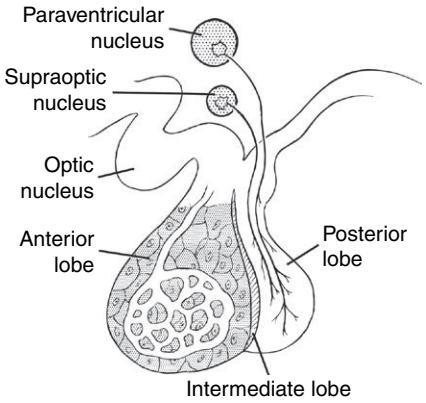

FIGURE **33-3** Nerve fibers arising from the supraoptic nucleus and the paraventricular nucleus transport antidiuretic hormone and oxytocin to the posterior pituitary.

osmolarity. Oxytocin stimulates contraction of myoepithelial cells of the breast for milk ejection during lactation. It also powerfully stimulates uterine smooth muscle contraction.[5] Oxytocin and its derivatives are used clinically for inducing labor and decreasing postpartum bleeding.

In contrast to the anterior pituitary lobe, which communicates with the hypothalamus via a vascular system, the posterior pituitary lobe communicates with the hypothalamus through a neural pathway. Unlike anterior pituitary hormones, posterior pituitary hormones are not synthesized within the pituitary gland itself but rather within two large nuclei of the hypothalamus, the *supraoptic nucleus* and the *paraventricular nucleus*. ADH is chiefly synthesized in the supraoptic nucleus and oxytocin in the paraventricular nucleus.[5,6] As shown in Figure 33-3, nerve fibers arising from these hypothalamic nuclei transport ADH and oxytocin down the pituitary stalk by axoplasmic flow to the posterior pituitary lobe. There, the hormones are stored in secretory granules at the nerve terminals. With proper excitation, nerve impulses originating in the cell bodies of the supraoptic or paraventricular nucleus are transmitted down the pituitary stalk and stimulate the release of ADH or oxytocin from the posterior pituitary lobe. The hormones then diffuse into nearby blood vessels and are transported to their distant target sites.

Three types of vasopressin receptors have been identified: V1, V2, and V3. Activation of receptor V1 mediates vasoconstriction. V2 receptors mediate water reabsorption in the renal collecting ducts. V3 receptors are found within the central nervous system and their stimulation modulates corticotrophin secretion.[9]

Antidiuretic Hormone

ADH is the body's principal preserver of water balance. It acts on V2 receptors on renal collecting ducts to increase the absorption of solute-free water through water channels called *aquaporins*. The integrated role of thirst, vasopressin, and renal response conserve water in the body and support normal body-fluid osmolarity. Plasma osmolarity is physiologically controlled within a small range (285 to 290 mOsm/L).[9] Without ADH, the collecting ducts are impermeable to water reabsorption; in this setting, water loss in the urine is excessive, and serious dehydration is provoked.[6]

ADH acts primarily to increase urine osmolarity, decrease serum osmolarity, and increase blood volume.[6] Additionally, high levels of ADH stimulate V1 receptors and cause potent systemic

vasoconstriction, especially in coronary, splanchnic, and renal vascular beds. ADH-induced vasoconstriction of vascular beds has been exploited therapeutically for the control of vasodilatory shock, hemorrhage, and sepsis.[9] Current advanced cardiac life support protocols recommend vasopressin as an adrenergic alternative to epinephrine for promoting the return of spontaneous circulation after cardiac arrest. Desmopressin (1-deamino-8-D-arginine vasopressin [DDAVP]), a synthetic arginine analog of ADH, increases circulating levels of von Willebrand factor and factor VIII, and is used to reverse coagulopathy associated with platelet adhesion defects.[9]

Consonant with its role of maintaining normal fluid homeostasis, ADH is secreted in response to an increase in plasma osmolarity or plasma sodium ion concentration, a decrease in blood volume, or a decrease in blood pressure.[6]

The osmolarity of body fluids is the main variable controlling ADH secretion. Serum osmolarity changes are sensed by hypothalamic *osmoreceptors*, which in turn alter ADH synthesis and secretion.[5] The plasma *osmotic threshold* for ADH release is only 2% to 4% higher than normal plasma osmolarity.[5,28] When the plasma tonicity increases even subtly, healthy individuals release ADH into the blood.

The interplay between ADH and water is controlled by a delicate negative feedback loop. Water deprivation (increased plasma osmolarity) initiates signals in the hypothalamic osmoreceptors that cause ADH release from the pituitary gland to increase three- to five-fold. ADH, in turn, enhances renal tubular water reabsorption, dilutes the extracellular fluid, and restores normal osmotic composition.[6] Conversely, water ingestion (decreased plasma osmolarity) suppresses the osmoreceptor signal for ADH release.

A 10% to 20% decrease in blood volume or blood pressure also provokes ADH release.[28] Changes in blood volume are sensed in peripheral baroreceptors (especially the great veins and pulmonary vessels) and atrial stretch receptors. When these baroreceptors sense underfilling (volume depletion), they transmit afferent signals through vagal and glossopharyngeal nerves to the hypothalamus.[5,28] The hypothalamus responds by increasing ADH synthesis and stimulating ADH release.

The perioperative period is characterized by enhanced ADH secretion.[29,30] Pain, emotional stress, nausea, hemorrhage, and various drugs can be potent stimuli to ADH release. Positive-pressure ventilation enhances ADH release by reducing central blood volume.[8] The mild hyponatremia sometimes observed postoperatively may be at least partly explained on the basis of ADH action. Box 33-2 lists factors that stimulate ADH release or enhance the action of ADH at the renal tubules.[11]

Thirst provides a second line of defense of water balance. The *thirst threshold* is set about 5% higher than the osmotic threshold for ADH.[6,28]

Deficient Antidiuretic Hormone and Anesthetic Implications. Inadequate ADH secretion from the posterior pituitary lobe or the inability of renal collecting duct receptors to respond to ADH (impaired receptor sensitivity) results in a disorder called *diabetes insipidus (DI)*. Decreased ADH release produces *neurogenic or central DI*, and renal tubular resistance to vasopressin is termed *nephrogenic DI*.[28]

Common causes of neurogenic DI include severe head trauma, neurosurgical procedures (e.g., trauma to the median eminence, pituitary surgery), infiltrating pituitary lesions, and brain tumors.[28] Neurogenic DI that develops after pituitary surgery is usually transient and often resolves in 5 to 7 days.[8,13]

BOX 33-2

Stimulators of Antidiuretic Hormone Enhancement or Release

- Increased plasma sodium ion concentration
- Increased serum osmolarity
- Decreased blood volume
- Decreased blood pressure
- Smoking (nicotine)
- Stress
- Pain
- Nausea
- Vasovagal reaction
- Various medications (chlorpropamide, clofibrate, thiazide diuretics, carbamazepine, nicotine, cyclophosphamide, vincristine, morphine, high-dose oxytocin)
- Angiotensin II
- Positive-pressure ventilation

Nephrogenic DI may occur in association with genetic mutations, hypercalcemia, hypokalemia, and medication-induced nephrotoxicity.[28] Ethanol, demeclocycline, phenytoin, chlorpromazine, and lithium all inhibit the action of ADH or its release.[8]

The hallmark of DI is polyuria. The inability to produce a concentrated urine results in dehydration and hypernatremia. The syndrome is characterized by a low urine osmolarity (less than 300 mOsm/L), urine specific gravity less than 1.010, and urine volumes greater than 2 mL/kg/hr.[28] The tremendous urinary water loss produces serum osmolarities greater than 290 mOsm/L and serum sodium concentrations greater than 145 mEq/L. Neurologic symptoms of hypernatremia and neuronal dehydration may be present and include hyperreflexia, weakness, lethargy, seizures, and coma.[28]

The thirst mechanism assumes a primary role in maintaining water balance in awake patients with DI. Ingestion of large volumes of water prevents serious hyperosmolarity and life-threatening dehydration.[8]

Treatment protocols for DI depend on the degree of ADH deficiency. Most patients have incomplete DI and retain some capacity to concentrate their urine and conserve water. Mild cases (incomplete DI) may be treated with medications that either augment the release of ADH or increase the receptor response to ADH. These drugs may include chlorpropamide (sulfonylurea hypoglycemic agent), carbamazepine (anticonvulsant), and clofibrate (hypolipidemic agent).

Significant deficiency (plasma osmolarity levels greater than 290 mOsm/L) may be treated with various ADH preparations. Desmopressin (DDAVP), a selective V2 agonist, is often a preferred agent because it has less vasopressor activity, a prolonged duration of action (8 to 12 hours), and enhanced antidiuretic properties.[9,28] DDAVP may be administered nasally, intravenously, subcutaneously, and orally. Dosages for nasal application range from 5 to 40 mcg/day. Subcutaneous dosages are 0.5 to 2 mcg twice daily.

Perioperative administration of vasopressin is usually not necessary in the patient with partial DI, because the stress of surgery causes enhanced ADH release.[8,30] The surgical patient with a total lack of ADH (complete DI) may be managed with desmopressin (1 mcg subcutaneously) or aqueous vasopressin (an intravenous bolus of 0.1 unit, followed by a continuous intravenous infusion of

TABLE 33-2 Syndrome of Inappropriate Antidiuretic Hormone (SIADH) and Diabetes Insipidus (DI)

	SIADH	DI
Serum osmolarity	Less than 270 mOsm/L	Greater than 290 mOsm/L
Serum sodium	Less than 130 mEq/L	Greater than 145 mEq/L
Urine volume	Low	High (greater than 2 mL/kg/hour)
Urine osmolarity	Hypertonic urine relative to plasma	Hypotonic urine relative to plasma
Treatment	Fluid restriction If patient symptomatic or serum Na^+ less than 115-120 mEq/L, consider hypertonic saline	DDAVP or vasopressin

DDAVP, 1-deamino-8-D-arginine vasopression.

vasopressin at 0.1 to 0.2 unit/hr).[8] Caution is advised when administering these drugs to patients with coronary artery disease or hypertension because of the arterial constrictive action of ADH.[28]

Plasma osmolarity, urine output, and serum sodium concentration should be measured hourly during surgery and in the immediate postoperative period.[8]

Isotonic fluids can generally be administered safely during the intraoperative period. If, however, the plasma osmolarity rises above 290 mOsm/L, hypotonic fluids should be considered and the vasopressin infusion increased above 0.2 unit/hr.[8]

Preoperative assessment of the patient with DI includes careful appraisal of plasma electrolytes (especially serum sodium), renal function, and plasma osmolarity. Dehydration will make these patients especially sensitive to the hypotensive effects of anesthesia agents. Intravascular volume should slowly be restored preoperatively over a period of at least 24 to 48 hours.

Hypersecretion of Antidiuretic Hormone and Anesthetic Implications. The *syndrome of inappropriate antidiuretic hormone (SIADH)* secretion is a disorder characterized by a high circulating vasopressin level relative to plasma osmolarity and serum sodium concentration. With SIADH, the kidneys, under ADH stimulation, continue to reabsorb water from the renal tubules despite the presence of hyponatremia and plasma hypotonicity. [8] Hormone-induced water reabsorption causes expansion of intracellular and extracellular fluid volumes, hemodilution, and weight gain. The urine is hypertonic relative to the plasma, and urine output is typically low. Table 33-2 compares SIADH and DI.

Clinical features of SIADH reflect water intoxication, dilutional hyponatremia, and resulting brain edema.[28] The swelling of brain cells may cause lethargy, headache, nausea, mental confusion, seizures, and coma. Hypertension and peripheral edema are not common. The severity of symptoms is related to the degree of hyponatremia and the rate of decrease of serum sodium.[31]

Inappropriate hypersecretion of ADH can result from various pathologic processes, including hypothyroidism, pulmonary infection or carcinoma, head trauma, intracranial tumors, and after pituitary surgery.[11] Secretion of ADH by neoplasms, especially small-cell carcinomas of the lung, is a common cause of SIADH.[8] The ectopic ADH produced by these tumors is identical to the ADH of hypothalamic origin. Certain drugs are associated with enhanced ADH secretion or response; these include carbamazepine, tricyclic antidepressants, chlorpropamide, cyclophosphamide, oxytocin, nicotine, and clofibrate.[28]

The patient with mild SIADH not associated with symptoms of hyponatremia is often managed effectively with fluid restriction of 800 to 1000 mL/day with 0.9% normal saline.[13,32] Patients with acute severe hyponatremia (plasma Na^+ less than 115-120 mEq/L) or acute neurologic symptoms may require more aggressive treatment with an intravenous infusion of hypertonic (3%) saline, with or without a loop diuretic.[28,32,33] To prevent acute loss of brain water and possible permanent neurologic damage (*central pontine demyelination syndrome*), the plasma sodium concentration must be corrected slowly. Many investigators recommend that acute hyponatremia be corrected at a rate not to exceed 1 to 2 mEq/L/hr or 6 to 8 mEq/L in 24 hours.[11,12] An intravenous infusion of hypertonic (3%) saline at a rate of 70 mL/70 kg/hr will increase the serum sodium level by approximately 1 mEq/L/hr.[31,33] Serum sodium levels should be measured at least every 2 hours during treatment.[28]

Demeclocycline, a tetracycline antibiotic, has been used to treat chronic SIADH by antagonizing the effects of vasopressin on the renal tubules.[8,28] Definitive treatment for SIADH is directed at the underlying disorder.

Clinical assessment of the patient's volume status is an essential part of the preoperative evaluation. Perioperative fluid management of the surgical patient with SIADH can usually be accomplished with fluid restriction that involves the use of isotonic solutions.[8] Estimating central volume status on the basis of central venous pressure measurements can help guide fluid replacement. Frequent determinations of urine output, urine osmolarity, plasma osmolarity, and serum sodium concentrations also can help direct fluid management. Nausea should be prevented, because it is a potent stimulus of ADH release.[28]

PARATHYROID GLAND

The parathyroid glands are small (approximately 3 × 6 × 2 mm) oval bodies located on the posterior surface of the thyroid gland. Most individuals have four parathyroid glands, one on each pole of the thyroid, but approximately 6% of individuals have five glands and 13% have only three. Blood supply to the parathyroid glands is via the inferior thyroid arteries.[34]

Calcium Regulation

The adult human body contains about 1 to 2 kg of the divalent cation calcium. Approximately 99% of the calcium exists in the bony skeleton, and only about 1% is in the extracellular space and soft tissues.[34-36] Bone therefore serves as a large reservoir that can store or release calcium as needed. Intracellular calcium is 10,000 times lower than ionized calcium concentration in the extracellular fluid.[35,36]

The concentration of the total serum calcium is tightly regulated within a range of about 8.6 to 10.6 mg/dL.[37] Serum calcium exists in three different forms (Figure 33-4):

1. Approximately 9% exists in a nonionized, chelated form. This calcium is bound to diffusible anions such as citrate, bicarbonate, and phosphate.
2. Approximately 41% is combined with plasma proteins (primarily albumin) in a nonionized, nondiffusible complex.
3. Approximately 50% exists in an ionized and diffusible form (normal level 4.7 to 5.2 mg/dL).

Only the free, ionized form of calcium exerts physiologic effects, hence measurement of serum ionized calcium levels provides the most clinically relevant determination.[34,35] Ionized calcium

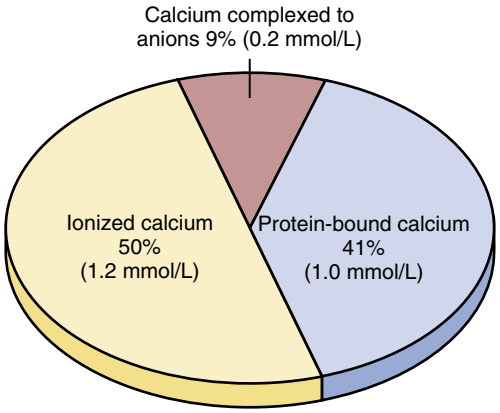

FIGURE **33-4** Serum calcium exists in three different forms: ionized, bound to serum proteins, and bound to diffusible anions. Only the ionized form of calcium exerts physiologic effects. (From Hall JE. *Guyton and Hall Textbook of Medical Physiology*. 12th ed. Philadelphia: Saunders; 2011:956.)

performs a wide range of vital physiologic functions, including hemostasis (platelet aggregation, blood coagulation), muscle contraction, neurotransmission, bone formation, cell division, and many other aspects of cell function. Even small changes in calcium levels can cause extreme and immediate physiologic effects.[34]

Total blood calcium levels may not always reflect the ionized calcium status. Changes in serum protein levels can alter total blood calcium levels without altering ionized calcium values. Changes in total calcium levels parallel the serum albumin.[35] A decrease in serum albumin causes an associated decrease in total serum calcium levels.

Alterations in the pH of blood affect ionized calcium levels. Plasma proteins are more ionized in an alkaline pH, providing an increase in the number of anion-binding sites for the positively charged calcium. Alkalosis decreases ionized serum calcium by increasing protein-calcium binding. Acidosis, on the other hand, increases ionized serum calcium by decreasing calcium-protein binding.[35,36]

Two principal hormones, vitamin D and parathyroid hormone (PTH), operate in concert to regulate the plasma concentration of calcium. Both vitamin D and PTH raise serum calcium levels, but of the two, PTH has by far the strongest effect.

Vitamin D

Vitamin D compounds ingested from food or formed by the action of ultraviolet light on the skin are inactive prohormones.[35,37] Inactive vitamin D, called *cholecalciferol*, is converted by a series of reactions in the liver and kidneys to an active metabolite. The final step in the conversion of vitamin D to an active form is controlled in the kidneys by PTH.[37] The in vivo conversion of inactive vitamin D to the final active product, *1,25-dihydroxycholecalciferol*, is shown in Figure 33-5.

Active vitamin D increases plasma calcium, magnesium, and phosphate ion concentrations by promoting their absorption across the intestinal epithelium to the extracellular fluid.

Inadequate vitamin D intake or absorption, or insufficient exposure to sunlight, can lead to poor intestinal absorption of calcium and phosphate. In children, the resulting calcium and phosphate deficiency leads to defective mineralization of bone, a condition known as *rickets*.[34,35] In adults, vitamin D deficiency results in impaired bone mineralization, a condition known as *osteomalacia*.[34,36]

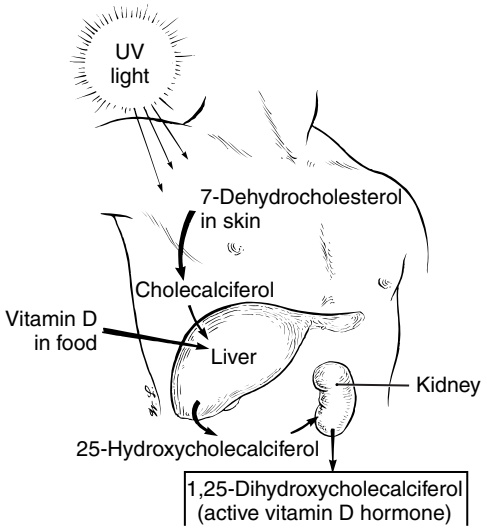

FIGURE **33-5** Conversion of cholecalciferol or vitamin D to an active form (1,25-dihydroxycholecalciferol) involves hydroxylation in the liver and kidneys. Active vitamin D is important in transporting calcium across the gastrointestinal tract. *UV,* Ultraviolet.

Parathyroid Hormone

PTH is secreted from *chief cells* of the parathyroid gland in response to low serum ionized calcium concentrations. Hyperphosphatemia (indirect effect) and acute hypomagnesemia also stimulate PTH secretion.[36]

PTH is the body's major hormonal regulator of calcium and phosphate metabolism. In PTH, the body possesses an extremely potent negative feedback agent for controlling serum calcium levels. In general, PTH increases the extracellular calcium concentration and decreases the extracellular phosphate concentration.[37] A small decline in the level of circulating ionized calcium produces a rapid increase in PTH secretion from the parathyroid glands. A sustained deficit in serum calcium levels (e.g., lactation, pregnancy) produces hypertrophy of the parathyroid glands, sometimes five-fold or greater, in order to maintain adequate PTH output.[34,36]

An elevation in serum calcium ion concentration produces an abrupt decline in PTH synthesis and output. Conditions associated with chronic elevations of serum calcium (e.g., immobility, malignancy, Paget disease) provoke a blunted PTH output and a diminution in gland size. In contrast to *acute* magnesium deficiency, parathyroid gland function and PTH secretion are inhibited by severe and *chronic* hypomagnesemia.[36,37]

The increase in serum calcium level in response to PTH secretion is the result of the hormone's direct effect on bone and the kidney and its indirect effect on the intestinal tract (Figure 33-6).

Effect on Bone. Bone is a living tissue that is constantly being remodeled.[35] In the healthy adult, bone-forming cells called *osteoblasts* are balanced by bone-destroying cells called *osteoclasts*.[34] Exchangeable calcium salts in bone serve as a large, rapid buffer that play a vital role in extracellular fluid calcium homeostasis. In addition to calcium, bone also provides an important reservoir for other ions such as magnesium and phosphorus.[34,36]

The most pronounced immediate control of blood calcium is due to PTH effects on bone.[37] When ionized serum calcium levels decline, PTH is released and acts directly on bone to mobilize skeletal calcium stores.[35] PTH promotes the activation and proliferation of osteoclasts, stimulating rapid absorption of calcium (and phosphate) from bone tissue to the extracellular fluid. Over time, abnormally high levels of circulating PTH can produce extensive absorption of calcium from the bone matrix.[34,37]

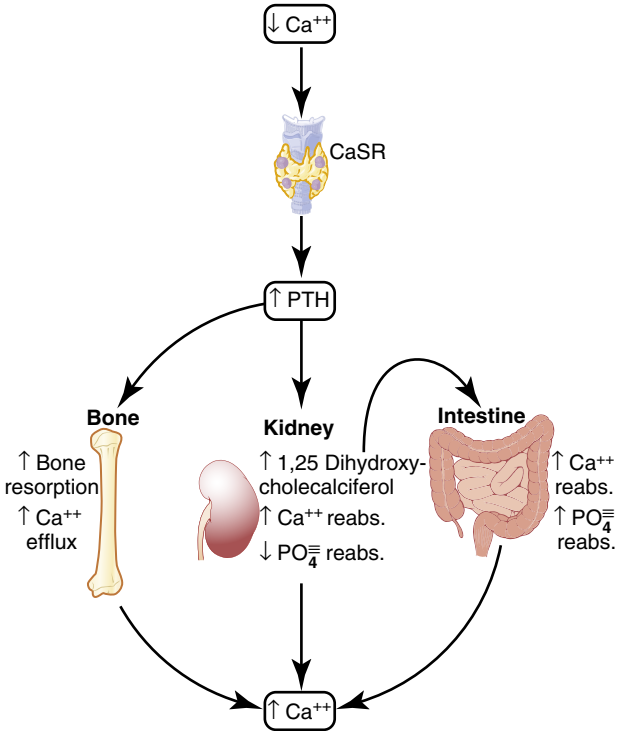

FIGURE **33-6** Summary of the effects of parathyroid hormone (PTH) on bone, the kidneys, and the intestine. CaSR, Calcium-sensitive receptor. (From Hall JE. *Guyton and Hall Textbook of Medical Physiology*. 12th ed. Philadelphia: Saunders; 2011:956.)

The reservoir of calcium in bone is about 1000 times greater than the amount of calcium in the extracellular fluid. Only after sustained PTH activation, therefore, does bone erosion and destruction become apparent. With protracted PTH stimulation, however, the bones eventually become severely depleted of calcium.[34]

An increase in extracellular fluid calcium causes PTH levels to decline. Decreased PTH levels stimulate rapid deposition of calcium and phosphate bone salts, an effect that lowers serum calcium levels back to normal.

Effect on the Intestinal Tract. Parathyroid hormone indirectly enhances both calcium and phosphate absorption from the intestines by promoting formation of 1,25-dihydroxycholecalciferol, the active form of vitamin D. When the plasma calcium level is low, PTH stimulates 1α-hydroxylase, an enzyme in the kidney necessary for the formation of 1,25-dihydroxycholecalciferol. Active vitamin D in turn increases intestinal absorption of calcium and phosphate.[35]

In the absence of PTH, or in the presence of severe kidney disease, 1,25-dihydroxycholecalciferol is not formed, and the effect of vitamin D on calcium and phosphate regulation is lost. Patients with chronic renal failure often suffer from hypocalcemia, in part because the diseased kidneys lose their ability to form active vitamin D. Consequently, these patients are unable to absorb a sufficient amount of calcium from the gastrointestinal tract.[37]

Effect on the Kidney. PTH has two major effects on the kidney: it increases calcium reabsorption, and it increases phosphate excretion. PTH elevates serum calcium by augmenting the reabsorption of calcium from nephron tubules to the extracellular fluid. The major site of PTH-mediated calcium reabsorption is the distal convoluted tubule.[34,37]

Accompanying calcium reabsorption is enhanced phosphate excretion. PTH promotes phosphaturia by reducing phosphate ion reabsorption from the proximal convoluted tubule. The PTH-mediated phosphate loss from the kidney is generally strong enough to overcome the PTH-induced phosphate absorption from bone and intestines.[34]

Calcitonin

Calcitonin is a hormone secreted from the thyroid *parafollicular cells*, or C *cells*, in response to elevated serum ionized calcium.[35] It has an effect opposite that of the PTH system, lowering the serum ionized calcium concentration. Calcium levels are reduced by a calcitonin-mediated inhibition of bone osteoclasts, which shifts the balance toward osteoblasts and bone deposition.[35,37]

The serum calcium–lowering effect of calcitonin is weak. Its effect in lowering serum calcium is rapidly outweighed by the more powerful activity of PTH.[34] The rather weak effect of calcitonin is demonstrated by the observation that removal of the thyroid gland causes no significant alterations in bone density or long-term serum calcium levels.[34,35,37]

Parathyroid Gland Dysfunction

Hypoparathyroidism

Hypoparathyroidism may be a hereditary or acquired disorder characterized by inadequate secretion of PTH or a peripheral resistance to its effect.[37] Patients with hypoparathyroidism typically have low plasma calcium levels (ionized calcium less than 4.5 mg/dL and total calcium less than 8.6 mg/dL).[11] The blood phosphate concentration may be elevated because of the decreased renal excretion of phosphate.

Hereditary hypoparathyroidism, inadvertent surgical removal of parathyroid tissue, parathyroid gland injury from irradiation, and chronic severe magnesium deficiency (e.g., alcohol abuse, poor nutrition, malabsorption) are possible causes of hypoparathyroidism. Clinical signs of hypoparathyroidism reflect the degree of hypocalcemia and the rapidity of calcium decline. A sudden drop in ionized calcium usually produces more severe symptoms than a slow decline.[36,37] Treatment of chronic hypoparathyroidism includes vitamin D and calcium supplementation.

The decreased serum calcium ion concentration accompanying hypoparathyroidism produces hyperexcitability of nerve and muscle cells by lowering the threshold potential of excitable membranes. Cardinal features of neuromuscular excitability are muscle spasms and spontaneous nerve discharge. Symptoms vary in severity and may take the form of muscle cramps, perioral paresthesias, numbness in the feet and toes, or hyperactive deep tendon reflexes. The patient may feel restless or hyperirritable. Life-threatening laryngeal muscle spasm may occur, producing stridor, labored respirations, and asphyxia.[34,37] Tetany occurs when the blood calcium falls to about 6 mg/dL.[34]

Two classic manifestations of latent hypocalcemic tetany are *Chvostek sign* and *Trousseau sign*. Chvostek sign is a contracture or twitching of ipsilateral facial muscles produced when the facial nerve is tapped at the angle of the jaw. Trousseau sign is elicited by the inflation of a blood pressure cuff slightly above the systolic level for a few minutes. The resultant ischemia enhances muscle irritability in hypocalcemic states and causes flexion of the wrist and thumb with extension of the fingers *(carpopedal spasm)*.[23] Figure 33-7 illustrates some of the clinical manifestations of hypoparathyroidism and hypocalcemia.

Anesthesia Implications for Hypoparathyroidism. Temporary hypocalcemia often is observed after successful parathyroid surgery for hyperparathyroidism.[37] This may occur within a few hours to a few days after surgery.[37] The transient postoperative hypocalcemia is the result of parathyroid gland suppression

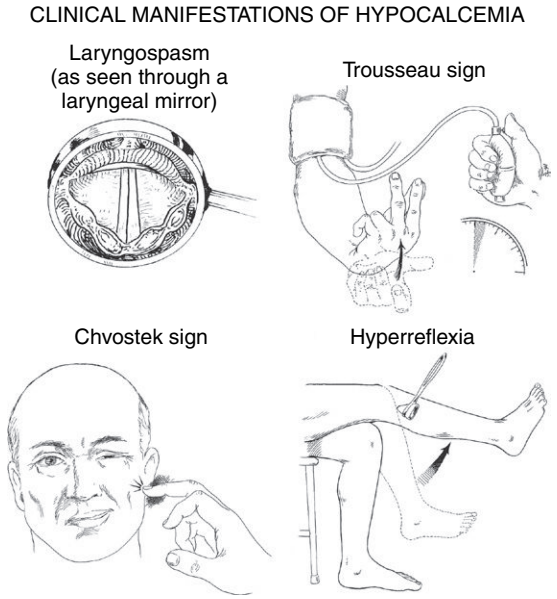

FIGURE **33-7** Hypocalcemia produces hyperexcitability of nerve and muscle cells. Chvostek sign and Trousseau sign are two classic manifestations of hypocalcemic tetany. Deep tendon reflexes may be hyperactive. Laryngeal muscles are sensitive to tetanic spasm.

(by preoperative hypercalcemia) and rapid bone uptake of calcium ("hungry bone syndrome").[36] Inadvertent removal of all parathyroid gland tissue induces a marked decline in total serum calcium concentration from normal levels to 6 to 7 mg/dL. Even a small amount of remaining parathyroid tissue usually is capable of sufficient hypertrophy to preserve normal calcium-phosphate balance.[34]

After parathyroid surgery, meticulous observation for signs of musculoskeletal irritability should be performed. The threshold for the development of signs of hypocalcemia is variable; however, manifestations of neuromuscular compromise often are observed at total serum calcium levels of 6 to 7 mg/dL.[34]

Laryngeal muscles are especially sensitive to tetanic spasm, and laryngospasm may cause life-threatening airway compromise in the hypocalcemic patient.[34] Respiratory distress following parathyroid surgery may be secondary to laryngeal muscle spasm, edema or bleeding in the neck, or bilateral recurrent laryngeal nerve injury. Unilateral recurrent laryngeal nerve injury produces hoarseness and usually requires only close observation. Bilateral recurrent laryngeal nerve injury causes aphonia and requires immediate airway support and intubation.[34]

Hypocalcemia may be apparent on electrocardiographic tracings as a prolonged QT interval, reflecting delayed ventricular repolarization.[11] Cardiac dysrhythmias, decreased cardiac contractility, and hypotension may occur, and congestive heart failure (although rare) is a danger.[36,38]

In addition to parathyroid surgery, circulating levels of ionized calcium can decline from other causes in the perioperative period. Precipitous increases in circulating levels of anions such as bicarbonate, phosphate, and citrate lower ionized calcium levels.[36] The rapid transfusion of citrated blood, or the rapid administration of bicarbonate may induce overt tetany in a previously asymptomatic hypocalcemic patient. Hyperventilation and alkalosis decrease ionized calcium levels by increasing calcium binding to proteins.[37] Vigorous diuresis can also augment calcium loss.

Patients with confirmed symptomatic hypocalcemia require prompt therapy. Acute hypocalcemia may be treated with an initial intravenous bolus of 10 mL of 10% calcium chloride or calcium gluconate administered over 10 minutes, followed by an infusion of 0.5 to 2 mg Ca^{+2}/kg/h.[36,37] Calcium, magnesium, phosphate, potassium, and creatinine levels should be monitored diligently during calcium replacement. Chronic magnesium deficiency impairs the secretion of PTH and should be corrected.[35]

Hyperparathyroidism

Primary hyperparathyroidism is characterized and diagnosed by the presence of elevated serum PTH levels despite high serum calcium levels. It may result from a parathyroid adenoma, gland hyperplasia, or parathyroid cancer.[27] In approximately 80% of cases, primary hyperparathyroidism is caused by hypersecretion of a single parathyroid adenoma.[36-39] Hyperplasia of one or more parathyroid glands accounts for about 15% of cases. Hereditary hyperparathyroidism may exist as part of a multiple endocrine neoplastic syndrome (MEN-1, MEN-2A).[36,37] Carcinoma of the parathyroid gland is found in less than 1% of patients and is associated with particularly high serum calcium levels.[39]

The incidence of primary hyperparathyroidism in the United States is approximately 0.1% to 0.5%, with a higher occurrence in females and a peak incidence between the third and fifth decades.[2,37] Stimulation of the parathyroid gland during pregnancy or lactation, prior neck irradiation, and a family history of parathyroid disease are predisposing etiologic factors.[37]

There are many causes of hypercalcemia, but hyperparathyroidism and cancer account for 90% of all cases.[37] Primary hyperparathyroidism is the most common cause of hypercalcemia in the general population.[11] Sustained overactivity of the parathyroid glands leads to hypercalcemia and hypophosphatemia. Most patients remain asymptomatic until the total serum calcium level rises above 12 mg/dL.[37] Severe hypercalcemia, generally defined as greater than 14 mg/dL, may be life threatening and demands immediate attention.[37,38]

With the development of sensitive laboratory assays for calcium and PTH, today more than half of patients with hyperparathyroidism are asymptomatic at diagnosis. Over time, sustained high levels of PTH lead to exaggerated osteoclast activity in bone, resulting in diffuse osteopenia, subperiosteal erosions, and elevated extracellular calcium levels. As osteoblasts attempt to reconstruct the ravaged bone, they secrete large amounts of the enzyme *alkaline phosphatase*.[34,35] A heightened serum alkaline phosphatase level, therefore, is a diagnostic feature of hyperparathyroidism.[39] Despite an increased mobilization of phosphorus from bone, serum phosphate concentration usually remains normal or low as a result of increased urinary excretion.

The effect of hyperparathyroidism on bone becomes clinically apparent when osteoclastic absorption of bone overwhelms osteoblastic deposition. With severe and protracted disease, the weakened bones become filled with decalcified cavities, making them painful and susceptible to fracture. Owing to early diagnosis, the destructive bone disease associated with hyperparathyroidism, *osteitis fibrosa cystica*, is rare today.

Many of the nonskeletal manifestations of primary hyperparathyroidism are related to the accompanying hypercalcemia.[39] Sustained and marked hypercalcemia may produce calcifications and other deleterious effects in the pancreas (pancreatitis), kidney (nephrolithiasis, nephrocalcinosis, polyuria), blood vessels (hypertension), heart (shortened ventricular refractory period, increased ventricular excitability, bradyarrhythmias), and acid-producing areas of the stomach (peptic ulcer).[38-40] The mnemonic "stones, bones, and groans" summarizes renal, skeletal, and gastrointestinal features of advanced hyperparathyroidism. Hypercalcemia raises

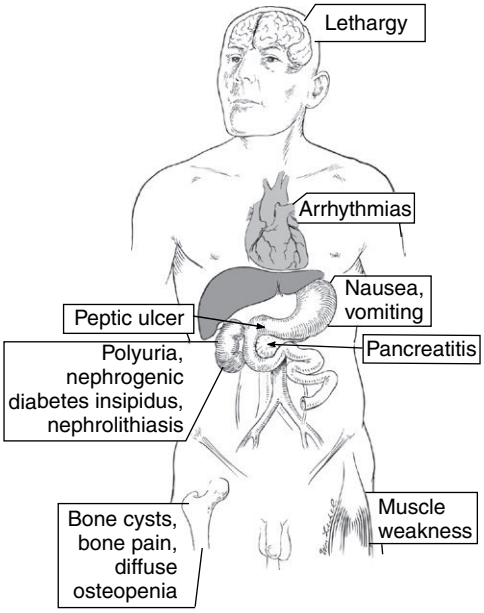

FIGURE **33-8** The patient with hyperparathyroidism exhibits manifestations of hypercalcemia. With severe, protracted disease, skeletal destruction becomes evident.

TABLE **33-3** Clinical Features of Hyperparathyroidism and Hypoparathyroidism

System	Hyperparathyroidism	Hypoparathyroidism
Cardiovascular	Hypertension, cardiac conduction disturbances, shortened QT interval	Prolonged QT interval, hypotension, decreased cardiac contractility
Musculoskeletal	Bone pain, pathologic fractures, muscle weakness, muscle atrophy	Neuromuscular excitability
Neurologic	Somnolence, cognitive impairment, depression, hypotonia	Tetany, paresthesias, numbness in fingers and toes, seizures
Gastrointestinal	Anorexia, nausea, vomiting, constipation, abdominal pain, pancreatitis, peptic ulcer	None significant
Renal	Tubular absorption defects, diminished renal function, kidney stones, polyuria	None significant

the threshold of excitable cells and causes progressive depression of the nervous system.[34] Depressive effects of hypercalcemia begin to appear in many patients when blood calcium levels rise above about 12 mg/dL. Profound muscle weakness, confusion, nausea, vomiting, and lethargy are additional features of the disorder. Figure 33-8 illustrates some of the clinical manifestations of hyperparathyroidism.

Secondary hyperparathyroidism develops in patients with chronically low levels of serum calcium, such as those with chronic renal failure, vitamin D deficiency, and gastrointestinal malabsorption. A compensatory parathyroid rise develops in response to the hypocalcemia. The clinical course is marked by the same PTH-mediated skeletal assault seen in the primary form of the disorder, but because it is an adaptive response, secondary hyperparathyroidism is seldom associated with hypercalcemia. The bone disease seen in patients with secondary hyperparathyroidism associated with chronic kidney disease is termed *renal osteodystrophy*.[37]

Hypercalcemia due to malignancy occurs in as many as 20% of cancer patients. Malignancy is the second most common cause of hypercalcemia in adults.[37] The hypercalcemia may be due to local invasion of bone by cancer cells, but many cases are due to elaboration of a PTH-like peptide (parathyroid hormone–related peptide, PTHrP) from tumor cells.[37] The overproduction of PTHrP by cancer cells mimics the effects of PTH, including bone destruction, hypophosphatemia, and hypercalcemia.

Table 33-3 compares common clinical features of hyperparathyroidism and hypoparathyroidism.

Anesthesia Implications for Hyperparathyroidism. The usual treatment for symptomatic primary hyperparathyroidism is surgical removal of abnormal parathyroid tissue. Surgical treatment for asymptomatic hyperparathyroidism is more controversial.[7] Parathyroidectomy may be performed with bilateral neck exploration under general anesthesia, but *minimally invasive parathyroidectomy* using cervical plexus block anesthesia and monitored anesthesia care is increasingly used, especially for excision of a single adenoma.[40-43]

Parathyroid tissue resembles brown fat, and this can occasionally make it difficult for the surgeon to locate. Further, parathyroid tissue is sometimes footloose and can be found in such ectopic places as the deep recesses of the mediastinum, pericardium, or the thymus gland.[35-37] The 5-minute half-life of PTH allows it to serve as a useful intraoperative marker.[43] Increasingly, surgeons use periodic intraoperative determinations of serum PTH and ionized calcium levels to help guide surgical resection.[40,41]

Blood loss from parathyroid surgery is usually minimal, and advanced monitoring is not required based on the surgical procedure. Serum calcium, magnesium, and phosphorus levels should be monitored in the postoperative period until stable. In most cases, serum calcium levels start to decline within 24 hours and return to normal within 3 to 4 days after successful surgery.[11]

With current methods of detection, most patients with hyperparathyroidism are asymptomatic. However, erosive effects of elevated PTH on bone and the systemic effects of chronic hypercalcemia should be considered in the anesthetic plan for patients with severe untreated disease.

Mild hypercalcemia (less than 12 mg/dL) can be managed by saline infusion (150 mL/hr).[11,37] Severe or symptomatic hypercalcemia (greater than 13 to 16 mg/dL) is treated aggressively. Isotonic saline hydration and loop diuretics (furosemide, 40 to 80 mg IV every 2-4 hours) can rapidly decrease serum calcium levels by hemodilution, increased glomerular filtration, and enhanced excretion.[8,11,38] Less frequently, intravenous bisphosphonates (pamidronate, zoledronate, etidronate) or calcitonin are used to lower serum calcium by inhibiting osteoclastic bone resorption.[8,11,37,38]

The hypercalcemic patient may be dehydrated because of anorexia, vomiting, and the impaired ability of the kidneys to concentrate urine.[37] In these patients, hydration with non–calcium-containing solutions should be maintained throughout the perioperative period to dilute serum calcium, maintain adequate glomerular filtration and calcium clearance, and ensure adequate intravascular volume. Vigorous hydration dictates the use of bladder catheterization, central venous pressure monitoring, and frequent determinations of serum electrolytes.

Elevated calcium levels may depress the central and peripheral nervous systems.[34] The use of preoperative sedatives in the

hypercalcemic patient who appears lethargic or confused should be avoided. General anesthetic requirements may be decreased as well in the patient with preoperative somnolence.[11]

Careful review of the patient's renal status is especially crucial in patients with secondary hyperparathyroidism. Associated complications of renal impairment (e.g., volume overload, anemia, electrolyte derangements) may affect anesthetic medication dosages and selection.[24,32]

Cardiac conduction disturbances and a shortened QT interval and a prolonged PR interval on the electrocardiogram are observed with hypercalcemia.[11]

Awareness of the effects of pH on the ionized portion of plasma calcium is important. Alkalosis shifts ionized calcium to the protein-bound form and decreases serum levels.

The response to neuromuscular blockade may be unpredictable.[11] Muscle weakness, hypotonia, and muscle atrophy may increase the patient's sensitivity to nondepolarizing skeletal muscle relaxants. Careful titration of muscle relaxants with use of a peripheral nerve stimulator is prudent.[11]

Patients with clinically significant bone disease are susceptible to fractures, and care must be exercised in positioning and padding.[7]

Hyperparathyroid patients are prone to postoperative nausea and vomiting.[44] Prophylactic antiemetic medications are advisable.

PANCREAS

The *pancreas* is a flattened, elongated, retroperitoneal organ that has both exocrine and endocrine functions. *Acinar cells*, which make up the exocrine portion of the pancreas, account for about 98% of the gland's weight. Digestive enzymes and bicarbonate are synthesized in acinar cells and secreted into the pancreatic ducts to aid the digestive process.

Islets of Langerhans

The *islets of Langerhans*, which make up 1% to 2% of the pancreas's weight, constitute the endocrine pancreas. The islets are microscopic collections of cells scattered throughout the gland. They produce hormones that do not enter ducts but rather are secreted directly into capillary blood vessels. Each islet cell has an abundant blood supply. Venous blood from the islets drains into the hepatic portal vein and then into the general circulation.[45]

At least four distinct cell types are found in the islets of Langerhans, identified as α (alpha), β (beta), δ (delta), and PP (pancreatic polypeptide) cells. Each cell type secretes a different peptide hormone. The β *cells* account for 60% to 70% of the islet mass and secrete the hormone *insulin*. They also secrete *amylin*, which can inhibit insulin secretion.[46] The α *cells* constitute about 25% of the islet cells and secrete the hormone *glucagon*. The δ *cells* represent about 10% of total cells and secrete the hormone *somatostatin*.[46]

Insulin and glucagon are crucial in regulating carbohydrate, fat, and protein metabolism. Their secretion is part of a hormonal regulatory system that accommodates repeated periods of feast and fasting throughout the day. Somatostatin may play a role in regulating gastrointestinal function by restraining the rate at which nutrients are digested and absorbed. It also inhibits the secretion of both insulin and glucagon.[46] Somatostatin also is distributed throughout the central nervous system and, as noted earlier in this chapter, is a hypothalamic inhibitor of anterior pituitary GH release. Pancreatic peptide inhibits exocrine pancreatic secretion.

Energy Balance

Glucose is the body's most abundant circulating fuel. The breakdown of glucose into simpler compounds releases energy the body uses for cellular metabolism. The energy-yielding breakdown of glucose to pyruvate or lactate is called *glycolysis* or the *Embden-Meyerhof pathway*.

Despite daily fluctuations between feeding and fasting states, plasma glucose concentration is maintained within an amazingly narrow range. This is accomplished by the counterbalancing effect of multiple hormones that control the storage of glucose and other nutrient fuels after meals and regulate fuel mobilization between meals. In most healthy individuals, the liver stores enough glycogen to maintain a normal plasma glucose during 8 to 12 hours of fasting.[47] An overnight fast usually lowers the blood glucose to 80 to 90 mg/dL. The blood glucose concentration increases briefly to 120 to 140 mg/dL after a meal before returning to control levels.[46] In a person with impaired glucose tolerance, the fasting plasma glucose (FPG) level is above 100 mg/dL, and in the diabetic patient, the FPG is equal to or greater than 126 mg/dL.[46,48]

Certain metabolic processes ensure the efficient storage of nutrients so they can be available for later use. *Glycogenesis*, or the storage of glucose as glycogen, occurs primarily in the liver and muscle. *Lipogenesis*, which represents the formation and storage of fat as triglycerides, occurs primarily in adipose tissue.

Other metabolic processes work in the opposite direction, providing adequate energy sources during times of fasting. *Gluconeogenesis* is the formation of glucose from lactate, pyruvate, amino acids, and glycerol; it is an important hepatic glucose production mechanism during fasting and starvation. *Glycogenolysis*, the breakdown of glycogen into glucose, occurs primarily in the liver. *Lipolysis*, the breakdown of stored triglycerides to free fatty acids and glycerol, is stimulated by the enzyme *hormone-sensitive lipase*.

The rates of glycogenesis, lipogenesis, gluconeogenesis, glycogenolysis, and lipolysis are determined largely by the actions of insulin and the opposing actions of so-called "counterregulatory hormones" (GH, cortisol, epinephrine, and glucagon). Insulin plays an important role as an *anabolic hormone*. It promotes growth and the constructive phase of metabolism. The potent anabolic effects of insulin are balanced by the opposing *catabolic actions* of the counterregulatory hormones. These hormones mobilize fuel substrates from protein, carbohydrate, and fat stores to meet the energy demands of various tissues.[45]

The "push and pull" effect of these two hormone systems helps maintain normal glucose concentrations in the healthy individual. In diabetes, when insulin concentrations are low or absent, the unopposed counterregulatory hormones begin to exert more prominent metabolic effects.

Obligate Versus Facultative Tissue

Different tissues have different glucose requirements, and some tissues are able to adapt to alternative sources of fuel when glucose is scarce. Muscle and most other tissues in the body are said to be *facultative* glucose organs. They use glucose for energy when it is available, but they can also shift to alternative sources of fuel (amino acids or fat) in the absence of glucose.

The brain is unique in that it is one of the few organs that uses only glucose for energy. It is said to be an *obligate* glucose organ. Erythrocytes and the adrenal medulla also depend on glucose as their sole source of energy. Unlike most other tissues, such as muscle, obligate glucose organs cannot immediately switch to alternative fuels when glucose levels fall. The brain's absolute, uninterrupted requirement for glucose dictates that the blood glucose concentration be maintained above a critical level. The central nervous system accounts for about 70% of total body glucose utilization, and normal cerebral function requires the delivery of

about 125 to 150 g of glucose per day. During prolonged starvation, ketone bodies can substitute for glucose as cerebral fuel.

Insulin

Of the hormones secreted from the islet cells, insulin is of greatest physiologic importance. In 1922, Banting and Best first isolated this critical hormone from the pancreas in its pure form. The clinical importance of this event is demonstrated by insulin's history of lifesaving effects in those with diabetes mellitus (DM), a previously uniformly fatal disease.

Insulin was the first mammalian peptide hormone produced with the use of recombinant DNA techniques. Genetically engineered insulin does not differ in biologic or chemical characteristics from pancreatic human insulin.

Storage and Release

Insulin is synthesized within the β cells of the pancreas, and it is packaged and stored in membrane-lined vesicles within the β-cell cytoplasm. About 200 units of insulin are stored in the pancreas in this form. With stimulation, insulin is released via exocytosis from the β cell to the surrounding capillaries, where it enters the portal circulation. In the first pass through the hepatic circulation, the liver removes 50% of the insulin delivered to it. Total daily insulin secretion is estimated to be about 60 units, but the total daily peripheral delivery is about 30 units.[45]

Insulin circulates unbound to any carrier protein. The circulating half-life of insulin is only 5 to 8 minutes, and the biologic half-life is about 20 minutes.[45] Almost all tissues in the body can metabolize insulin, but the major sites of hormone degradation are the liver and the kidney.[46] Very little insulin is excreted unchanged in the urine.

Effects of Insulin

Insulin is a hormone of energy or fuel storage. It is important to many cellular mechanisms related to growth, and it is intimately involved in the regulation of carbohydrate, fat, and protein metabolism.

Following ingestion of a meal, insulin levels increase sharply in response to stimulation by abundant circulating nutrient substrates. Insulin promotes the storage of carbohydrate, fat, and protein for future use when substrate supply is low.[46] Figure 33-9 outlines the effects of insulin on nutrient substrates.

The peripheral effects of insulin are initiated by a reversible binding to specific cell-membrane insulin receptors. Most cells in the body have insulin receptors, but the major targets of insulin action are the liver, muscle, and adipose tissue.[45]

Effects on Carbohydrate Metabolism. Insulin is the body's key hormone controlling glucose removal from the plasma. It facilitates the transport of glucose by stimulating its uptake into liver, muscle, and adipose tissue. The brain is one of the few tissues in the body that does not require insulin for glucose transport into its cells.[46]

In the liver, and to a lesser extent in muscle cells, insulin promotes the efficient storage of excess glucose in the form of glycogen (glycogenesis).[45] Under normal circumstances, about 60% of the glucose ingested with a meal is stored in the liver as glycogen. In addition to promoting hepatic glucose storage, insulin limits hepatic glucose output by inhibiting enzymes responsible for gluconeogenesis.[45,46]

Between meals, when the blood glucose and blood insulin levels decrease, the stored glucose can be released back into the blood (through gluconeogenesis and glycogenolysis) and be made available for local energy use or delivery to the central nervous system.

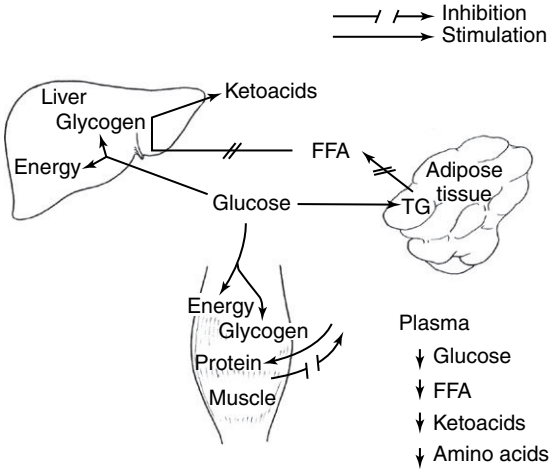

FIGURE **33-9** The effect of insulin on the overall flow of metabolic substrates. Insulin promotes the uptake of glucose into insulin-responsive tissue to meet energy needs. In the liver and skeletal muscle, insulin promotes the storage of excess glucose as glycogen. In adipose tissue, excess glucose is stored as triglyceride (TG). Insulin inhibits the breakdown of triglyceride into glycerol and free fatty acids (FFA). Amino acid uptake into muscle is increased for protein synthesis, and protein breakdown is inhibited.

Effects on Protein Metabolism. The actions of insulin on protein metabolism are also directed toward nutrient storage and growth (anabolism). Insulin stimulates the uptake of amino acids from the extracellular fluid to the cell. Once inside the cell, it promotes the synthesis of specific proteins. Insulin also conserves amino acids in existing proteins by inhibiting the breakdown of protein stores. Because insulin is required for protein synthesis, it is firmly established as an essential hormone for normal development and maintenance of healthy tissues.[46]

Effects on Fat Metabolism. The acute effects of insulin on fat metabolism are not as readily apparent as the effects on carbohydrate metabolism, but in the long run they are no less important.

Insulin favors fat storage. After a meal, carbohydrates not used for energy or stored as glycogen are converted, under the direction of insulin, to fatty acids and glycerol. These two substances combine in adipose tissue to form triglyceride, the storage form of fat. Insulin not only stimulates triglyceride storage in adipose tissue but also strongly inhibits the breakdown of stored triglyceride to free fatty acids and glycerol. Insulin blocks triglyceride hydrolysis and the liberation of free fatty acids into the circulating blood by suppressing the enzyme *hormone-sensitive lipase*. Increased free fatty acid release decreases insulin sensitivity in both muscle and liver and may also play a role in the pathology associated with type 2 DM.[49] Under ordinary conditions, insulin continually exerts a "braking" effect on free fatty acid release. A major consequence of lower concentrations of circulating free fatty acids is the decreased use of fatty acids for fuel.[45] Insulin suppresses fatty acid mobilization in the fed state when glucose is readily available to meet energy needs.

In the fasted state, when insulin levels are low, free fatty acid release is accelerated to provide metabolic fuel. The oxidation of fatty acids for energy during fasting spares glucose use.[45,46] Organic acids called *ketoacids* or *ketone bodies* are generated in the liver from fatty acid oxidation. Ketoacid production is increased in the fasted state when insulin levels are low, and it is markedly reduced when insulin levels are high. Insulin is the body's major antiketogenic hormone.[46-48]

Effects on Ion Transport. Insulin stimulates the translocation of vital electrolytes from the extracellular compartment into cells.

BOX **33-3**

Factors That Influence Insulin Release

Stimulators
- Glucose, mannose, fructose
- Amino acids
- Gastrointestinal hormones
- Acetylcholine (parasympathetic stimulation)
- β-Adrenergic stimulation

Inhibitors
- Hypoglycemia
- Somatostatin
- Glucagon, cortisol, growth hormone
- α-Adrenergic stimulation

Potassium, phosphate, and magnesium uptake into cells is mediated by an insulin mechanism.[45] Exogenous insulin administration may appreciably lower serum potassium, phosphate, and magnesium levels. The precipitation of hypokalemia secondary to vigorous insulin treatment can be of great clinical significance.

Insulin's actions are complex and wide ranging. Overall, insulin promotes the formation of complex molecules for nutrient storage and growth and fosters glucose use, instead of fat or protein, for energy.

Control of Insulin Secretion

Insulin synthesis and secretion are stimulated by "feast" or energy abundance. Ingestion of a meal (fuel excess) increases the rate of insulin secretion four- to five-fold.[48] Plasma insulin levels rise, reaching peak values 30 to 60 minutes after eating is initiated.[45] High insulin levels in turn direct nutrients to appropriate storage sites.

Between meals, insulin levels drift downward, the storage process is reversed, and metabolic substrates are mobilized in the form of glucose, free fatty acids, and amino acids. Plasma glucose is by far the most important stimulator of insulin release. Elevated plasma glucose levels directly activate β cells of the pancreas, stimulating insulin synthesis and secretion. Low plasma glucose concentrations inhibit this response. A maximal insulin response occurs at blood glucose levels of about 300 mg/dL.[45] Very little insulin, known as basal insulin secretion, is secreted at plasma glucose levels of 50 mg/dL and below.[45,49]

Amino acids also are potent stimulators of insulin release, although the β-cell response to amino acids is not as pronounced as the response to glucose. Fat has little if any stimulating effect on insulin release.[45]

Both adrenergic and cholinergic fibers of the autonomic nervous system innervate the islets. Parasympathetic vagal activity and β-adrenergic receptor stimulation increase insulin release. A general sympathetic discharge has a suppressive effect on insulin release through α-adrenergic receptor stimulation.[8] Pancreatic insulin secretion, however, does not *require* intact autonomic innervation; appropriate secretion responses occur in the transplanted pancreas as well.

Gastrointestinal hormones that accompany the digestive process potentiate insulin secretion. Food ingestion seems to send an "anticipatory" signal to the pancreas to discharge insulin in preparation for the absorption of glucose and amino acids.[46] Box 33-3 lists some of the factors that influence insulin secretion.

Glucagon

Glucagon is a linear polypeptide hormone produced by the α cells of the pancreatic islets as a biologic antagonist to insulin.[45,46] The most important role of glucagon is to enhance hepatic glucose output and increase plasma glucose. A decrease in blood glucose concentration below 90 mg/dL increases the plasma glucagon level by several-fold. Hyperglycemia, on the other hand, decreases glucagon release from the α cells.

Insulin and glucagon have opposing biologic actions. Whereas insulin is considered a hormone of energy storage, glucagon is considered a hormone of energy release.[46] Between meals, when blood glucose levels are low, the concentration of glucagon increases to maintain fuel production at a level that meets the energy needs of the individual. Special priority for glucose delivery is given to the brain.

Glucagon works in concert with the counterregulatory hormones epinephrine, GH, and cortisol. These hormones are strong defenders against hypoglycemia and are critical in restoring normal glucose levels during periods of hypoglycemic stress. They also are secreted in response to various other stresses such as infection, toxemia, severe injury, and surgery.[45] Nondiabetic surgical patients experience an increased plasma blood glucose, as much as 60 mg/dL above their preoperative levels, in response to surgical stress.[50]

DIABETES MELLITUS

Diabetes mellitus is a complex metabolic derangement caused by relative or absolute insulin deficiency. Diabetes has been called "starvation in a sea of food." Glucose is present in abundance, but because of insulin lack or insulin resistance, it is unable to reach cells for energy provision. Guidelines for diagnosing diabetes include an FPG level of 126 mg/dL or greater or a random glucose level above 200 mg/dL. The FPG diagnostic level was reduced from a previous value of 140 mg/dL based on findings that patients with an FPG of 126 mg/dL are at risk for diabetes-related complications.[51]

The incidence of diabetes has increased dramatically over the last 40 years. Today it affects nearly 26 million Americans or 8.3% of our population.[52] Diabetes is the leading cause of renal failure, blindness, and nontraumatic lower limb amputations.[52,53] Additionally, prediabetes, a condition in which blood glucose is higher than normal but below the criteria for a diabetic diagnosis, affects an estimated 79 million Americans.[52]

The rise can be attributed to a combination of three factors: (1) an overweight population, (2) more sedentary lifestyles, and (3) a rise in the elderly population.[53] As more of our population advances in age into the decades in which most cases of diabetes occur, the effect of the disease will become even more alarming. As outlined in Figure 33-10, many pathophysiologic features of DM are directly attributable to a lack of the normal effects of insulin on carbohydrate, fat, and protein metabolism.

Type 1 Diabetes Mellitus

About 5% to 10% of diabetic patients have *type 1 DM*. [52,53] This type of diabetes was formerly known as *insulin-dependent diabetes* or *juvenile-onset diabetes*. Individuals with type 1 DM have an absolute deficiency of insulin and are therefore entirely dependent on exogenous insulin therapy. In the absence of sufficient exogenous insulin, the disease course may be complicated by periods of ketosis and acidosis.

In most cases, type 1 DM is caused by an unusually vigorous autoimmune destruction of the β cells of the pancreatic islets. Environmental factors such as infection or exposure to specific antigenic proteins are cited as possible initiators of the immune assault.[54] Type 1 DM patients are also more likely to have other autoimmune diseases such as thyroid disease or Addison's disease.[55,56] A genetic predisposition for development of the disease also is involved.[48]

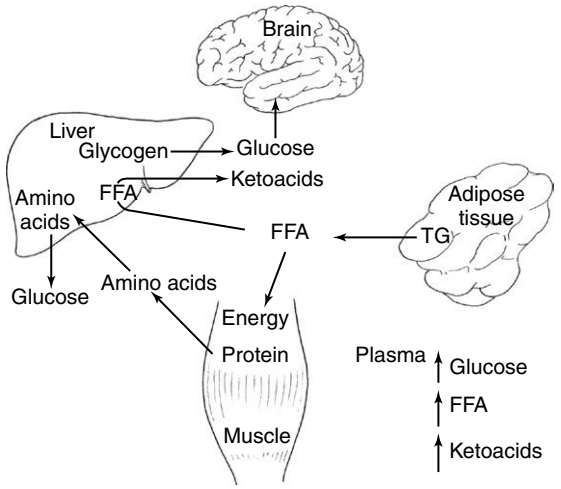

FIGURE **33-10** The pattern of substrate flow in the diabetic state. Lack of insulin enhances hepatic glucose production because of increased gluconeogenesis and glycogenolysis. The diabetic state promotes protein breakdown, and the released amino acids are converted to glucose in the liver (gluconeogenesis). Lipolysis is augmented, and this increases free fatty acid supply to the liver, resulting in enhanced ketogenesis. Free fatty acids provide an energy source to muscle and other facultative tissue. Glucose uptake by the brain is sustained. *FFA*, Free fatty acids; *TG*, triglyceride.

Type 1 DM usually develops before the age of 30 years, but it can develop at any age.[48] The classic symptoms of type 1 DM appear only when at least 80% of the β cells are destroyed.[48] The remaining β cells usually are eliminated inexorably over 2 or 3 years. In patients with type 1 DM, daily exogenous insulin therapy is essential for life. Some type 1 DM patients may be candidates for pancreatic transplant. The transplantation of isolated pancreatic islets has been plagued by graft survival and islet isolation setbacks, but it holds out promise for a future cure.

Type 2 Diabetes Mellitus

About 90% to 95% of the patients with diabetes have *type 2 DM*.[52] Type 2 DM is characterized by impaired insulin secretion, peripheral insulin resistance (a decreased number of insulin receptors or an insulin receptor or postreceptor defect), abnormal fat metabolism, and excessive hepatic glucose production.[48] Obesity is strongly associated with type 2 DM with over 80% of type 2 DM patients considered obese, primarily of the visceral or central type.[48] Type 2 DM was formerly known as *non–insulin-dependent diabetes* or *maturity-onset diabetes*.

Type 2 DM occurs in patients who have some degree of endogenous insulin production but produce quantities insufficient for sustaining normal carbohydrate homeostasis. Early in the disease process, insulin resistance contributes to an increase in insulin secretion and subsequent hyperinsulinemia. The exact mechanism causing insulin resistance remains unclear, although it is present in a number of metabolic abnormalities classified as metabolic syndrome. Eventually a decline in insulin secretion occurs, which leads to an increase in hepatic glucose production and ultimately a hyperglycemic state. Insulin levels may be low, normal, or even elevated, but a *relative* insulin deficiency exists. Typically, type 2 DM occurs in patients who are older than 30 years, obese (80%), and with a family history of the disease.[48] Type 2 DM has an insidious onset; indeed, it is estimated that half of those who have type 2 DM are not even aware of it. The disease course is rarely associated with ketosis or acidosis, but it may be complicated by a nonketotic, hyperosmolar, hyperglycemic state.

Treatment for this class of diabetes consists primarily of oral hypoglycemic agents, exercise, and diet therapy. Weight reduction in the obese diabetic patient improves tissue responsiveness to endogenous insulin and often restores normoglycemia.

The distinction between *insulin-treated* diabetics and *insulin-dependent* diabetics is important. Some type 2 diabetics may benefit from exogenously administered insulin, especially during times of illness or stress. Type 1 diabetics, on the other hand, are insulin-dependent and require exogenous insulin daily to live.

Diabetes Associated with Other Conditions

Diabetes may result from other conditions such as pancreatectomy, cystic fibrosis, or severe pancreatitis. Certain endocrine conditions, including Cushing syndrome, glucagonoma, pheochromocytoma, and acromegaly also may be associated with a diabetic state. Steroid-induced diabetes may occur in the patient taking supraphysiologic doses of glucocorticoids. Gestational diabetes occurs in approximately 2% to 10% of pregnancies in the United States.[48,52] Women who have had gestational DM have a 35% to 60% chance of developing type 2 DM 10 to 20 years postpartum.[52,53]

Insulin Deficiency

Effect of Insulin Deficiency on Carbohydrates

Insulin deficiency results in a decreased uptake and use of glucose by insulin-sensitive cells. Glycogen storage is decreased, and gluconeogenesis is uninhibited with insulin lack, causing the liver to increase its glucose output. This produces an intracellular deficit and an extracellular surplus of glucose.[45]

The hyperglycemia produced by insulin lack has immediate adverse consequences. When the blood glucose concentration increases to a threshold level (about 180 to 200 mg/dL), the amount of glucose filtered at the kidney glomerulus cannot be totally reabsorbed. The excess filtered glucose spills into the urine *(glucosuria)* and acts as an osmotic diuretic, pulling water with it. The increased urine output *(polyuria)* contributes to extracellular dehydration and electrolyte depletion. Intracellular dehydration also occurs because of the osmotic transfer of water out of cells and into the hypertonic extracellular fluid. In an attempt to compensate for the hypovolemia, the diabetic patient may drink large quantities of water *(polydipsia)*.[45,46,48]

Effect of Insulin Deficiency on Fat

As the diabetic state evolves, glucose-deprived cells meet their energy requirements by drawing on fat and protein reserves. Fat breakdown occurs normally between meals, when insulin levels are low, but it is enhanced greatly in diabetes. The lack of insulin activates hormone-sensitive lipase, which causes uninhibited lipolysis of stored triglycerides to free fatty acids and glycerol. This fat mobilization increases circulating lipids and may contribute to the atherosclerotic and angiopathic changes that complicate the disease course.[46]

Insulin deficiency produces a shift from carbohydrate to fat metabolism. Free fatty acids become the main energy substrate for essentially all tissues (the brain excluded). With uncontrolled diabetes, the excess free fatty acids are converted in the liver to ketone bodies (*acetoacetic acid*, *β-hydroxybutyric acid*, and *acetone*). This ultimately leads to greater circulating levels of ketoacids and an elevated hydrogen ion concentration in body fluids. The ketone body acetone is a volatile acid and is excreted via the lungs. Consequently, one can frequently identify ketonemia in uncontrolled diabetes by detecting a fruity "acetone breath."

Effect of Insulin Deficiency on Protein

The insulin deficiency of diabetes causes protein storage to halt and catabolism to ensue. When insulin levels are low or absent, the plasma amino acid concentration increases, and the excess circulating amino acids are converted in the liver to glucose (gluconeogenesis). The protein-wasting effects accompanying diabetes lead to weight loss, weakness, and widespread organ dysfunction. The diabetic may attempt to compensate for the protein loss and caloric drain by increasing food intake *(polyphagia)*.

Many proteins, including hemoglobin and structural tissue proteins, become glycosylated in the presence of high circulating blood glucose levels. Glucose adducts can alter protein function and may contribute to the organ damage and functional derangements observed in individuals with longstanding diabetes.[45]

Long-Term Diabetic Complications

Diabetic patients are subject to long-term complications that confer substantial morbidity and premature mortality. These complications include extensive arterial disease, cataracts, sensory and motor neuropathy, infection, and autonomic nervous system dysfunction.

Arterial thrombotic lesions in the diabetic population are widely distributed in the extremities, kidneys, eyes, skeletal muscle, myocardium, and nervous system. Owing to these diffuse lesions, diabetes carries a serious risk for the development of microvascular (e.g., nephropathy, retinopathy, neuropathy) and macrovascular (e.g., atherosclerosis, stroke, coronary artery disease) complications.[57,58] Cardiovascular disease is markedly increased in patients with DM and responsible for the cause of death in 80% of diabetic patients.[58] According to data from the Centers for Disease Control, the incidence of circulatory insufficiency to the legs and feet is four-fold to seven-fold greater in diabetic men and women compared with their nondiabetic counterparts. Gangrene is 17-fold more common in the diabetic than in the nondiabetic individual.[52,53,60] Not surprisingly, lower-extremity bypass grafting and amputations are common surgical procedures in the diabetic population. Heart disease is the leading cause of diabetes-related deaths. Cardiomyopathy in diabetic patients is independent of coronary artery disease and valvular heart disease and often progresses to impaired myocardial relaxation and ultimately diastolic dysfunction.[61] Adults with diabetes have heart disease death rates about two to four times higher than adults without diabetes.[52,53] Systolic dysfunction, decreased ejection fraction, and congestive heart failure may occur with severe and longstanding disease. Guidelines for perioperative cardiovascular evaluation, published by The American College of Cardiology/American Heart Association, list diabetes as an intermediate clinical predictor of cardiovascular risk.[62]

Further, more than 70% of diabetic individuals have a medical history of hypertension, a rate of occurrence two- to three-fold that for nondiabetic people. In many of these patients, the hypertension is uncontrolled. The risk of stroke is two to four times higher in people with diabetes, and their recovery rate after a stroke is poor.[63] Glucose-induced vasodilation further complicates an organ's ability to defend against an increase in systemic blood pressure.

The eyes are vulnerable to vascular disease because of the dense network of capillary vessels in the retina. Individuals with DM are 25 times more likely to be legally blind than individuals without DM.[48] Diabetic retinopathy is characterized by microaneurysm formation, swelling and narrowing of retinal blood vessels, and neovascularization. These vascular lesions may result in vitreous hemorrhage and retinal scarring or detachment. Loss of vision from diabetic retinopathy is the leading cause of new cases of blindness in people aged 20 to 74 years in the United States.[52,63]

Diabetic renal disease is the leading cause of end-stage renal disease in the United States.[48,60] The nephropathy may be caused by hemodynamic alterations, inflammation, and thickening of the glomerular capillary basement membrane and other structural changes in the glomerulus.[48] Renal insufficiency or chronic renal failure is often the end result. Diabetics commonly are candidates for kidney transplantation.

The diabetic process also interferes with normal nerve function. Diabetic neuropathy occurs in over 50% of individuals with longstanding disease.[48,52,53] Both the peripheral and autonomic nervous systems may be involved. Vagal denervation may occur early in the course of the disease. Dysfunction of the cardiac vagus nerve may be manifested as resting tachycardia, cardiac dysrhythmias, and the absence of heart-rate variability with deep breathing. Postural hypotension may occur in the diabetic with autonomic neuropathy as a result of dysfunctional sympathetic nervous system vasoconstrictive processes. Manifestations of orthostatic hypotension may include postural syncope, dizziness, and lightheadedness.

Diabetic patients with autonomic neuropathy are at increased risk for developing painless myocardial ischemia. The possibility of a myocardial infarction should be considered in the presence of unexplained hypotension in these patients.[64,65]

Other signs of autonomic neuropathy in the diabetic patient include early satiety, lack of sweating, impotence, and nocturnal diarrhea.[8] The patient with diabetic autonomic neuropathy has impaired gastric emptying and is at risk for aspiration of stomach contents in the perioperative period. Box 33-4 summarizes major chronic complications of DM.

There is a strong relationship between the hyperglycemia of diabetes and end-organ diseases. Sustained hyperglycemia seems to be prerequisite for significant nephropathy, retinopathy, and neuropathy to occur in type 1 and type 2 diabetes.[66,67] Other factors—genetic, environmental, or both—may have roles in determining end-organ complications. The hemoglobin A1c test, or glycosylated hemoglobin level, provides an estimate of the patient's overall plasma glucose control during the past 2 to 3 months. A value less than 7.0% suggests adequate blood glucose control.[48]

BOX 33-4

Chronic Complications of Diabetes Mellitus

Microvascular
- Retinopathy
- Neuropathy (sensory, autonomic, motor)
- Nephropathy

Macrovascular
- Coronary artery disease
- Peripheral vascular disease
- Cerebrovascular disease

Other
- Infection
- Cataracts
- Stiff joint syndrome
- Glaucoma
- Poor wound healing

Anesthetic Management of the Diabetic Patient

Diabetes is the most common endocrine disorder encountered in surgical patients. Long-standing diabetes predisposes the patient to many diseases that require surgical intervention. Cataract extraction, kidney transplantation, ulcer debridement, and vascular repair are some of the operations frequently performed on diabetic patients.

Diabetic patients have higher morbidity and mortality in the perioperative period compared with nondiabetics of similar age. Increased complications are not because of the disease itself but primarily because of organ damage associated with long-term disease.[8] Ischemic heart disease is the most common cause of perioperative mortality in the diabetic patient.[11]

Preoperative Considerations

The diabetic patient may come to the operating room with a spectrum of metabolic aberrations and end-organ complications that warrant careful preanesthetic assessment.

Cardiovascular complications account for most of the surgical deaths in diabetic patients.[8] The presence of hypertension, coronary artery disease, or autonomic nervous system dysfunctions can result in a labile cardiovascular course during anesthesia. It is essential that the cardiovascular and volume status of the patient be thoroughly evaluated before surgery. Preoperative electrocardiography is advised for all adult diabetic patients because of the high incidence of cardiac disease.

Autonomic nervous system dysfunction may result in delayed gastric emptying, making these patients prone to aspiration, nausea and vomiting, and abdominal distention. Preoperative aspiration prophylaxis with H_2-receptor blockers, gastroprokinetic agents, and/or preinduction antacids are recommended for patients with a prolonged history of poor glycemic control.[8,59,67] Intubation during general anesthesia is a logical choice for the patient with gastroparesis.

Patients with significant autonomic neuropathy may have an impaired respiratory response to hypoxia. These patients are especially sensitive to the respiratory-depressant effects of sedatives and anesthetics and require particular vigilance in the perioperative period.[8,11] Autonomic neuropathy contributes to a diminished thermoregulatory response to hypothermia requiring careful monitoring of core temperature.[59] Peripheral neuropathies (e.g., paresthesias, numbness in the hands and feet) should be adequately documented in the preanesthetic evaluation. Their presence may affect the decision to use regional anesthesia. Neuraxial blockade may exacerbate neural deficits in patients with diabetic polyneuropathy.[68]

Glycosylation of tissue proteins may produce a stiff-joint syndrome in diabetics. An estimated 30% to 40% of type 1 diabetics demonstrate restricted joint mobility.[11] Limited motion of the atlantooccipital joint can make endotracheal intubation in diabetic patients more difficult compared with nondiabetic patients.[69-71] Demonstration of the "prayer sign," an inability to approximate the palms of the hands and fingers, may help identify patients with tissue protein glycosylation and potentially difficult airways.

Evidence of kidney disease should be sought, and basic tests of renal function (e.g., urinalysis, serum creatinine, blood urea nitrogen) evaluated preoperatively. The presence of renal impairment may influence the choice and dosage of anesthetic agents, and potentially nephrotoxic drugs should be avoided. Patients should be well hydrated after radiocontrast dye exposure.

The anesthetist should examine the patient's history of glycemic control, including a fasting blood sugar on the morning of surgery, to ensure preoperative optimization of the patient's metabolic state. It is not clear what level of glycemic control is associated with the best risk/benefit ratio in the perioperative period, but a recommended target blood glucose range is 80 to 180 mg/dL.[72,73] Sustained hyperglycemia with attendant osmotic diuresis should alert the anesthetist to possible fluid deficits and electrolyte depletion. Preoperative electrolyte levels should be evaluated. Lactate-containing intravenous solutions are generally avoided because lactate conversion to glucose may contribute to hyperglycemia.

An important part of the preoperative evaluation is a review of oral hypoglycemic and insulin regimens.

Oral Glucose-Lowering Agents. Oral glucose-lowering agents and insulin are used as adjuncts to diet therapy and exercise for treating type 2 DM. Currently available oral hypoglycemic agents fall into the following classifications: (1) sulfonylureas, (2) nonsulfonylurea secretagogues, (3) α-glucosidase inhibitors, (4) thiazolidinediones, (5) biguanides, (6) DPP-4 inhibitors, (7) GLP-1 agonists, and (8) others. Often patients are on a combination of therapeutic agents. Table 33-4 lists medications commonly used to treat type 2 diabetes.

Sulfonylurea agents increase the secretion of insulin from the pancreas and thus require the presence of functioning β cells. These agents are not effective in patients with type 1 DM. Persistent and severe hypoglycemia is a possible adverse effect of sulfonylureas. The syndrome of inappropriate ADH secretion and hyponatremia has been associated with chlorpropamide, a first-generation sulfonylurea.

Newer nonsulfonylurea secretagogues such as the *meglitinides* (repaglinide) and *D-phenylalanine* (nateglinide) increase insulin production by pancreatic β cells in a manner similar to the sulfonylureas.[48,74] Caution must be used in patients with liver disease because these drugs are metabolized by the CYP34A enzyme pathway.

Acarbose (Precose) and miglitol (Glyset) are *α-glucosidase inhibitors*. These medications block the intestinal enzymes that digest starches into absorbable monosaccharides, resulting in a slower and lower rise in postprandial plasma glucose.

Rosiglitazone (Avandia) and pioglitazone (Actos) are *thiazolidinedione derivatives*. Thiazolidinediones decrease hepatic glucose output and reduce insulin resistance in the type 2 DM patient by sensitizing the insulin receptor for glucose uptake.[74] Liver enzymes must be monitored closely with these agents. The thiazolidinedione troglitazone (Rezulin) was withdrawn from the U.S. market for serious liver complications associated with the drug. In August 2007, the U.S. Food and Drug Administration (FDA) issued a "black box" warning on the drugs Avandia, Actos, and combination drugs that include these agents because of a significant increased risk of heart failure. As of November 2011, rosiglitazone has restricted availability in the United States.

Metformin, a *biguanide*, decreases hepatic glucose production and increases peripheral insulin use. Lactic acidosis, a rare but potentially fatal problem, has been reported with biguanides. Lactic acidosis is precipitated by drug accumulation; therefore, even mild renal impairment or nephrotoxicity is a contraindication to metformin therapy. Metformin is also not prescribed to patients with conditions that predispose to acidosis (e.g., liver disease, congestive heart failure).[75,76]

Sitagliptin phosphate (Januvia) is the first in a new class of oral glucose-lowering drugs known as *DPP-4 (dipeptidyl peptidase-4) inhibitors*. This class of drugs enhances insulin release from the pancreas in response to hyperglycemia. Two other DPP-4 inhibitors include saxgliptin (Onglyza) and linagliptin (Tradjenta).[74]

Exenatide (Byetta), and liraglutide (Victoza) are part of the newer class of drugs called GLP-1 (*glucagon-like polypeptide 1*) agonists also referred to as *incretin mimetics*. These drugs are approved as alternatives to starting insulin in type 2 DM and are only available via subcutaneous injection. Exenatide is derived from the saliva of the gila monster, with an amino acid sequence similar to that of human glucagon-like peptide. In the presence of glucose, the drug stimulates insulin release and lowers serum glucagon levels.[74]

Pramlintide (Symlin) is an injected antihyperglycemic medication for use in patients with type 2 or type 1 diabetes treated

TABLE 33-4 Oral Drugs for Type 2 Diabetes

Drug	Usual Daily Dosage
DPP-4 Inhibitor	
Sitagliptin (Januvia)	100 mg once
Saxgliptin (Onglyza)	2.5-5 mg once
Linagliptin (Tradjenta)	5 mg once
Sulfonylurea: First Generation	
Chlorpropamide (Diabinese)	250 to 375 mg once
Tolazamide (Tolinase)	250 to 500 mg once or divided
Tolbutamide (Orinase)	1000 to 2000 mg divided
Sulfonylurea: Second Generation	
Glimepiride (Amaryl)	1 to 4 mg once
Glipizide (Glucotrol)	10 to 20 mg once or divided
(Glucotrol XL sustained-release tablets)	5 to 20 mg once
Glyburide (DiaBeta, Micronase)	5 to 20 mg once or divided
(Glynase micronized tablets—Glynase Prestab)	1.5 to 12 mg once or divided
Alpha-glucosidase Inhibitors	
Acarbose (Precose)	50 to 100 mg tid with meals
Miglitol (Glyset)	50 to 100 mg tid with meals
Thiazolidinediones	
Rosiglitazone (Avandia) (restricted availability after November 18, 2011)	4 to 8 mg once or divided
Pioglitazone (Actos)	15 to 45 mg once
Biguanides	
Metformin (Glucophage)	1500 to 2550 mg divided
(Glucophage XR)	1500 to 2000 mg once
Glumetza (sustained release)	500-2000 mg once
Fortamet (sustained release)	1500-2500 mg once
Riomet (liquid)	1500-2550 mg divided
Nonsulfonylurea Secretagogues	
Repaglinide (Prandin)	1 to 4 mg tid before meals
Nateglinide (Starlix)	60 to 120 mg tid before meals
GLP-1 Agonists	
Exenatide (Byetta)	5 or 10 mcg subcut bid before breakfast and dinner
Liraglutide (Victoza)	1.2 or 1.8 mg subcut once
Amylin Analog	
Pramlintide (Symlin)	60-120 mcg subcut tid before main meals
Combination Drugs	
Metformin/glyburide (Glucovance)	500 mg/5 mg bid
Metformin/rosiglitazone (Avandamet)	500 mg/2 mg bid
Metformin/glipizide (Metaglip)	500 mg/2.5 mg bid
Metformin/pioglitazone (Actoplus Met)	500 mg/15 mg bid
(Actoplus Met XR sustained release)	1000 mg/15 mg once
Metformin/repaglinide (Prandimet)	500 mg/1-2 mg bid-tid
Metformin/sitagliptin (Janumet)	500 mg/50 mg bid
Metformin/saxagliptin (Kombiglyze XR)	1000-2000 mg/5 mg once
Glimepiride/rosiglitazone (Avandaryl)	4 mg/4 mg bid
Glimepiride/pioglitazone (Duetact)	4 mg/30 mg once

Modified from Treatment guidelines: drugs for type 2 diabetes. *Med Lett.* 2011;108:47-54.
DPP-4 inhibitor, Dipeptidyl-peptidase-4 inhibitor; *GLP-1*, glucagon-like peptide; *subcut*, subcutaneous.

with mealtime insulin. It is a synthetic analog of human amylin, a naturally occurring hormone synthesized from pancreatic β cells that contributes to glucose control during the postprandial period. Amylin, similar to insulin, is absent or deficient in patients with diabetes.[74]

Insulin Preparations. Insulin preparations are generated today by DNA recombinant technology, mimicking the amino acid sequence of human insulin. All insulin formulations in the United States are prepared as U-100 (100 units/mL).

Insulin preparations differ in onset and duration after subcutaneous administration. In addition to subcutaneous injections, insulin delivery devices (e.g., implantable pumps, mechanical syringes) are used to facilitate exogenous administration. The greatest risk with all forms of insulin is hypoglycemia. Table 33-5 identifies major classes of exogenous insulin: rapid acting, short-acting regular, intermediate-acting, long-acting, and premixed.

It is imperative to know the surgical patient's normal insulin dosage regimen and treatment compliance. Some diabetic patients are on a fixed regimen that consists of a mixture of rapid- and intermediate-acting insulins taken before breakfast and again at the evening meal.[11] Other patients are on multiple injection regimens designed to provide more physiologic glycemic control.[48]

Insulin glargine (Lantus) and insulin detemir (Levemir) are biosynthetic human insulin analogs taken once a day. These insulins have delayed absorption from subcutaneous tissue, which prolongs their effects. Unlike neutral protamine Hagedorn and Lente, they have no peak effects, but rather provide steady plasma concentrations.[77]

Continuous subcutaneous insulin infusion is increasingly used by motivated patients desiring an optimal physiologic regimen.[78] Sophisticated infusion devices deliver small doses (microliters/min) of rapid-acting insulin lispro or insulin aspart at various programmable delivery rates. The pumps may be discontinued and a continuous insulin infusion implemented for the perioperative period. Alternatively, if continued into the perioperative period, the pump can be programmed to deliver a basal insulin dose supplemented with dextrose and potassium as needed, with rate adjustment based on serial blood-glucose measurements.[48,79,80]

Intraoperative Management

The diabetic surgical patient's operation should be scheduled early in the day if possible to minimize disruptions in treatment and nutrition regimens. Surgery produces a catabolic stress response and elevates stress-induced counterregulatory hormones.[11] In the diabetic patient, the hyperglycemic, ketogenic, and lipolytic effects of the counterregulatory hormones compound the state of insulin deficiency. For this reason, perioperative hyperglycemia and other metabolic aberrations are common in the surgical diabetic patient.

No specific anesthetic technique is superior overall for diabetic patients. Both general anesthesia and regional anesthesia have been used safely. General anesthesia, however, has been shown to

TABLE 33-5 Pharmacokinetics of Insulin Preparations

Insulin Type	Onset	Peak	Duration	Route
Long-Acting				
Insulin detemir—Levemir (Novo Nordisk)	1-4 hr	Relatively flat	12-20 hr	subcut
Insulin glargine—Lantus (Sanofi-Aventis)	1-4 hr	No peak	22-24 hr	subcut
Rapid-Acting				
Insulin aspart—Novolog (Novo Nordisk)	10-30 min	30 min to 3 hr	3-5 hr	subcut
Insulin lispro—Humalog (Lilly)	10-30 min	30 min to 3 hr	3-5 hr	subcut
Insulin glulisine—Apidra (Sanofi-Aventis)	10-30 min	30 min to 3 hr	3-5 hr	subcut
Short-Acting Regular Insulin				
Humulin R (Lilly)	30-60 min	2½-5 hr	4-12 hr	IV, subcut, IM
Novolin R (Novo Nordisk)	30-60 min	2½-5 hr	4-12 hr	IV, subcut, IM
Intermediate-Acting				
NPH				
Humulin N	1-2 hr	4-8 hr	10-20 hr	subcut
Novolin N	1-2 hr	4-8 hr	10-20 hr	subcut
Premixed Analogs				
Novolin 70/30 (Novo Nordisk) (70% NPH, human insulin isophane susp and 30% regular human insulin)	30-60 min	2-12 hr	18-24 hr	subcut
Novolog 70/30 (Novo Nordisk) (70% insulin aspart protamine susp and 30% insulin aspart injection)	10-20 min	1-4 hr	18-24 hr	subcut
Humalog Mix 75/25 (Lilly) (75% insulin lispro protamine susp and 25% insulin lispro)	10-30 min	1-6½ hr	14-24 hr	subcut

Adapted from Treatment guidelines: drugs for type 2 diabetes. *Med Lett.* 2011;108:47-54.
Time course is based on subcutaneous administration.
IM, Intramuscular; *IV*, intravenous; *subcut*, subcutaneous; *NPH*, neutral protamine Hagedorn.

induce hormonal changes that accentuate glycogenolysis and gluconeogenesis, compounding the diabetic patient's hyperglycemic state. Regional anesthesia may produce fewer deleterious changes in glucose homeostasis.[73]

Cardiovascular autonomic neuropathy contributes to hemodynamic instability and may complicate the anesthetic course. Indeed, the compensatory mechanisms to anesthesia-induced vasodilation may be impaired, requiring the use of vasoactive drugs.[64] Withholding angiotensin-converting enzyme inhibitors preoperatively is gaining acceptance in an effort to avoid intraoperative hypotension.[61]

Special care must be taken in positioning and padding the diabetic patient on the operating table. Decreased tissue perfusion and peripheral sympathetic neuropathy may contribute to the development of skin breakdown and ulceration.

Diabetic patients represent a heterogeneous group requiring individualized perioperative care. The specific approach to metabolic management depends on the type of diabetes (type 1 or type 2), the history of glycemic control, and the type of surgery being performed. Frequent blood glucose determinations are an integral part of any diabetic management technique. A glucose meter or other accurate and rapid means of monitoring blood glucose levels should be available. During a long surgical procedure or for major surgery, at least hourly intraoperative blood glucose measurement is the prudent course for the brittle diabetic patient.

Strict control of even short-term elevations in blood glucose improves perioperative morbidity.[81,82] Persistent hyperglycemia has been shown to impair wound healing and wound strength.[83] In addition, reports suggest that postoperative infection is more prevalent in diabetic patients with uncontrolled blood sugar levels.[84,85] Studies also provide evidence that hyperglycemia worsens the neurologic outcome after ischemic brain injury.[86-88] Avoiding perioperative hyperglycemia is advisable, especially in patients at risk for acute neurologic insult (e.g., carotid endarterectomy, intracranial surgery, cardiopulmonary bypass).

Various regimens have been tendered on how to best manage the metabolic changes that occur in the surgical diabetic patient.[8,89-93] Experts differ on optimal protocols for case management and precisely defined target glucose levels. Current debate centers on the risk/benefit ratio of intensive or "tight" blood glucose control versus "nontight" control during surgery. The universal goal with all techniques is to avoid hypoglycemia and minimize metabolic derangements. Patients under anesthesia are generally maintained with a mild transient hyperglycemia to avoid the potentially catastrophic effects of hypoglycemia.[8,72] Frequent blood glucose determinations during surgery and in the immediate postoperative period are central to safe practice.[11]

Following are three different approaches to the metabolic management of the adult surgical diabetic patient, but the reader should note that there are numerous variations.

Intermediate-Acting Insulin Use. This is a traditional nontight method of managing the surgical diabetic patient and involves less intensive control of plasma glucose but aims to avoid marked hyperglycemia and dangerous hypoglycemia. Variations of this technique are used for stable diabetics undergoing elective operative procedures.[8,11]

1. On the morning of surgery, fasting blood sugar level is measured.
2. An intravenous (IV) infusion containing 5% dextrose is started at 100 to 150 mL/hr.

3. After the IV infusion is started, half of the patient's normal morning intermediate- or long-acting insulin dose is administered subcutaneously.
4. The glucose-containing IV infusion is continued throughout surgery. Additional fluid requirements are met with the administration of a second glucose-free infusate.
5. Blood glucose levels are checked every 1 to 2 hours during surgery.
6. If the blood glucose level exceeds an established maximum level, commonly 180 mg/dL, regular insulin is administered according to an established "sliding scale." Insulin sensitivity varies markedly from one patient to the next, but on the average, 1 unit of regular insulin can be expected to decrease the blood glucose level 40 to 50 mg/dL.[94] This time-tested regimen is easy to implement, and it is usually successful in preventing significant hypo- or hyperglycemia.[8,95,96]

The disadvantages of this technique are as follows:

1. Absorption of preoperatively administered subcutaneous insulin is unpredictable and erratic in the surgical patient because of blood pressure, blood flow, and temperature variations that occur with anesthesia.
2. The onset and peak effect of the preoperative intermediate-acting insulin may not correspond to the time of surgical stress, especially if the operation is delayed or prolonged.
3. The half-life of regular insulin is short, and a "rollercoaster" glucose profile may occur. Plasma glucose levels will vary considerably.

Insulin Infusion. An insulin intravenous infusion management technique may be used to maintain the blood glucose concentration within relatively narrow boundaries. Intensive perioperative regulation of blood glucose prevents hyperglycemia, but it carries the risk of hypoglycemia, and therefore necessitates more frequent blood glucose assays.[8,73,81] Regular insulin infusion may range from 0.5 to 5 units/hr, depending on the clinical situation and insulin resistance.[48] Intraoperative insulin infusion may be considered for the type 1 diabetic having major or prolonged surgery, the poorly controlled diabetic, the pregnant diabetic, the diabetic undergoing coronary artery bypass grafting, and the diabetic with serious concurrent illness.[8] An example of this regimen would be as follows:

1. On the morning of surgery, a fasting blood glucose level is measured.
2. An infusion of 5% dextrose (D_5W, 5% dextrose in water) is started at a rate of 50 mL/hr per 70-kg body weight.
3. A regular insulin infusion is begun, piggy-backed to the glucose infusion. The insulin infusion rate is set at insulin (units/hr) = last plasma glucose (mg/dL) ÷ 150. (If the patient is obese, has infection, or is on corticosteroids, the divisor is changed to 100.)
4. Blood glucose levels are measured every hour during insulin infusion and potassium levels checked after the first hour of the infusion.
5. Additional fluid requirements are met with the administration of a second glucose-free infusate.

Blood glucose levels less than 80 mg/dL may be treated with $D_{50}W$ and remeasured in 30 minutes. In a 70-kg patient, 15 mL of $D_{50}W$ can be expected to raise the blood glucose concentration by about 30 mg/dL. Surgical patients undergoing renal transplantation or coronary artery bypass graft procedures, obese and septic patients, and patients on steroid therapy usually have higher insulin-infusion requirements.[8,92,97]

The advantages of tight glucose management in the perioperative period are as follows:

1. The insulin infusion can be finely regulated to correspond to hourly variations in blood glucose levels.
2. Periods of hyperglycemia are less likely. Deleterious effects of hyperglycemia (e.g., hyperosmolarity, osmotic diuresis, impaired wound healing, infection) may be prevented.
3. The insulin-glucose infusion can be continued into the postoperative period until the patient is ready to eat, at which time subcutaneous insulin or an oral hypoglycemic agent can be reinstated.

Type 2 Diabetes and Oral Hypoglycemic Agents. Patients treated with oral hypoglycemic agents demand the same individualized perioperative management as those with type 1 diabetes. The duration of action of the patient's oral agent must be noted.

For the well-controlled surgical patient with type 2 diabetes who is scheduled for minor to moderate surgery, the patient's short-acting oral hypoglycemic agent may be continued until the evening before surgery. Discontinuing long-acting agents 2 to 3 days before surgery and converting to shorter-acting agents or insulin affords better perioperative glucose control.[97] Metformin should be discontinued 2 days or more before surgery because the surgical risks of hypotension and renal hypoperfusion place patients on this drug at increased risk for lactic acidosis.[75,76]

Glucose-containing fluids may be administered intraoperatively to protect against possible residual effects of oral hypoglycemic agents. Other experts adhere to a "no glucose, no insulin" technique for well-controlled type 2 diabetic patients. Regardless of the technique chosen, plasma glucose should be measured regularly throughout the procedure and hyperglycemia treated with insulin on a "sliding" scale.[95,96]

Acute Derangements in Glucose Homeostasis

Hypoglycemia

Hypoglycemia is encountered more often in the diabetic patient than in the healthy adult, and it can develop insidiously during the perioperative period.

Medications (e.g., insulin, sulfonylureas, β-adrenergic receptor blocking agents) and toxins (e.g., ethanol) are common causes of hypoglycemia. Severe liver disease (impaired hepatic glucose output), the altered physiology associated with gastric bypass surgery, sepsis, or an insulin-secreting tumor of the islets of Langerhans (an insulinoma) are conditions that are often complicated by hypoglycemia.

The blood glucose concentration at which signs and symptoms of hypoglycemia appear varies widely from one person to the next, but blood glucose levels in the range of 45 to 50 mg/dL commonly produce mild symptoms in the otherwise healthy patient. Because the brain is the predominant organ of glucose consumption, it is most sensitive to glucose deprivation.[46,47,98] Manifestations of impaired cerebral function (e.g., confusion, dizziness, headache, weakness) are associated with glucose lack. As the blood sugar level declines below 50 mg/dL, aberrant behavior, seizures, and loss of consciousness may occur. Other signs of hypoglycemia (e.g., tachycardia, diaphoresis, anxiety, tremors, piloerection, pupillary dilation, and vasoconstriction) reflect sympathetic-adrenal hyperactivity.[46] Acute treatment for the hypoglycemic surgical patient is the intravenous administration of 25 to 50 mL of 50% dextrose, followed by a continuous infusion of 5% dextrose.[11,48] Unless prompt glucose therapy is provided, irreversible brain damage may result.

Hypoglycemia is potentially catastrophic during surgery because most of the neural indications of glucose lack are masked by general anesthesia. Signs of sympathetic adrenal discharge also may be blunted by general anesthesia or severe diabetic autonomic neuropathy, making the diagnosis of hypoglycemia extremely difficult. β-Adrenergic receptor blocking agents can reduce the hyperglycemic effects of epinephrine, in addition to diminishing the

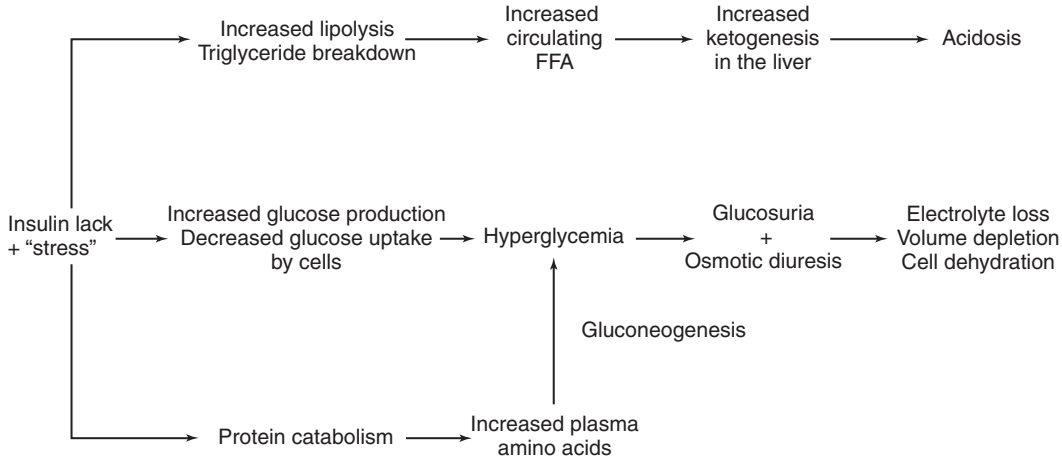

FIGURE **33-11** Substrate flow with diabetic ketoacidosis. *FFA*, Free fatty acid.

symptomatic warning signs of hypoglycemia.[48,98] Frequent blood glucose determinations, maintenance of mild hyperglycemia, and diligent monitoring help to avoid this serious complication during anesthesia.

Diabetic Ketoacidosis

Diabetic ketoacidosis (DKA) is a medical emergency with a mortality rate of 5% to 10% (National Diabetes Information Clearinghouse [NDIC], 2011). DKA is triggered by a hyperglycemic event, usually in a patient with type 1 DM. Treatment errors, critical illnesses (e.g., myocardial infarction, trauma, cerebral vascular accident, burns), and infections are common precipitants of DKA.[99,100,101]

Stressful events stimulate the release of hyperglycemic counterregulatory hormones (e.g., glucagon, GH, epinephrine, cortisol).[46,48] The insulin-dependent diabetic is unable to secrete insulin to counterbalance the serum elevations of glucose, free fatty acids, and ketone bodies produced by these stress-induced hormones. Unless exogenous insulin is provided, the glycemic event may progress to severe ketoacidosis, dehydration, and acute metabolic decompensation.

DKA usually develops over 24 hours. Major signs and symptoms include hyperglycemia, volume depletion (average fluid deficit 5 L), tachycardia, metabolic acidosis, a calculated anion gap greater than 10, electrolyte depletion, hyperosmolarity (greater than 300 mOsm/L), nausea and vomiting, abdominal pain, and lethargy.[48,99] Blood levels of ketone bodies are elevated to above 5 mEq/L, and the patient's breath may have a fruity odor from excess acetone production. The respiratory center is typically stimulated by the low plasma pH, resulting in rapid, deep breathing (*Kussmaul respiration*). Acidosis, hyperosmolarity, and dehydration may depress consciousness to the point of coma.[48,99,100] Hypotension, hyperkalemia, and tissue catabolism also may be present. Figure 33-11 outlines the pathophysiologic events leading to diabetic ketoacidosis.

Gangrene and infection of an ischemic lower extremity are common surgical conditions associated with DKA. Preoperative management of the surgical patient with DKA requires an aggressive approach to restore intravascular volume, correct electrolyte abnormalities, improve acid-base balance, and reduce blood glucose levels with intravenous insulin.[48,99,100] The airway must be protected in the obtunded patient. Once the surgical problem that initiated DKA has resolved, medical management often is more effective.[8,101]

TABLE 33-6 Features of Diabetic Ketoacidosis (DKA) and Hyperglycemic Hyperosmolar Syndrome (HHS)

	DKA	HHS
Plasma glucose	Greater than 250 mg/dL	Greater than 600 mg/dL
pH	Less than 7.3	Greater than 7.3
Serum bicarbonate	Less than 18 mmol/L	Greater than 15 mmol/L
Serum osmolarity	+	++
Ketonemia	++	Normal or slight +
Mental obtundation	Variable	Present
Hypovolemia	Present	Present
Serum potassium	Normal or slight +	Normal

+, Increase; ++, large increase.

Hyperglycemic Hyperosmolar State

Hyperglycemic hyperosmolar state (HHS) is a life-threatening hyperosmolar condition triggered by a hyperglycemic event. This syndrome commonly occurs in elderly patients with type 2 DM, but it also develops in patients with no history of diabetes. Patients generally have some endogenous insulin secretion, but the hyperglycemic episode overwhelms the pancreas and produces severe hyperglycemia and glucosuria.[48,99,100] The amount of insulin secreted is usually sufficient to prevent lipolysis and ketone production. Therefore, unlike DKA, this syndrome usually is not associated with acidosis or significant ketogenesis. Table 33-6 compares common features of diabetic ketoacidosis and HHS.

Common precipitating factors of HHS include infection, sepsis, pneumonia, stroke, and myocardial infarction.[48,99,100]

A spectrum of symptoms is associated with HHS, culminating in mental confusion, lethargy, and coma.[48,99,100] Profound dehydration is present, resulting in hypotension and tachycardia. Laboratory evaluation may reveal a biochemical profile of marked hyperglycemia, normal arterial pH, absent or minimal ketonemia, and hyperosmolarity (greater than 330 mOsm/L).[48,99,100] Despite depleted total body potassium stores, the serum potassium levels at presentation may be normal or elevated due to acidosis and insulin-lack.[48,99,100] Even with appropriate treatment, the mortality figures for HHS are substantially higher (15%) than

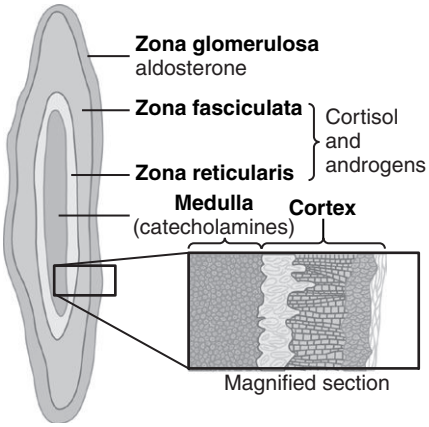

FIGURE **33-12** Secretion of adrenocortical hormones by the different zones of the adrenal cortex and secretion of catecholamines by the adrenal medulla. (From Hall JE. *Guyton and Hall Textbook of Medical Physiology.* 12th ed. Philadelphia: Saunders; 2011:921.)

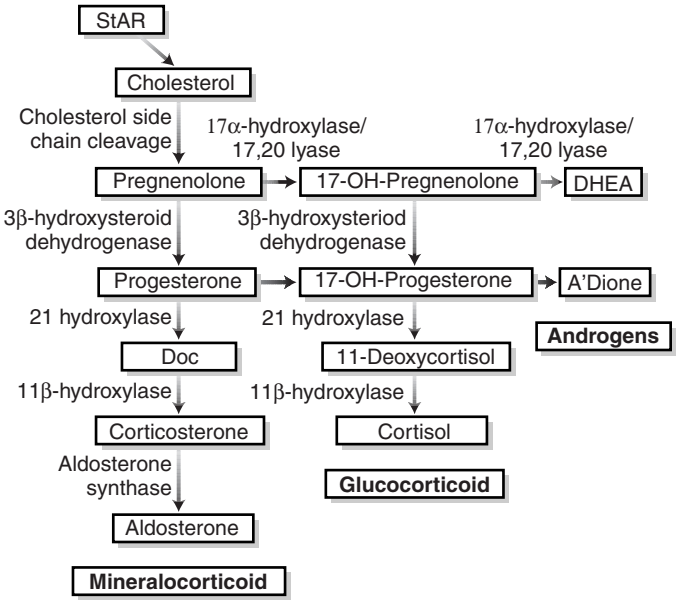

FIGURE **33-13** Adrenal steroidogenesis. Aldosterone, cortisol, and adrenal androgens are synthesized by a series of steroidogenic enzymes in a zone-specific fashion. *A'Dione,* Androstenedione; *DHEA,* dehydroepiandrosterone; *Doc,* deoxycorticosterone. (From Stewart PM. The adrenal cortex. In: Kronenberg HM, et al. *Williams Textbook of Endocrinology.* 11th ed. Philadelphia: Saunders; 2008:449.)

those for DKA (less than 5%), in part because HHS commonly affects an older patient population, often with accompanying comorbidities.[11,48,99,100]

Treatment goals are similar to those for DKA and include identification and management of the precipitating problem, vigorous isotonic rehydration (average total body water deficit 9 L), correction of hyperglycemia, and electrolyte replacement.[48,99,100] An IV insulin infusion is necessary to reduce elevated serum glucose levels. The hazards inherent in aggressive fluid administration in the elderly patient dictate central hemodynamic monitoring during treatment.

ADRENAL GLANDS

The adrenal glands are located at the superior poles of each kidney and consist of two distinct anatomic and physiologic entities, the adrenal cortex and the adrenal medulla. The *adrenal medulla* comprises the central 20% of the adrenal gland and secretes the hormones epinephrine and norepinephrine. The *adrenal cortex* constitutes the outer part of the adrenal gland and secretes three main types of hormones: mineralocorticoids (e.g., aldosterone), glucocorticoids (e.g., cortisol), and androgenic hormones (e.g., dehydroepiandrosterone).[102]

Adrenal Cortex

The adrenal cortex is composed of three layers, each having distinct properties. The *zona glomerulosa* is the outermost tissue of the cortex; it secretes mineralocorticoid hormones. The *zona fasciculata* is the middle layer; it secretes primarily cortisol and other glucocorticoid hormones. The *zona reticularis* is the innermost layer of the adrenal cortex; it secretes primarily adrenal androgenic hormones[102,103] (Figure 33-12).

Hormones Secreted from the Adrenal Cortex

The adrenal cortex synthesizes more than 30 types of steroid hormones. All hormones secreted from the adrenal cortex have a steroidal structure and share a common cholesterol backbone. As a group, these hormones are termed *corticosteroids*. Corticosteroids have similar chemical structures but widely diverse functions.

Glucocorticoid and adrenal androgenic hormone production and release is controlled in major part by ACTH from the anterior pituitary gland. ACTH stimulates glucocorticoid hormone synthesis by activating the *P450 side chain cleavage enzyme* (P450ssc or *desmolase*). P450scc catalyzes the conversion of cholesterol to pregnenolone, the first step in corticosteroid hormone synthesis (Figure 33-13). The adrenal androgens, of which dehydroepiandrosterone is the most important, have effects similar to the male sex hormone testosterone and account for secondary sexual characteristics in females.[102] The glucocorticoids and mineralocorticoids are discussed in more detail in the following sections.

Glucocorticoids. Cortisol (hydrocortisone) is the prototypical glucocorticoid, and it accounts for 95% of the glucocorticoids released from the adrenal cortex.[103] Cortisol secretion is largely controlled by ACTH or corticotrophin. In turn, cortisol is the most potent regulator of ACTH. Cortisol has a direct negative feedback effect on the hypothalamus, inhibiting the release of corticotropin-releasing hormone (CRH), and on the anterior lobe of the pituitary gland, decreasing ACTH synthesis and release. When cortisol concentration is high, the feedback system reduces ACTH production. Figure 33-14 summarizes the mechanisms regulating cortisol release. Secretion rates of CRH, ACTH, and cortisol follow a circadian rhythm: levels are elevated in the early morning and decrease in the evening.[102,103]

The daily cortisol production is 15 to 30 mg, and most of this is produced and released in the morning.[102-104] Physical and mental stress increase the secretion of CRH, ACTH, and cortisol (Box 33-5). Stress, including surgery, typically raises cortisol production levels to more than 100 mg/day.[11,102,103,105] The normal cortisol blood concentration averages 12 mcg/dL, and this may increase to 30 to 50 mcg/dL during and after major surgery.[8,11]

After release from the adrenal cortex, cortisol circulates in the blood as free cortisol (the physiologically active form) or bound to cortisol-binding globulin (transcortin) or albumin. Approximately 90% to 95% of cortisol is transported in the bound form, and 6% is free. Cortisol is cleared from the blood in 1 to 2 hours but has a prolonged end-organ effect. Like other steroid hormones, cortisol exerts its effects by binding to target cell nuclear receptors and altering gene transcription and translation. Most of the metabolic effects of cortisol are therefore not immediate, but may take several

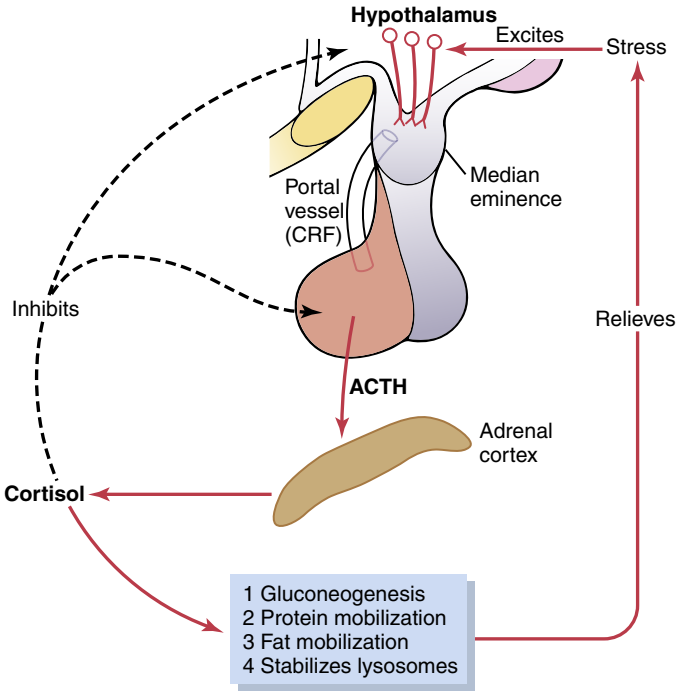

FIGURE **33-14** Mechanism for regulation of cortisol secretion. *ACTH,* Adrenocorticotropic hormone; *CRF,* corticotrophin-releasing factor. (From Hall JE. *Guyton and Hall Textbook of Medical Physiology.* 12th ed. Philadelphia: Saunders; 2011:932.)

BOX **33-5**

Control of ACTH Hormone Secretion

Stimulation
- Corticotropin-releasing hormone
- Sleep-to-waking period
- Stress
- Hypoglycemia
- Sepsis
- Trauma
- Decreased plasma cortisol
- α-Adrenergic receptor stimulation

Inhibition
- Elevated plasma cortisol
- Opioids

ACTH, Adrenocorticotropic hormone.

hours to fully develop. Cortisol is inactivated mainly in the kidney and liver and excreted in the urine as 17-hydroxycorticosteroids.[103]

Cortisol Actions. Glucocorticoids have effects in virtually all cells in the body.[102] They are needed for the proper use of proteins, carbohydrates, and fats by the body. Glucocorticoids permit catecholamine synthesis and help mediate their effects on the heart and vasculature. Cortisol is central to the body's response to physical and mental stress.[102,103] Almost any stress, psychologic or physical, causes an immediate and marked increase in ACTH and cortisol secretion. Important perioperative stressors may include pain, anxiety, trauma, infection, intense heat or cold, and surgery. Inadequate cortisol during critical illness and surgery can lead to hypotension, shock, and death.[102,104]

Glucocorticoids have some mineralocorticoid and androgenic effects that may become especially apparent with hormone excess or supraphysiologic replacement dosages.

Effect on Carbohydrate Metabolism. Overall, glucocorticoids enhance the production of high-energy fuel for metabolic needs.[102] A key function is their ability to stimulate gluconeogenesis in the liver. The rate of gluconeogenesis increases 6- to 10-fold in the presence of cortisol.[103] Further, cortisol mobilizes amino acids from extrahepatic tissues (mainly muscle), making them available for gluconeogenesis and glycogenesis in the liver.[103] In extrahepatic tissues, cortisol moderately decreases the rate of glucose uptake and use. Cortisol is called "diabetogenic" because it increases blood glucose concentrations.

Effect on Protein Metabolism. Cortisol decreases protein synthesis and increases protein catabolism in essentially all body cells except those of the liver.[103] In the presence of sustained cortisol excess, the catabolic effects are marked. This is especially apparent in skeletal muscles, which become weak and atrophic.

Effect on Fat Metabolism. Plasma free fatty acids are mobilized from adipose tissue under cortisol's effect. Cortisol also enhances oxidation of fatty acids in the cells. In times of starvation or other stress, these two effects help shift metabolic systems to the use of fatty acids instead of glucose for energy. Excess cortisol results in a distinctive obesity, with chest, abdominal, interscapular, and facial fat expansion, leading to a "buffalo-like" torso and "moon facies."[102-104]

Effect on Inflammation and Immunity. Cortisol can diminish the body's inflammatory responses by suppressing proinflammatory cytokines. Migration of white blood cells into the inflamed area is also decreased. At pharmacologic doses, cortisol stabilizes lysosomal membranes and decreases antibody production.[102] These effects are the basis for therapeutic use of corticosteroids to reduce inflammatory responses associated with asthma, allergic reactions, and other inflammatory disorders.

Cortisol decreases the number of eosinophils and lymphocytes in the blood. T lymphocyte and antibody output are decreased from the atrophy of lymphoid tissue. As a result, with pharmacologic doses of cortisol, the level of immunity to foreign invaders of the body is reduced, and infection may ensue from infection that would otherwise not be pathologic. The ability of cortisol and other glucocorticoids to suppress immunity makes exogenous administration of these hormones useful in preventing the immunologic rejection of transplanted organs and in treating several autoimmune disorders.

Mineralocorticoids. *Mineralocorticoids* are required for life. They play a major role in the regulation of extracellular sodium and potassium ion concentrations and total body fluid balance. *Aldosterone* is the body's principal mineralocorticoid, accounting for 90% of all mineralocorticoid activity.[103] It is secreted from the zona glomerulosa, the thin zone of cells on the surface of the adrenal cortex. In large part, this zone functions autonomously of the other two adrenal cortex zones. Most distinctly, control of aldosterone secretion from the zona glomerulosa is largely independent of ACTH control (Figure 33-15). After secretion from the adrenal cortex, aldosterone circulates 60% bound to serum proteins. It has a relatively short half-life of about 20 minutes.[103]

The four main physiologic stimulants of aldosterone release are as follows, in order of importance[103]:

1. Hyperkalemia
2. Angiotensin II (activation of the renin-angiotensin system)
3. Hyponatremia
4. ACTH

With a total loss of mineralocorticoid secretion, death would ensue within days without treatment.[103,104]

Aldosterone Functions. One of our body's most significant protectors of volume status is the renin-angiotensin-aldosterone system. Renin is a proteolytic enzyme released from the *juxtaglomerular cells* of the kidney afferent arteriole in response to hypovolemia, sympathetic nervous system stimulation, hypotension, or hyponatremia.[106,107] Renin acts on the plasma protein

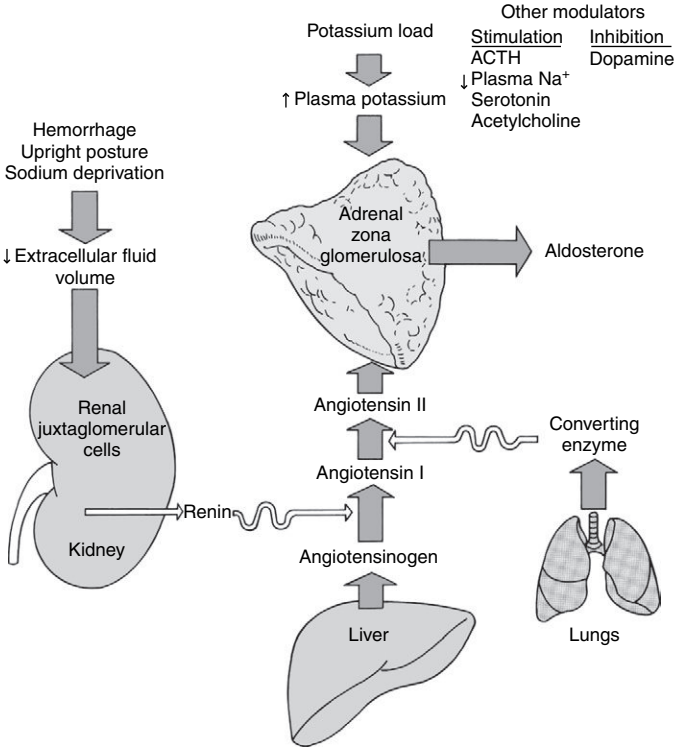

FIGURE **33-15** Regulation of aldosterone secretion. Hyperkalemia and activation of the renin-angiotensin system in response to hypovolemia are the predominant stimuli to aldosterone production. Adrenocorticotropin hormone (ACTH) has only a minor tonic stimulatory effect. (From Berne RM, et al, eds. *Physiology.* 5th ed. St Louis: Mosby; 2004:905.)

angiotensinogen to form angiotensin I (a 10–amino acid peptide), which is acted on by *angiotensin-converting enzyme* (primarily in the lung) to form angiotensin II (an 8–amino acid peptide). Angiotensin II is an extremely powerful vasoconstrictor and a potent stimulus of aldosterone synthesis and release.[102]

Aldosterone's primary target cells are *principal cells*, located in the kidney distal convoluted tubules and cortical collecting ducts. Here, aldosterone causes the reabsorption of Na^+ from the tubular fluid and in exchange, secretion of K^+ into the tubular fluid for excretion. Aldosterone's effect on the extracellular sodium ion *concentration* is limited because simultaneous with the Na^+ absorption is absorption of nearly equivalent amounts of water. Sodium and water reabsorption expands the extracellular fluid volume and elevates arterial blood pressure.[103]

Aldosterone's action on sweat and salivary glands is similar to that on renal tubules. The effect on sweat glands is important in hot environments, where body salt conservation is needed.

Disorders Associated with the Adrenal Cortex

An excess or deficiency of corticosteroids is associated with distinctive clinical syndromes.

Primary Aldosteronism. J.W. Conn described the first case of primary mineralocorticoid excess in 1954, a year after the biochemical composition of aldosterone was identified.[108] *Conn's syndrome* results from hypersecretion of aldosterone from an adrenal adenoma independent of stimulus. Primary aldosteronism also may be caused by adrenocortical hyperplasia or, rarely, carcinoma.[102] An increase in the plasma concentration of aldosterone and an increase in the urinary excretion of potassium with coexisting hypokalemia are pathognomonic of hyperaldosteronism.[102]

Manifestations of the syndrome reflect the exaggerated effects of aldosterone. Aldosterone's action of promoting renal excretion of K^+ (or hydrogen $[H^+]$) in exchange for Na^+ results in hypokalemic metabolic alkalosis. Hypertension associated with mineralocorticoid excess results from aldosterone-induced sodium retention and subsequent increase in extracellular fluid volume. Sodium levels tend to be normal due to concurrent fluid retention.[102,106,107] Primary aldosteronism accounts for less than 1% of all cases of hypertension.[11]

Primary aldosteronism is associated with low renin levels, a result of the elevated blood pressure's negative feedback to the juxtaglomerular cells. With *secondary hyperaldosteronism* the stimulus of excess aldosterone resides outside of the adrenal gland and is often associated with an increase in circulating renin levels.[102]

Treatment. Treatment of primary aldosteronism involves surgical removal of the adenoma or medical management. Surgical intervention is more successful for primary aldosteronism caused by adrenocortical adenoma than for gland hyperplasia because adenomas are almost always unilateral. When the affected adrenal gland is removed, the patient is cured in most cases. For patients with adrenal hyperplasia, pharmacologic antagonism of the mineralocorticoid receptor with spironolactone or eplerenone has been used successfully.[102,109]

Management of Anesthesia. Preoperative management of the patient with Conn's syndrome includes correcting electrolyte and blood glucose levels and managing hypertension.[8,11] Potassium should be replaced slowly to allow for equilibration of intracellular and extracellular potassium stores. Severe hypokalemia may produce muscle weakness and enhance nondepolarizing muscle relaxant responses, making peripheral nerve stimulation monitoring especially valuable. Electrocardiographic signs of potassium depletion include prominent U waves and arrhythmias. Plasma electrolyte concentrations and acid-base status should be checked often during the perioperative period. Inadvertent hyperventilation may further decrease plasma potassium concentration.

Hypertension may be controlled preoperatively with sodium restriction and aldosterone antagonists such as spironolactone.[110,111] Spironolactone, 25 to 100 mg every 8 hours, slowly increases potassium levels by inhibiting the action of aldosterone on the distal convoluted tubule. Patients with primary aldosteronism have a higher incidence of left ventricular hypertrophy, albuminuria, and stroke than patients with essential hypertension.[102,110,111] Measurement of cardiac filling pressures may be needed to assess fluid volume status in the perioperative period.[11]

Laparoscopic adrenalectomy is advocated as the operation of choice for surgically remediable mineralocorticoid excess. Compared with open laparotomy, patients who undergo laparoscopic adrenalectomy have similar improvement in blood pressure control and correction of hypokalemia.[112,113]

Glucocorticoid Excess (Cushing's Syndrome). *Cushing's syndrome* is a diverse complex of symptoms, signs, and biochemical abnormalities caused by excess glucocorticoid hormone. Clinical features reflect cortisol excess, either from overproduction of the adrenal cortex or exogenously administered glucocorticoid (Box 33-6). The catabolic effects of cortisol result in muscle atrophy and skin that is thin, atrophic, and unable to withstand the stresses of normal activity. The clinical picture includes central obesity with thin extremities, glucose intolerance, plethoric facies, purplish striae, muscle weakness, easy bruising, and osteopenia.[102,103] Mineralocorticoid effects include fluid retention and hypokalemic alkalosis. Most patients are hypertensive. Women manifest a degree of masculinization (e.g., hirsutism, hair thinning, acne, amenorrhea), and men manifest a degree of feminization (e.g.,

gynecomastia, impotence) due to androgenic effects of glucocorticoid excess.[102,103]

Causes of Cushing's syndrome can be ACTH-dependent (e.g., pituitary adenoma, ectopic secretion of ACTH by nonpituitary tumor), ACTH-independent (e.g., adrenal tumor, adrenal carcinoma), or iatrogenic (e.g., administration of supraphysiologic doses of glucocorticoids for conditions such as arthritis, allergies, and asthma). Overall, the most common cause of Cushing's syndrome today is the pharmacologic administration of glucocorticoids for various autoimmune and inflammatory conditions.[102]

Cushing's disease, first described by Harvey Cushing in 1932, specifically denotes an anterior pituitary tumor cause of the syndrome, and it accounts for 75% of all cases of endogenous Cushing's syndrome. The pituitary tumor produces excessive amounts of ACTH and is associated with bilateral adrenal hyperplasia.[102] Patients often develop skin pigmentation as a result of the melanocyte-stimulating properties of ACTH.

Ectopic Cushing's syndrome results from autonomous ACTH production by extrapituitary malignancies. Bronchial, thymic, or pancreatic carcinoid tumors account for most of these cases.[114] Small cell lung cancer and medullary carcinoma of the thyroid also can cause ectopic production of ACTH.[102,115]

About 5% to 10% of the cases of endogenous Cushing's syndrome are caused by autonomous cortisol production (ACTH-independent) by an adrenal tumor, usually an adenoma, and most often unilateral.[102] This form of hyperadrenalism is associated with suppressed plasma ACTH levels.[102-104] Adrenal tumors that are malignant are usually large by the time Cushing's syndrome becomes manifest.

Diagnosis. A widely used test for the diagnosis of hyperadrenocorticism is measurement of the plasma cortisol concentration in the morning after a dose of dexamethasone.[114] Dexamethasone suppresses CRH, ACTH, and plasma cortisol secretion in normal patients but not in those with endogenous hyperadrenocorticism. Diagnosis of Cushing's syndrome also may be based on elevated levels of salivary cortisol and urinary free cortisol.[102,114]

Treatment. Treatment for Cushing's syndrome depends on the cause. For Cushing's disease, selective removal of the pituitary corticotrope tumor (microadenomectomy), usually by a transsphenoidal approach is the primary treatment option.[114,116] Complications occur in less than 5% of patients and include diabetes insipidus (usually transient) and cerebrospinal fluid rhinorrhea.[99]

Management of Cushing's syndrome caused by an adrenal tumor consists of surgical removal. For smaller adrenal adenomas, a minimally invasive laparoscopic approach can be employed.[114,117] For larger tumors or those suspected of malignancy, an open laparotomy is preferred.[102] Because the contralateral adrenal gland is preoperatively suppressed, glucocorticoid replacement may be necessary for several months after surgery until adrenal function returns.[102,118]

The treatment of choice for an ectopic ACTH-secreting tumor is surgical removal, but this may not always be feasible because of the nature of the underlying process (e.g., metastatic carcinoma).[115] Ketoconazole, an antifungal drug that blocks the early stages of steroid synthesis, or metyrapone, an 11-β-hydroxylase inhibitor may be used to help normalize cortisol levels. Mitotane, an agent that blocks steroidogenesis at several levels, is used to treat cancer of the adrenal gland that cannot be treated with surgery.[102]

Management of Anesthesia. Important perioperative considerations for the patient with Cushing's syndrome include normalizing blood pressure, blood glucose levels, intravascular fluid volume, and electrolyte concentrations.[8,11] The aldosterone antagonist spironolactone effectively decreases extracellular fluid volume and corrects hypokalemia under these conditions.

Osteopenia is an important consideration in positioning the patient for the operative procedure.[8] Special attention must be given to the patient's skin, which can easily be abraded by tape or minor trauma. Glucocorticoids are lympholytic and immunosuppressive, placing the patient at increased risk for infection and mandating particular enforcement of aseptic techniques as indicated.[8,102]

The choice of drugs for induction and maintenance of anesthesia is not specifically influenced by the presence of hyperadrenocorticism.[8,11] Muscle relaxants may have a more exaggerated effect in patients with hypokalemia and preexisting myopathy, and a conservative approach to dosing is warranted when significant skeletal muscle weakness is present.

If adrenal resection or microadenomectomy is planned, glucocorticoids may be indicated postresection, administered at doses equivalent to adrenal output for maximum stress (hydrocortisone, 100 mg, IV, over 24 hours).[11]

Thromboembolic phenomena occur more often in patients with Cushing's syndrome, with an 11% incidence of deep venous thrombosis and a 2% to 3% incidence of pulmonary embolus postoperatively. The thromboembolic events are believed to be secondary to the prevalence of obesity, hypertension, elevated hematocrit, and increased factor VIII levels.

Primary Adrenocortical Insufficiency (Addison's Disease). In 1855, an English physician, Dr. Thomas Addison, first described a relatively rare clinical syndrome characterized by wasting and skin hyperpigmentation and identified its cause as destruction of the adrenal glands. *Primary adrenocortical insufficiency (Addison's disease)* becomes apparent when 90% of the gland is destroyed. Tuberculosis is a common cause of primary adrenocortical insufficiency worldwide, but in the United States, most cases are the result of autoimmune destruction.[102,119] Less commonly, primary adrenal insufficiency is congenital or caused by infection, adrenal hemorrhage, malignancy, or trauma.[102] Human immunodeficiency virus infection is the most common infectious cause of primary adrenal insufficiency in the United States.[120]

Clinical symptoms of Addison's disease reflect destruction of all cortical zones, resulting in adrenal androgen, glucocorticoid, and mineralocorticoid hormone deficiency[105,120] (Box 33-7). Weakness and fatigue are cardinal features. Reduced appetite with weight loss, vomiting, abdominal pain, and diarrhea are frequently reported. Hypoglycemia is often present.[121] Volume depletion is a common feature of the disease and may be manifested by orthostatic hypotension. Hyponatremia and mild acidosis are commonly revealed by laboratory screening.

BOX **33-6**

Clinical Features of Glucocorticoid Excess (Cushing Syndrome)

- Hyperglycemia
- Hypertension
- Weight gain; central obesity; fat pad on back of neck ("buffalo hump"); moon face
- Increased susceptibility to infection; increased leukocyte count
- Hypokalemia
- Alkalosis
- Hirsutism; acne
- Osteopenia
- Muscle weakness
- Skin stria; ecchymoses; facial plethora
- Mood disorders

Hyperkalemia may be evident, and is associated with serious cardiac toxicity and dysrhythmias.[103,121]

The adrenal-pituitary axis is intact in primary adrenal insufficiency, and ACTH concentrations are elevated as a result of the reduced production of cortisol. Increased melanin formation in the skin and hyperpigmentation of the knuckles of the fingers and toes, knees, elbows, lips, and buccal mucosa are distinguishing features.

Treatment. Treatment for adrenal insufficiency aims to replace both glucocorticoid and mineralocorticoid deficiency.[102] Normal adults secrete about 15 to 30 mg of cortisol (hydrocortisone) and about 100 to 150 mcg of aldosterone per day. Corticosteroids used for therapy aim to replace physiologic mineralocorticoid and glucocorticoid effects (Table 33-7).[11,102,104,119,120] Patients with Addison's disease are highly susceptible to the deteriorating effects of stress and require supplementation of standard replacement dosages[103,105,119] (see Perioperative Steroid Replacement).

Secondary Adrenocortical Insufficiency. Secondary adrenocortical insufficiency is caused by ACTH deficiency from two primary etiologies: (1) iatrogenic hypothalamic-pituitary-adrenal (HPA) axis suppression after exogenous glucocorticoid therapy, or (2) ACTH deficiency secondary to hypothalamic or pituitary gland dysfunction (e.g., tumor, infection, surgical or radiologic ablation).

Iatrogenic suppression of the HPA axis may follow long-term treatment with glucocorticoids, resulting in negative feedback to the hypothalamus and pituitary, decreased ACTH output, and eventual adrenal cortex atrophy.[11,120,121] The longer the duration of glucocorticoid administration, the greater the likelihood of suppression.[122] Sustained and clinically important adrenal suppression usually does not occur with treatment of 5 mg/day or less of prednisone or steroid treatment for periods less than 14 days.[120,123] Treatment periods long enough to provoke signs of Cushing's syndrome are usually associated with adrenal suppression of clinical importance.[121,124]

Clinical manifestations of secondary adrenal insufficiency resemble the primary disease, except secondary insufficiency is less likely to be associated with severe hypovolemia, hyperkalemia, or hyponatremia because mineralocorticoid secretion is usually preserved.[11,124] Hyperpigmentation is absent because ACTH levels are low.

Acute Adrenal Crisis. Acute adrenal crisis is a sudden exacerbation or onset of severe adrenal insufficiency. It is a rare event associated with high morbidity and mortality if allowed to progress unrecognized.[125,126] A patient with chronic adrenal insufficiency may deteriorate rapidly into an acute insufficiency state as a result of some superimposed stress, such as infection, acute illness, or sepsis. The stress of surgery or trauma in the patient with inadequate adrenal reserves can precipitate acute adrenal crisis in the perioperative period.[8,125,126]

Symptoms of adrenal crisis reflect acute deficiency of corticosteroids and include severe weakness, nausea, hypotension, fever, and decreasing mental status. In the surgical setting, hemodynamic instability or cardiovascular collapse may herald adrenal crisis. The index of suspicion for adrenal crisis should be particularly high if the patient has hyperpigmentation, hyponatremia, and/or hyperkalemia; a history of autoimmune disease (hypothyroidism, diabetes); or recent prior use of exogenous steroids.[121,124] The anesthetist should be mindful of the adrenal suppressive effects of etomidate.[119,127] Even a single dose of etomidate for induction of anesthesia can cause acute adrenocortical insufficiency and should be avoided in patients susceptible to adrenal insufficiency.[127,128]

Acute adrenal crisis is a medical emergency requiring aggressive treatment of the steroid insufficiency and associated hypoglycemia, electrolyte imbalance, and volume depletion. Early recognition and intervention are crucial steps in altering the course of acute adrenal insufficiency. Initial therapy begins with rapid intravenous administration of a physiologic saline solution with continuous cardiac monitoring.[102,119,125,126] If the patient is hemodynamically unstable, inotropic support may be necessary. Steroid

BOX 33-7

Clinical Features of Primary Adrenocortical Insufficiency

- Hypoglycemia
- Hypotension
- Anorexia, weight loss
- Nausea; vomiting; abdominal pain
- Hyponatremia; hyperkalemia; acidosis
- Mucosal and skin pigmentation
- Asthenia, muscle weakness

TABLE 33-7 Physiologic Effects of Endogenous Corticosteroids

Steroids	Average Plasma Concentration (Free and Bound, mcg/100 mL)	Average Amount Secreted (mg/24 hr)	Glucocorticoid Activity*	Mineralocorticoid Activity*
Adrenal Steroids				
Cortisol	12	15	1.0	1.0
Corticosterone	0.4	3	0.3	15.0
Aldosterone	0.006	0.15	0.3	3000
Deoxycorticosterone	0.006	0.2	0.2	100
Dehydroepiandrosterone	175	20	—	—
Synthetic Steroids				
Cortisone	—	—	0.8	1.0
Prednisolone	—	—	4	0.8
Methylprednisone	—	—	5	—
Dexamethasone	—	—	30	—
9α-fluorocortisol	—	—	10	125

From Hall JE. *Guyton and Hall Textbook of Medical Physiology*. 12th ed. Philadelphia: Saunders; 2011:924.
*Glucocorticoid and mineralocorticoid activities of the steroids are relative to cortisol, with cortisol being 1.0.

replacement therapy begins with hydrocortisone, 100 mg IV, followed by hydrocortisone, 100 to 200 mg IV over 24 hours.[102,119] Mineralocorticoid effects are present at these doses.[102]

Perioperative Steroid Replacement. Case reports of perioperative cardiovascular collapse in surgical patients on pharmacologic doses of glucocorticoids were first reported in 1952.[122,129] These reports and subsequent knowledge regarding the stress response associated with surgery and the suppression of the HPA axis with supraphysiologic doses of corticosteroids has led to the practice of administering perioperative glucocorticoids to patients who have taken steroids in the preoperative period.

Synthesis and secretion of cortisol can increase 5- to 10-fold under conditions of severe stress, such as surgery, trauma, or infection.[8,120] In general, major surgery of long duration produces a greater adrenal output response than minor surgery of short duration.[122] For the adult patient who has received supraphysiologic doses of glucocorticoids (oral, topical, or inhaled), it may take 6 to 12 months from the time of discontinuation of steroids for the adrenal gland to recover full function.[11,120,130]

Debate exists regarding who should receive perioperative steroid coverage and what the appropriate steroid dose should be.[105,120,131] Many experts suggest that patients are at risk for adrenal insufficiency (AI) and therefore require steroid supplementation if the following have occurred[8,11]:

1. They have taken pharmacologic doses of glucocorticoids greater than 5 mg prednisone equivalent per day (5 mg prednisone is approximately bioequivalent to 20 mg hydrocortisone).
2. The period of treatment was for 2 to 3 weeks or longer.
3. The treatment occurred during the immediate 12 months before surgery.

Under these conditions, supplemental intravenous administration of hydrocortisone is advocated to compensate for the amount the body may be unable to produce in response to maximal stress.[11,122] The precise amount of glucocorticoids required for adequate supplementation has not been established. Therapeutic aims are to tailor the steroid dose considering the length and severity of surgical stress, while administering the minimal dose that will fully protect the patient.[105,120,124] A common perioperative protocol for steroid supplementation is included in Table 33-8. If the surgical patient is undergoing treatment with glucocorticoids at the time of surgery, supplemental doses are administered in addition to the patient's daily maintenance dose.[8,11,105,120]

The benefits of perioperative steroid supplementation are tempered by the potentially negative effects of decreased glucose tolerance, induction of stress ulcers, immunosuppression, and impaired wound healing.[120] Because acute adrenal crisis is life threatening, most clinicians believe that the potential risks associated with short-term glucocorticoid administration are outweighed by the benefits.[8,11,105]

Adrenal Medulla

The adrenal medulla is a catecholamine-producing endocrine gland that is derived embryologically from neuroectodermal cells. The gland is enervated by preganglionic cholinergic fibers of the sympathetic nervous system and can be thought of as analogous to a postganglionic neuron. Preganglionic fibers bypass the paravertebral ganglia and run directly from the spinal cord to the adrenal medulla. Epinephrine accounts for approximately 80% of the hormone secreted by the adrenal medulla, and norepinephrine accounts for 20%. The majority of norepinephrine synthesized in the adrenal medulla is converted to epinephrine by the enzyme *phenylethanolamine-N-methyltransferase (PNMT)*. The ability of the adrenal medulla to synthesize epinephrine is probably influenced by the flow of glucocorticoid-rich blood from the cortex through the medulla because high concentrations of glucocorticoids stimulate the enzyme PNMT (Figure 33-16).

Catecholamines in the adrenal medulla are stored in chromaffin granules.[132,133] Stimulation of the sympathetic nerves to the adrenal medulla causes large quantities of epinephrine and norepinephrine to be released into the circulation. The effects of circulating epinephrine and norepinephrine are similar to the effects of direct sympathetic stimulation but last 5 to 10 times longer because of the slow removal of these hormones from the blood. Norepinephrine and epinephrine are metabolized in the liver and kidney by the enzyme *catechol-O-methyltransferase*. The byproducts of metabolism, vanillylmandelic acid (VMA) and metanephrines, and free unchanged catecholamines are excreted in the urine[132,133] (Figure 33-17).

Norepinephrine stimulates α- and β-adrenergic receptors. It causes constriction of most blood vessels of the body, increasing total peripheral resistance. High circulating norepinephrine levels increase the heart's activity, inhibit gastrointestinal function, and dilate the pupils. Epinephrine has a greater affinity for β-adrenergic receptors. Its actions are seen primarily in the heart, producing chronotropic and inotropic effects. Epinephrine causes less constriction of blood vessels than norepinephrine. Norepinephrine and epinephrine release from the adrenal medulla can increase the metabolic rate of the body by as much as 100% above normal.

Pheochromocytoma

In 1905 the term *pheochromocytoma* was first used to describe the appearance of a tumor noted during autopsy resection to be a dusky *(pheo)* color *(chromo)*. Cesar Roux of Lausanne, Switzerland, and Charles Mayo of the United States were the first surgeons to successfully remove a pheochromocytoma.

Pheochromocytomas are catecholamine-secreting tumors derived most commonly from adrenomedullary chromaffin cells. The tumors synthesize, store, and secrete catecholamines, mostly norepinephrine and epinephrine. Unlike a normal adrenal medulla, most of these tumors predominantly secrete norepinephrine. In the majority of cases, however, it is impossible to predict the precise catecholamine secretion from the clinical features. The tumors are not innervated, and neural stimulation does not stimulate hormone release.[134]

TABLE 33-8 Guidelines for Perioperative Adrenal Supplementation Therapy

Type of Surgery	Hydrocortisone Dose
Superficial Surgery	
Dental Biopsies	None
Minor Surgery	
Inguinal hernia Colonoscopy	25 mg IV
Moderate Surgery	
Nonlaparoscopic cholecystectomy Colon resection Total abdominal hysterectomy Total joint replacement	50-75 mg IV, taper over 1 to 2 days
Major Surgery	
Cardiovascular Thoracic Liver	100-150 mg IV, taper over 1 to 2 days

Pheochromocytomas are sometimes broadly defined as following the "rule of 10s." They involve both adrenal glands in approximately 10% of adult patients with the tumor, 10% of the tumors arise from extraadrenal chromaffin cells, and 10% of the tumors are malignant (Table 33-9). Malignant pheochromocytomas are primarily extraadrenal and secrete norepinephrine exclusively.[135] Metastasis usually proceeds through venous and lymphatic channels to the liver.[134]

Biochemical testing and subsequent diagnosis of a catecholamine tumor is based on findings of elevated urinary or plasma catecholamines and their methylated metabolites, VMA, metanephrine, and normetanephrine (Table 33-10).[134,136-138]

Incidence and Associated Diseases. Pheochromocytomas are rare, occurring in approximately 0.1% of hypertensive patients.[134] Approximately 25% of tumors primarily arise from three inherited genetic syndromes that develop from germ-line mutations. These are von Hippel-Lindau (VHL) syndrome, multiple endocrine neoplasia type 2 (MEN 2), and Recklinghausen's disease.[14,139] Approximately 50% of patients with MEN type 2A or 2B develop pheochromocytomas[140] (Table 33-11). It is recommended that

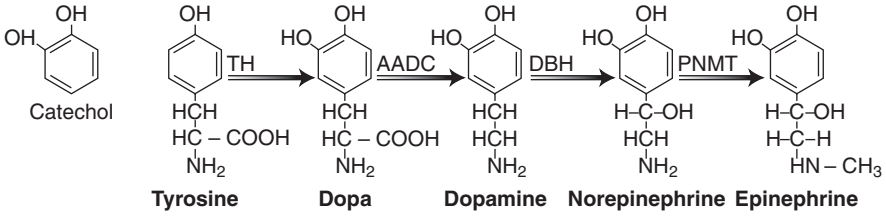

FIGURE **33-16** Biosynthetic pathway for catecholamines. The term *catecholamines* comes from the catechol (ortho-dihydroxybenzene) structure and a side chain with an amino group—the "catechol nucleus" *(left)*. Tyrosine is converted to 3,4-dihydroxphenylanine (dopa) (rate-limiting step) by tyrosine hydroxylase (TH); TH inhibitor, α-methyl-para-tyrosine (metyrosine). Aromatic L-amino acid decarboxylase (AADC) converts dopa to dopamine. Dopamine is hydroxylated to norepinephrine by dopamine β-hydroxylase (DBH). Norepinephrine is converted to epinephrine by phenylethanolamine *N*-methyltransferase (PNMT); cortisol serves as a cofactor for PNMT, which is why epinephrine-secreting pheochromocytomas are almost exclusively localized to the adrenal medulla. (From Melmed S, et al, eds. *Williams Textbook of Endocrinology*. 12th ed. Philadelphia: Saunders; 2011:546.)

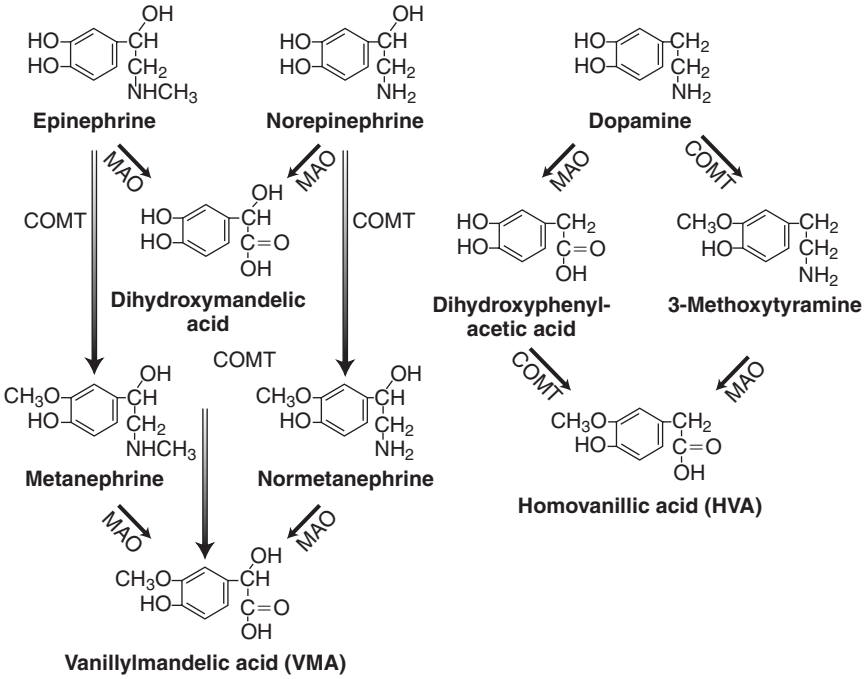

FIGURE **33-17** Catecholamine metabolism. Metabolism of catecholamines occurs through two enzymatic pathways. Catechol-*O*-methyltransferase (COMT) converts epinephrine to metanephrine and converts norepinephrine to normetanephrine by meta-*O*-methylation. Metanephrine and normetanephrine are oxidized by monoamine oxidase (MAO) to vanillylmandelic acid (VMA) by oxidative deamination. MAO also may oxidize epinephrine and norepinephrine to dihydroxymandelic acid, which is then converted by COMT to VMA. Dopamine is also metabolized by MAO and COMT to the final metabolite homovanillic acid (HVA). (Modified and redrawn from Young WF. Endocrine hypertension. In: Melmed S, et al, eds. *Williams Textbook of Endocrinology*. 12th ed. Philadelphia: Saunders; 2011:548.)

patients with a family history of MEN syndrome be regularly screened for pheochromocytoma.

Pheochromocytomas can occur at any age, but usually occur within the third to the fifth decade of life, with equal frequency in both sexes in adults.[133,141]

Clinical Manifestations. Manifestations of a pheochromocytoma reflect massive catecholamine release and include hypertension, diaphoresis, headache, tremors, and palpitations.[142] Hypertension may be paroxysmal or sustained.[134] The combination of paroxysmal diaphoresis, tachycardia, and headache in the hypertensive patient is a recognized triad of symptoms for pheochromocytoma.[8,11,133,139] Increasingly, patients are being diagnosed based on incidental radiographic findings or by having established familial syndromes.[134,140,143]

A catecholamine-mediated paroxysm typically consists of a sudden and alarming increase in blood pressure, a severe throbbing headache, profuse sweating, palpitations, tachycardia, a sense of doom, anxiety, pallor (or flushing), and nausea.[134] Orthostatic hypotension may result from plasma volume deficit or a lack of tone in the postural reflexes that defend upright blood pressure, due to the sustained excesses of catecholamines. Paroxysmal symptoms may last several minutes to days and are often followed by physical exhaustion. Clinical symptoms associated with pheochromocytoma are outlined in Table 33-12.

A paroxysm may be triggered by abdominal palpation, defecation, or any event that provokes pressure on the tumor.[134] Micturition may trigger symptoms if the pheochromocytoma is present in the urinary bladder wall. In some patients, no clearly defined precipitating factor can be found. Mental or psychologic stress does not usually initiate a crisis.[134]

Owing to the predominance of norepinephrine secretion, the symptoms associated with a pheochromocytoma reflect α-adrenergic activity over β-adrenergic effects. As a result of α-adrenergic inhibition of insulin and enhanced hepatic glucose output, hyperglycemia may be present. The cardiac output and heart rate may be significantly increased. An overall increase in metabolism accelerates oxygen consumption and can cause hyperthermia. Vasoconstriction in the extremities may produce pain, paresthesias, intermittent claudication, or ischemia.[134]

Hypertension is the most common symptom, occurring in more than 90% of patients.[133,134,136] Severe paroxysmal hypertension is present in approximately 40% of patients and is a distinctive manifestation of the disease.[133,134] Sustained hypertension is often resistant to conventional treatment. When pheochromocytomas are predominantly epinephrine secreting, hypertension can alternate with periods of hypotension associated with syncope. Hypotension reflects surges of epinephrine, causing disproportionate β-adrenergic stimulation with vasodilation in the presence of a contracted vascular space.

A catecholamine-induced increase in myocardial oxygen consumption, hypertension, and coronary artery spasm can precipitate myocardial infarction or congestive heart failure even in the absence of coronary artery disease.[11,134] Electrocardiogram (ECG) changes are common. Nonspecific ST-segment and T-wave changes and prominent U waves may be seen. Sinus tachycardia, supraventricular tachycardias, and premature ventricular contractions are commonly noted. Right and left bundle branch blocks and ventricular strain sometimes occur. Ventricular tachycardia also has been reported.[133,134]

Some pheochromocytomas may first present as a hypermetabolic state during anesthesia for unrelated surgery. The hypertension, tachycardia, hyperthermia, and respiratory acidosis of a pheochromocytoma may mimic light anesthesia, thyroid crisis, malignant hyperthermia, or sepsis.[142]

Preoperative Management. The pharmacologic effects of released catecholamines present major anesthetic challenges. Medical management prior to tumor excision aims to reverse the

TABLE 33-11 Manifestations of Multiple Endocrine Neoplasia*

Syndrome	Manifestations
MEN type 1 (Wermer syndrome)	Hyperparathyroidism, pituitary adenomas, pancreatic islet-cell tumors
MEN type 2A (Sipple syndrome)	Medullary thyroid cancer, hyperparathyroidism, pheochromocytoma
MEN type 2B (mucosal neuroma syndrome)	Medullary thyroid tumor, pheochromocytoma, neuromas of the oral mucosa, marfanoid habitus

*Multiple endocrine neoplasia (MEN) is a group of rare diseases caused by genetic defects that lead to hyperplasia and hyperfunction of two or more components of the endocrine system.

TABLE 33-9 Locations of Pheochromocytomas

Location	Percentage
Solitary adrenal	80
Extraadrenal	10
Bilateral adrenal	10

TABLE 33-10 Values for Catecholamines and Catecholamine Metabolites

Hormone/Metabolite	Normal Value
Vanillylmandelic acid, urine	2-7 mg/24 hr
Metanephrines, urine	Less than 1.3 mg/24 hr
Norepinephrine, urine	Less than 100 mcg/24 hr
Norepinephrine, plasma	150-450 pg/mL
Epinephrine, plasma	Less than 35 pg/mL
Catecholamines, free urinary	Less than 110 mcg/24 hr

TABLE 33-12 Frequency of Symptoms in Patients with Pheochromocytoma

Symptom	%	Symptom	%
Headache	80	Chest pain	19
Excessive perspiration	71	Dyspnea	19
Palpitation (with or without tachycardia)	64	Flushing or warmth	18
Pallor	42	Numbness or paresthesia	11
Nausea (with or without vomiting)	42	Blurring of vision	11
Tremor or trembling	31	Tightness of throat	8
Weakness or exhaustion	28	Dizziness or faintness	8
Nervousness or anxiety	22	Convulsions	5
Epigastric pain	22	Neck-shoulder pain	5
		Extremity pain	4
		Flank pain	4

TABLE 33-13 Drugs Used in the Management of Pheochromocytoma

Drug	Action	Pressor Crisis	Preoperative Blood Pressure Control	Comment
Phentolamine	α-Blocker	IV 2-5 mg	—	Rapid onset, short-acting; bolus every 5 min or infuse initially 1 mg/min
Phenoxybenzamine	α-Blocker	—	Oral 30 mg/day, increasing daily dosage by 30 mg	Long half-life; may accumulate; administer two or three times daily
Doxazosin	Selective α_1 antagonist	1 mg/day PO up to 8 mg/day PO	—	First-dose phenomenon; may cause syncope
Propranolol	β-Blocker	IV 1-mg bolus to total of 10 mg	Oral 40 mg bid; increase to 480 mg/day	Should not be administered without first creating α blockade
Atenolol	β-Blocker	—	Oral 50 mg/day initially; may increase to 100 mg/day	Long-acting, selective β_1 antagonist eliminated unchanged by kidney
Esmolol	β-Blocker	IV 500 mcg/kg/min loading followed by maintenance infusion	—	Ultrashort-acting selective β_1 antagonist; may be used during anesthesia
Labetalol	α- and β-Blocker	IV 10-mg bolus to 150 mg	Oral 200 mg tid	A much weaker α-blocker than β-blocker; may cause pressor response in pheochromocytoma
Nitroprusside	Vasodilator	IV infusion initially 0.5-1.5 mcg/kg/min	—	Powerful vasodilator; short-acting; may be used during anesthesia
Magnesium sulfate	Vasodilator	Initial loading dose of 50 mg/kg over 10 minutes followed by 15 mg/kg/hr	—	May potentiate neuromuscular blockade
Nicardipine	Calcium channel blocker	IV 2-6 mcg/kg/min	—	Better vasodilator than diltiazem
α-Methyl-tyrosine	Inhibitor of biosynthesis of catecholamines	—	Oral 1-4 g/day	Suitable for patients not amenable to surgery; may be nephrotoxic
Dexmedetomidine	Selective alpha 2 adrenergic receptor agonist	IV infusion: initially 1 mcg/kg over 10 minutes, then 0.5 mcg/kg/hr		

Modified from Schwartz JJ, Shamsuddin A, Rosenbaum S. Endocrine function. In: Barash PG, et al, eds. *Clinical Anesthesia*. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2009:1279-1304.
adm., Administer; *IV*, intravenous.

effects of excessive adrenergic stimulation. Preoperative antihypertensive therapy and volume replacement have helped to decrease the surgical mortality rate from about 50% to the current 1% to 3%.[8] The preoperative use of α-adrenergic antagonists in concert with reexpansion of the intravascular fluid compartment greatly improves cardiovascular stability intraoperatively. Table 33-13 outlines drugs used in the management of pheochromocytoma.

α-Adrenergic Receptor Blockade. Phenoxybenzamine (Dibenzyline) remains the most commonly used drug for preoperative α-adrenergic blockade and blood pressure stabilization. It is a noncompetitive presynaptic (α_2) and postsynaptic (α_1) adrenergic receptor antagonist of long duration (24 to 48 hours).[133] Most patients with pheochromocytoma require an oral dose between 60 and 250 mg/day.[8,134]

Typically, patients require 10 to 14 days of α-adrenergic antagonist therapy to stabilize blood pressure, restore fluid volume, and decrease symptoms. Establishing normotension facilitates reexpansion of the intravascular fluid compartment. Satisfactory α-adrenergic blockade is implied if the hematocrit decreases by 5% during treatment.[11] Half to two thirds of the normal oral phenoxybenzamine dose may be given the morning of surgery.[8]

Prazosin (Minipress), a postsynaptic α_1-adrenergic receptor antagonist, also has been used successfully to treat the hypertension of pheochromocytoma preoperatively. The rising appeal of this selective α1-receptor antagonist is that, in theory, it leaves the α2-receptor intact, thereby inhibiting the release of norepinephrine and allowing a more effective management of blood pressure and heart rate.[144,145] Labetalol (Trandate, Normodyne), a mixed α- and β-receptor antagonist, has not been as effective as a first-line drug in controlling the blood pressure response, but it may be used as an adjunctive agent.[11,133,146]

β-Adrenergic Receptor Blockade. A β-adrenergic receptor antagonist is usually introduced in the preoperative period for control of tachycardia, hypertension, and catecholamine-induced supraventricular dysrhythmias. An important caveat is that β-adrenergic receptor antagonists should not be administered until after α-adrenergic blockade is established. Blocking β-receptor–mediated vasodilation in skeletal muscle without prior α-adrenergic blockade can increase the blood pressure even further in the patient with pheochromocytoma.[142] A helpful mnemonic for the reader is "a before b."

Other Treatment Regimens. Calcium channel blockers and magnesium sulfate infusion have been used with variable success as monotherapy for the perioperative management of pheochromocytoma. Some regimens use these agents in conjunction with adrenergic blocking drugs.[147]

To date, no specific preoperative management technique has been shown to be superior in terms of clinically significant outcomes.[147,148] The following criteria are proposed as end-points for the patient awaiting surgery for pheochromocytoma resection.[8,148]

1. No in-hospital blood pressure reading higher than 160/90 mmHg 24 hours prior to surgery
2. No blood pressure on standing lower than 80/45 mmHg
3. No ST-segment or T-wave abnormality on the ECG that cannot be attributed to a permanent defect
4. No marked symptoms of catecholamine excess; no more than one premature ventricular contraction every 5 minutes

Anesthetic Management. Effective anesthetic management is based on (1) selecting drugs that do not stimulate catecholamine release and (2) implementing monitoring techniques that facilitate early and appropriate intervention when catecholamine-induced changes in cardiovascular function occur.

The use of selective α2-receptor agonists such as clonidine and dexmedetomidine may be useful in managing blood pressure and heart rate.[149] Activating α2-receptors results in sympathetic inhibition and has been shown to reduce the release of catecholamines resulting in decreased blood pressure and heart rate.[150-153]

Pheochromocytomas are excised by open laparotomy or laparoscopy.[147,154-156] Laparoscopic resection is considered the gold standard for resection over the open approach due to better perioperative outcomes, less analgesia use, and a faster recovery period.[156-159] However, during pneumoperitoneum for laparoscopy, significant catecholamine release has been reported and should be anticipated by the anesthetist.[160]

A number of drugs and conditions can precipitate hypertension in the surgical patient with pheochromocytoma. Dopamine antagonists (metoclopramide, droperidol), radiographic contrast media, indirect-acting amines (ephedrine, methyldopa), drugs that block neuronal catecholamine reuptake (tricyclic antidepressants, cocaine), histamine, and glucagon may enhance the physiologic effect of tumor product.[11,134]

Pheochromocytomas are vascular tumors. Large-bore intravenous lines and a peripheral arterial catheter should be established preoperatively. Central venous pressure monitoring will help guide fluid management and intervention with inotropes or vasoactive drugs.[11,133] Arterial blood gases, electrolyte concentrations, and blood glucose levels should be assessed regularly during the anesthetic.

Critical intraoperative junctures are (1) during induction and intubation of the trachea, (2) during surgical manipulation of the tumor, and (3) after ligation of the tumor's venous drainage. Anesthesia induction may be accomplished with barbiturates, etomidate, or propofol. Anesthetic depth can be enhanced by mask ventilation of the lungs with a volatile anesthetic prior to laryngoscopy and intubation. Lidocaine (1 to 2 mg/kg IV) administered 1 minute prior to intubation may help attenuate the hemodynamic response to laryngoscopy. Short-acting opioids administered prior to intubation also may help blunt the blood pressure responses to intubation. Morphine sulfate should be avoided because of its propensity for histamine release. Rapid-acting vasodilating drugs such as nitroprusside should be readily available to treat hypertension.[11]

Sevoflurane and short-acting opioids provide cardiovascular stability and possess the ability to rapidly change anesthetic depth—attractive features in the anesthetic management of the patient with pheochromocytoma.[8,11,133,161] The tachycardia and increased sympathetic stimulation associated with desflurane makes it a less desirable choice for these cases.

The use of succinylcholine has been questioned because compression of an abdominal tumor by drug-induced skeletal muscle fasciculations may provoke catecholamine release. However, a predictable adverse effect of succinylcholine has not been supported clinically when administered to patients with pheochromocytoma. Skeletal muscle paralysis with a nondepolarizing muscle relaxant devoid of vagolytic or histamine-releasing effects is desirable. Pancuronium should be avoided for its known chronotropic effect.[8,11,133]

The anesthetist should anticipate a labile cardiovascular course during surgery. Hypertension can be treated with intravenous nitroprusside and high concentrations of inhaled anesthetic.[8,11,133] Lidocaine, labetalol, or esmolol may be given intravenously to decrease tachydysrhythmias. β-adrenergic receptor antagonists must be used cautiously in patients with catecholamine-induced cardiomyopathy because even minimal β-adrenergic blockade can accentuate left ventricular dysfunction.[11,133] The short half-life of esmolol makes it the preferred choice for β-adrenergic blockade. Dysrhythmias associated with hypertension may be resolved by simply lowering an abnormally high blood pressure. Indirect-acting sympathomimetics have an unpredictable pressor effect in these patients and should be avoided.

After surgical ligation of the veins that drain a pheochromocytoma, the rapid decrease in circulating catecholamines and the associated downregulation of adrenergic receptors may precipitate a decrease in blood pressure.[161] Intravenous administration of phenylephrine hydrochloride (Neo-Synephrine) or dopamine may be needed until the peripheral vasculature can adapt to the decreased level of endogenous α-stimulation. Hyperglycemia is common before excision of the pheochromocytoma. With tumor removal, the sudden withdrawal of catecholamine stimulation can result in hypoglycemia. Blood glucose levels should be monitored at frequent intervals intraoperatively and postoperatively.

Postoperative Management. Fluid shifts, pain, hypoxia, hypercapnia, autonomic instability, urinary retention, or residual tumor are all causes of postoperative hypertension. Invasive monitoring is indicated during the initial postoperative period to assess blood pressure changes and cardiac status. Fifty percent of patients remain hypertensive during the immediate postanesthesia recovery period, despite removal of the pheochromocytoma.[11,148] Postoperative catecholamine levels decrease to normal over several days. In 75% of patients, normal blood pressure returns within 14 days postsurgery.[134]

THYROID GLAND

The thyroid gland is an endocrine gland located anterior to the trachea between the cricoid cartilage and suprasternal notch. It produces and secretes two important thyroid hormones: 3,5,3-triiodothyronine (T_3) and thyroxine (T_4). The vascular supply to the gland is derived from the superior and inferior thyroid arteries. Blood flow is equivalent to about five times the weight of the gland, which is a blood supply as rich as almost any tissue in the body. The gland consists of two lobes and an isthmus. The recurrent laryngeal nerves run along the lateral borders of each thyroid lobe.[162]

Microscopically, the thyroid is divided into lobules, each of which is composed of 20 to 40 follicles. The follicles are the functional units of the thyroid gland. They are lined by epithelial cells that surround central deposits of a proteinaceous substance called *colloid*. The major constituent of the colloid is a large glycoprotein called *thyroglobulin*, which serves as the backbone for the synthesis and storage of thyroid hormones.[162]

Synthesis of Thyroid Hormones

Iodide Trapping

Approximately 1 mg of ingested iodine is required each week to form normal quantities of thyroid hormones. Dietary iodine is then reduced in the gastrointestinal tract to *iodide*. Common table salt is iodized with sodium iodide for the prevention of iodine deficiency.

The first stage of thyroid hormone formation is the transport of iodides from the extracellular fluid into the thyroid cells and follicles. About one fifth of the circulating iodide is removed from the blood by the thyroid cells and used for the synthesis of thyroid hormones, a process called *iodide trapping*. The iodide pump normally concentrates the iodide to about 30 times its concentration in the blood. Iodide trapping is the rate-limiting step in thyroid hormone synthesis and is under the control of TSH from the anterior pituitary. Once inside the thyroid gland, iodide ions are oxidized back to iodine.[162]

Thyroid Hormone Formation

Thyroid hormones are formed in the follicles of the thyroid gland under the control of TSH. Thyroglobulin contains the amino acid tyrosine, which combines with iodine to form various iodotyrosines, including the two major thyroid hormones. Thyroxine and triiodothyronine remain part of the thyroglobulin molecule, stored as colloid within the thyroid follicle until release. Enough hormone is synthesized and stored under basal conditions to supply the body with its normal hormone requirements for 2 to 3 months. As a result, if complete thyroid hormone synthesis ceases, the physiologic effects are not seen for several months.[162,163]

Although iodine is required for hormone synthesis, paradoxically, excess iodine can cause the gland to recede and inhibit production of thyroid hormone.

Release of Thyroxine and Triiodothyronine

TSH controls the release of hormones from the thyroid gland. On release, T_4 and T_3 are cleaved from the thyroglobulin molecule and secreted into the circulating blood. Thyroglobulin remains within the colloid.[162]

Under normal conditions, about 93% of the hormone released from the thyroid gland is T_4 and 7% is T_3.[162] The secretion of T_4 from the thyroid gland is 80 to 100 mcg/day. When thyroid hormones reach their target tissues, most of the T_4 is deiodinated to T_3—T_4 serving mostly as a hormone precursor. Triiodothyronine is more potent and less protein bound than T_4 and is the primary metabolically active hormone that stimulates target tissues.[163]

Transport of Thyroxine and Triiodothyronine to Tissues

Thyroid hormone exists in circulation in both free and bound forms. The amount of free hormone, which is the metabolically active fraction, is extremely small, less than 0.03% of total circulating T_4 and 0.3% of total circulating T_3. The majority of circulating hormone (99.9%) is bound to plasma proteins. Most of the thyroid hormones bind to the circulating proteins *thyroxine-binding globulin*, *transthyrotin*, and *albumin*.[164]

Because of the very high affinity of the plasma-binding proteins for thyroid hormones, the hormones are released to the tissue cells very slowly. The half-life of T_4 in the circulation is 6 to 7 days, and the half-life of T_3 is about 24 hours.[162,163]

Functions of Thyroid Hormones

Increased Cellular Metabolic Activity

Thyroid hormones initiate protein formation in virtually all cells of the body. Consequently, the level of enzymes, structural proteins, transport proteins, and other substances increases considerably under the direction of T_4 and especially T_3. The net result is a generalized increase in metabolic activity, heat production, and oxygen consumption of all or almost all tissues in the body.[164] The basal metabolic rate can increase by as much as 60% to 100% above normal when large quantities of thyroid hormones are secreted.[161] The rate and depth of respiration increase due to the enhanced metabolic rate and increased oxygen use and carbon dioxide formation by cells. The use of energy substrates is greatly accelerated. Protein synthesis is increased; however, protein catabolism also is increased. When the quantity of thyroid hormone is slightly increased, the muscles react with vigor; however, when the quantity is excessive, muscles become weakened from excess protein catabolism.

Effect of Thyroid Hormone on Growth

Thyroid hormones are necessary for normal growth in infants and children. In a hypothyroid state, the rate of tissue growth is greatly reduced. Thyroid hormone is required for normal growth and development of the brain during fetal life and for the first few years of postnatal life.[161,162]

Effect of Thyroid Hormone on Specific Systems

Thyroid hormones have direct and indirect effects on the excitability of the heart. The heart rate and the force of contraction are augmented with increasing thyroid hormone production. Vasodilation occurs from increased cellular oxygen consumption and results in increased blood flow to most tissues.[161,162]

Thyroid hormones increase the rate of hormone secretion from most endocrine glands, especially the pancreas. The heightened cellular requirement for glucose mandates higher insulin secretion. Thyroid hormones also enhance the secretion of digestive juices and the motility of the gastrointestinal tract, in addition to increasing an individual's appetite and food intake. In adults, thyroid hormones enhance the rapidity of cerebration.[161]

Regulation of Thyroid Hormone Secretion

Specific feedback mechanisms operate through the hypothalamus and anterior pituitary gland to precisely control the rate of thyroid secretion. Thyrotropin-releasing hormone (TRH) from the hypothalamus causes cells of the anterior pituitary lobe to produce and secrete TSH. Potent stimuli to TRH and TSH release include low levels of T_3 and T_4, stress, and exposure to cold.[161] TSH increases all known activities of thyroid gland cells, resulting in increased gland size and vascularity and increased hormone synthesis and release. High circulating levels of primarily T_3, and to a lesser extent T_4, inhibit the secretion of TRH and TSH through a negative feedback effect on the hypothalamus and anterior pituitary. Figure 33-18 summarizes the regulation of thyroid secretion.

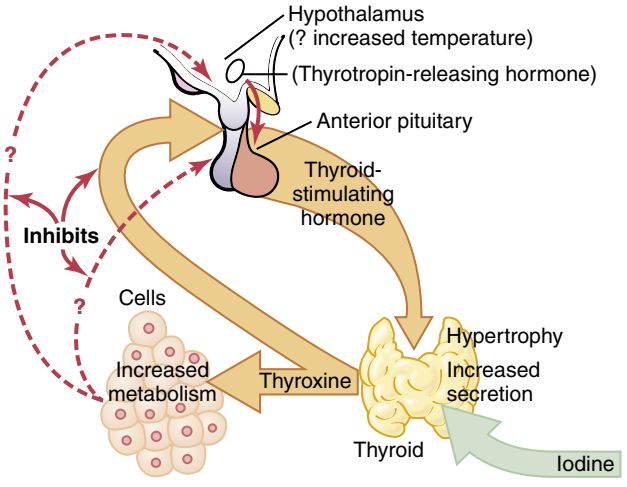

FIGURE **33-18** Regulation of thyroid secretion. (From Hall JE. *Guyton and Hall Textbook of Medical Physiology*. 12th ed. Philadelphia: Saunders; 2011:915.)

Thyroid Gland Disorders

Thyrotoxicosis and Graves' Disease

Hyperthyroidism is defined as thyroid gland hyperactivity. *Thyrotoxicosis* is more specifically defined as a state of thyroid hormone excess.[164] The most common cause of thyrotoxicosis in the United States is *Graves' disease*, affecting approximately 0.5% of the population and accounting for 60% to 80% of thyrotoxicosis cases.[164,165] Graves' disease is an autoimmune disease in which TSH-receptor antibodies bind to and stimulate the thyroid gland, causing excessive production and secretion of T_4 and T_3.[164,165] Immunoglobulin G (IgG) autoantibodies mimic the action of TSH, but their effects are longer, lasting up to 12 hours compared with 1 hour for normal TSH.[162] Graves' disease occurs most often in women (prevalence 1% to 3% in women; 0.1% in men). The peak incidence occurs between 40 and 60 years of age.[165]

Thyrotoxicosis also can be caused by benign follicular adenomas that secrete large quantities of thyroid hormone. Thyroid adenomas are not believed to have an autoimmune etiology. Exogenous iodine excess (radiocontrast agents or angiography dye) or the administration of thyroid hormones may induce iatrogenic thyrotoxicosis. The antiarrhythmic agent amiodarone is iodine rich and may cause either hypo- or hyperthyroidism.[165] Toxic multinodular goiter, subacute viral thyroiditis, TSH-secreting pituitary tumors, and thyroid cancer are less common causes of thyrotoxicosis. There is a three-fold increase in Graves' disease in the postpartum period.[164]

Signs and Symptoms. Clinical manifestations associated with thyrotoxicosis reflect the widespread hypermetabolic effects of excess thyroid hormones. Physical manifestations include tachycardia, tremor, and muscle weakness. The thyroid gland is usually enlarged two to three times normal with Graves' disease. Sleep is often difficult. Weight loss (despite increased food consumption), anxiety, fatigue, and increased thermogenesis and oxygen consumption are clinical findings of thyrotoxicosis.[164,165]

The aberrant immunologic response associated with Graves' disease targets primarily the thyroid gland but also other tissues, including extraocular muscles and skin. Ophthalmopathy is observed in 30% to 50% of patients with Graves' disease.[164,165] Thyroid-associated ophthalmopathy may cause exophthalmos, eye redness, and periorbital edema. Papilledema and loss of visual acuity rarely occurs. Graves' ophthalmopathy results from autoimmune-mediated inflammation and swelling of the periorbital connective tissue and extraocular muscles.[164,165]

The blood volume increases slightly under the influence of excess thyroid hormone, a result of vasodilation. Mean arterial pressure usually remains unchanged, but the pulse pressure increases.[166] The systolic blood pressure is typically elevated 10 to 15 mmHg, and the diastolic pressure is reduced. Blood flow to the skin increases in response to the increased need for heat elimination.[166]

The effects of thyrotoxicosis on the heart are pronounced. Thyroid hormones have a direct effect on the excitability of the heart by increasing the number of β-adrenergic receptors. Palpitations, tachycardia, and cardiac dysrhythmias affect most patients.[166] About 10% of thyrotoxic patients have atrial fibrillation. The cardiac output increases with thyrotoxicosis, sometimes to 50% or more above normal.[166] Mitral valve prolapse is more common in patients with Graves' disease than in the general population.[166] With protracted high thyroid hormone levels, heart muscle strength may become depressed because of protein catabolism. Diagnosis of thyrotoxicosis is more difficult in the elderly because many of the hyperkinetic manifestations of hyperthyroidism are absent.[167] Elderly patients may initially present with myocardial failure or atrial fibrillation.[164,165,167]

The hyperthyroid individual may feel constant fatigue from the exhausting effect of thyroid hormone on the musculature and the central nervous system.

Diagnosis. The diagnosis of primary hyperthyroidism is established in most cases by the combined findings of an abnormally high unbound serum T_4 assay and depressed TSH levels. With Graves' disease, the diagnosis may be supported by the presence of thyroid-stimulating immunoglobulins.[164,168] Serum alkaline phosphatase and calcium concentrations are elevated in approximately 20% of patients with Graves' disease and reflect bone turnover.[164]

Other autoimmune diseases such as myasthenia gravis, rheumatoid arthritis, systemic lupus erythematosus, and DM are more common in patients with Graves' disease.

Treatment. A variety of treatment options are available for patients with Graves' disease. The three primary treatment options for thyrotoxicosis are radioactive gland ablation, surgery, and antithyroid drug therapy.[166,169,170]

Radioactive Iodine. A common therapy for Graves' disease in the United States is ablation of the thyroid gland with radioactive iodine ($Na^{131}I$). Two to four months is needed to reverse the hyperthyroidism with this approach. Hypothyroidism is common after treatment. Use of $Na^{131}I$ is contraindicated during pregnancy and breast feeding.

Thyroidectomy. Surgery for treatment of Graves' disease is an option when antithyroid drugs are ineffective, if radioiodine treatment is refused, in children or pregnant women, or if the thyroid goiter is exceptionally large. Patients should be treated preoperatively with antithyroid medication and rendered euthyroid prior to surgery. Complications associated with thyroid surgery occur in less than 1% of cases and include damage to the recurrent laryngeal nerve (RLN), hypoparathyroidism, and neck hematoma. Various nerve integrity monitors may be used during thyroid surgery to help the surgeon identify the RLN and avoid injury and vocal cord paralysis.[172-175]

Thyroidectomy is usually performed under general anesthesia, but local anesthesia with a bilateral cervical plexus block can be used for those patients who pose a general anesthesia risk.[176]

Antithyroid Drugs and β-Adrenergic Receptor Blockade. The main class of antithyroid medications is the *thionamides*, which include propylthiouracil (PTU), methimazole, and carbimazole. All thionamides inhibit thyroid hormone synthesis by interfering with the incorporation of iodine into tyrosine residues of thyroglobulin. PTU also inhibits conversion of T_4 to T_3. A euthyroid state is usually obtained in 6 to 7 weeks. Hepatitis and agranulocytosis are the most serious side effects of these drugs.[171]

About 10 days before surgery, oral potassium iodide (saturated solution of potassium iodide [SSKI], Lugol solution) may be added to the course of therapy to decrease gland size and vascularity and block hormone synthesis and release. Propranolol also may be added to the antithyroid regimen to reduce cardiovascular symptoms and inhibit the peripheral conversion of T_4 to T_3.[169,171]

Preoperative Assessment—Hyperthyroidism. The key to successful preoperative preparation of the hyperthyroid surgical patient is a careful assessment of the extent of thyrotoxicosis and the severity of end-organ manifestations. Thyrotoxicosis is associated with increased operative risk, so elective surgery should not proceed until the patient has been rendered euthyroid by medical management.[8,11,164] Antithyroid medications should be continued through the morning of surgery.[8]

Hyperthyroid patients have increased blood volume, decreased peripheral resistance, and a wide pulse pressure. The cardiac

output, heart rate, and systolic blood pressure may be increased. Appropriate corrections of the patient's fluid volume and electrolyte status should be accomplished before surgery.

A careful preoperative evaluation of the airway is mandatory in all hyperthyroid patients undergoing surgery. Thyroid gland enlargement can cause tracheal deviation and tracheoesophageal compression.[165] Although an enlarged thyroid gland is not in itself a predictor of a difficult intubation, a cancerous goiter is a major factor predicting difficult endotracheal intubation.[177,178] A patient with a large goiter and an obstructed airway poses the same challenge as any other patient in whom airway management is problematic. An awake fiberoptic intubation with topical anesthesia is of proven value under these conditions. Computed tomography, magnetic resonance imaging, or ultrasonography of the neck may be required.[165] Tracheomalacia weakens thyroid cartilage from chronic pressure, and its presence may necessitate a more prolonged intubation and vigilant observation after surgery. Hoarseness, sore throat, a feeling of pressure in the neck, coughing, or dyspnea suggests tracheal compression that can be caused by thyromegaly.

Only life-threatening emergency surgery should be performed in an untreated symptomatic hyperthyroid patient.[8,11] In an emergency situation, the otherwise healthy patient can be expeditiously prepared for surgery with the oral administration of potassium iodide (3 to 5 drops every 6 hours) and carefully titrated intravenous propranolol (1 to 10 mg) or esmolol (50 to 300 mcg/kg).[8] Elderly patients who require emergency surgery and have rapid ventricular rates require central pressure monitoring to guide therapy.

Intraoperative Management. A major goal of the perioperative management of the hyperthyroid patient is prevention of sympathetic nervous system stimulation. This is accomplished by providing sufficient anesthetic depth and avoiding medications that directly or indirectly stimulate the sympathetic nervous system.[8,11]

A preoperative anxiolytic medication is generally warranted. Atropine should be avoided as an antisialagogue because of its vagolytic effects and its ability to impair sweating.

Induction of anesthesia may be achieved with a number of intravenous medications. Ketamine should be avoided because it can stimulate the sympathetic nervous system. Pancuronium should be avoided because it has the potential to increase the heart rate.

Because of the increased incidence of myasthenia gravis and skeletal muscle weakness in the hyperthyroid patient, precaution dictates careful titration of muscle relaxant doses with use of a peripheral nerve stimulator. Respiratory failure has been described in surgical patients with uncontrolled hyperthyroidism.[179]

Isoflurane or sevoflurane are attractive choices for inhalation anesthetics because of their ability to offset sympathetic nervous system responses to surgical stimulation and because they do not sensitize the myocardium to catecholamines. Hyperthyroid patients do not generally require a higher minimum alveolar concentration (MAC) for inhalational anesthesia.[8,11] The increased cardiac output accompanying hyperthyroidism may accelerate the uptake of an inhaled anesthetic, resulting in the need to increase the delivered concentration, and this may be perceived clinically as an increased anesthetic requirement.[8,11]

Monitoring of the hyperthyroid patient should focus on early recognition of increased thyroid gland activity suggesting the onset of thyroid storm. Core body temperature should be monitored closely. The ECG should be assessed for tachycardia or dysrhythmias. Hypotension occurring during surgery is better treated with direct-acting vasopressors than with indirect-acting vasoactive drugs that stimulate the release of catecholamines. Hypercarbia and hypoxia should be stringently avoided because they stimulate the sympathoadrenal axis.

Meticulous care of the eyes is required. The patient with proptosis is at risk for corneal exposure and damage, so special care should be taken to lubricate and protect the eyes perioperatively. Box 33-8 summarizes key anesthesia implications for patients with hyperthyroidism.

BOX 33-8

Anesthesia Implications for the Hyperthyroid Patient

- Determine the extent of thyrotoxicosis and end-organ complications.
- Ensure a euthyroid state prior to surgery.
- Evaluate the airway closely.
- Avoid sympathetic nervous system activation and sympathomimetic drugs.
- Titrate muscle relaxants carefully, considering possible myopathy.
- Position carefully (decreased bone density and predisposition to osteoporosis).
- Monitor closely for early signs of thyroid storm.
- Pad and protect the eyes.

BOX 33-9

Clinical Manifestation of Thyroid Storm

- Fever greater than 38.5° C
- Tachycardia
- Confusion and agitation
- Dysrhythmias
- Nausea and vomiting
- Hypertension
- Congestive heart failure
- Abnormal liver function tests

Thyroid Storm. A feared complication in the hyperthyroid patient is *thyroid storm* or *thyrotoxic crisis*. Thyroid storm is an uncommon event that is caused by acute stress in the previously undiagnosed or incompletely treated hyperthyroid patient. Precipitating events may include trauma, surgery (especially thyroid surgery), the peripartum period, radioiodine treatment, acute illness, and infection.[180-181]

Thyroid storm is a life-threatening medical emergency that represents a severe exacerbation of hyperthyroid signs and symptoms. The clinical manifestations may include marked tachycardia, hyperthermia, hypertension, atrial fibrillation, sweating, tremor, vomiting, weakness, agitation, shock, and congestive heart failure (Box 33-9). Metabolic acidosis may be present secondary to increased lactate production from overactive metabolism. Similarities exist between the clinical features of thyroid storm and those of pheochromocytoma, neuroleptic malignant syndrome, light anesthesia, and malignant hyperthermia, making clinical diagnosis challenging in some cases.[180-182]

Thyroid storm associated with surgery may occur anytime in the perioperative period but is more likely to occur 6 to 18 hours after surgery.[182] To prevent substantial morbidity and mortality, treatment must be initiated as soon as the diagnosis is made. Mortality rates are as high as 20% to 30%, even with early diagnosis and management.[164] The high mortality associated with thyroid storm underscores the importance of achieving a euthyroid state before surgery.

Management of perioperative thyroid storm includes identifying and treating the precipitating cause, administering antithyroid medications, and providing hemodynamic support. Carefully titrated β-adrenergic receptor blockers blunt adrenergic manifestations. Antithyroid drugs (PTU or methimazole), administered via a nasogastric tube or rectally, block thyroid hormone synthesis.[171] Supplemental glucocorticoids should be administered because the turnover of endogenous steroids is accelerated by the hypermetabolism of thyrotoxicosis.

Supportive measures include intravenous hydration with glucose-containing crystalloid solutions, correction of electrolyte and acid-base imbalances, and management of hyperthermia. Salicylates may displace T_4 from its carrier protein; therefore, acetaminophen is the recommended antipyretic for lowering body temperature.[164] Adequate oxygenation is of paramount importance during thyroid storm. Vasoactive medications and advanced hemodynamic monitoring may be necessary to help manage the labile cardiovascular course.[164]

Hypothyroidism

Hypothyroidism is a state of thyroid gland hypofunction resulting in decreased circulating concentrations of thyroid hormones. Laboratory findings show decreased plasma T_4 concentrations and increased TSH levels in patients with primary hypothyroidism.[164] The clinical spectrum of thyroid hormone deficiency can range from the asymptomatic patient with no overt physical findings to the classic myxedematous patient with profound symptoms. Hypothyroidism is the most common disorder of thyroid function, occurring in 5% to 10% of women and 0.5% to 2% of men.[164]

Primary hypothyroidism accounts for 95% of all cases of hypothyroidism. An autoimmune-mediated inflammation and destruction of the thyroid gland, known as *Hashimoto thyroiditis*, is the most common form of hypothyroidism in the United States.[180] The disorder most often occurs in females of middle age and is associated with other autoimmune disorders such as myasthenia gravis, type 1 diabetes mellitus, and adrenal insufficiency.

In addition to autoimmune-mediated gland destruction, primary hypothyroidism also may be the result of severe iodine deficiency, nodular goiter, or iatrogenic causes (e.g., previous thyroid surgery, neck irradiation, radioiodine therapy).[164] The antiarrhythmic agent amiodarone is associated with hyper- and hypothyroidism.[166] Lithium inhibits the release of thyroid hormone and causes hypothyroidism in some patients.

Rarely, secondary hypothyroidism is the result of pituitary or hypothalamic disorders. Secondary hypothyroidism is associated with decreased concentrations of both thyroid hormones and TSH.[164] Regardless of the etiology, the clinical manifestations of hypothyroidism are similar.

Signs and Symptoms. Most cases of hypothyroidism are subclinical, with laboratory findings of increased plasma TSH but no overt signs. Patients with more significant disease develop signs and symptoms that reflect a slowed metabolism and impaired cellular functions. The thyroid gland usually is enlarged (goiter), nontender, and firm. A bruit over the gland reflects increased vascularity. Patients may have dry skin, cold intolerance, paresthesias, slow mental functioning, ataxia, puffy face, and constipation. The hair and nails frequently are brittle.[8,164,180] Lack of thyroid hormone causes the muscles to become weak. Patients with severe hypothyroidism may be hypersomnolent with a decreased ventilatory response to hypoxia and hypercarbia.[180]

The accumulation of proteinaceous fluid in serous body cavities is a well-recognized feature of hypothyroidism. The most common sites of effusions associated with hypothyroidism are the pleural, pericardial, and peritoneal cavities.[164,166] Inappropriate ADH secretion and impaired free water clearance can lead to hyponatremia. Accumulation of mucopolysaccharides and fluid imparts the characteristic edematous appearance called *myxedema*.[164]

Cardiovascular complications include sinus bradycardia, dysrhythmias, cardiomegaly, impaired contractility, congestive heart failure, and labile blood pressure.[166] Symptoms of low exercise tolerance and shortness of breath with exertion may be partially the result of decreased cardiac function. Chronic vasoconstriction produces diastolic hypertension and decreases the intravascular fluid volume.[164,166] The autonomic nervous system response is blunted, and there is a decrease in the sensitivity and number of β-receptors.[166,181-184]

Overt hypothyroidism is associated with a number of abnormalities in lipid metabolism that may predispose patients to accelerated coronary artery disease. Hypothyroidism is associated with anemia and decreased erythrocyte production of 2,3-diphosphoglycerate, leading to a leftward shift of the oxyhemoglobin dissociation curve.

These "classic" clinical features of hypothyroidism are often lacking in the elderly hypothyroid patient. In the older patient, thyroid status cannot always be predicted from clinical signs and symptoms, making the diagnosis of hypothyroidism more difficult.

Extreme hypothyroidism during fetal life, infancy, or childhood is termed *cretinism*. The condition is characterized by physical and mental growth retardation. In the newborn, unless cretinism is treated with adequate iodine or thyroxine within the first few weeks after birth, mental retardation remains permanent.[162-164] Neonatal screening (T_4 or TSH levels) has played a major role in preventing severe cretinism.

Treatment. Treatment of hypothyroidism requires replacement with thyroid hormone. The agent of choice is synthetic *levothyroxine sodium* (T_4) because of its long half-life (7 days) and its ability to attain physiologic levels of T_3. Replacement dosages range from 75 to 150 mcg/day, depending on the underlying autonomous thyroid function.[164]

An area of particular concern during thyroid hormone replacement is the effect on the cardiovascular system. Initiation of thyroid hormone replacement in a patient with coexisting angina pectoris or underlying risk factors for coronary artery disease is potentially hazardous and requires careful monitoring of both cardiovascular and thyroid status. Myocardial oxygen consumption is augmented by thyroid hormone, and a hypothyroid patient with deficient coronary artery circulation may not tolerate full replacement doses.

Anesthetic Management—Hypothyroidism. Patients with subclinical hypothyroidism have an overall low risk of complications when undergoing anesthesia and surgery. These patients should receive a careful preoperative evaluation and preoperative continuation of levothyroxine therapy.[8,11] Patients with overt or severe hypothyroidism are predisposed to multiple complications with anesthesia. Depression of myocardial function, abnormal baroreceptor function, and reduction in plasma volume may be present.[8,11] Slowed hepatic metabolism and renal clearance of injected drugs may prolong their effects, but MAC is not decreased significantly for inhaled agents.[8,11] Regional anesthesia is a prudent choice if the surgery permits it and there are no patient contraindications.[11] Elective surgical procedures should be postponed in the presence of severe or symptomatic hypothyroidism until normal thyroid status can be restored.[8,11]

All patients with hypothyroidism should undergo careful preoperative evaluation of the airway. A large goiter may cause airway compromise in the form of tracheal deviation or compression. In some patients with severe hypothyroidism, adequate air exchange

may be compromised by an enlarged tongue and myxedematous infiltration of the vocal cords.[8,11] Depression of the ventilatory responses to hypoxia and hypercarbia must be considered. Preoperative sedation should be avoided in the patient with macroglossia or preexisting hypoventilation. The risk of pulmonary aspiration is increased because of associated somatic obesity and delayed gastric emptying [8]

Hypothyroid patients may respond to opioids with increased central nervous and respiratory system depression. Potent inhalational agents may exacerbate hypotension and myocardial depression. Although ketamine has been proposed as the ideal induction agent, even ketamine can produce cardiovascular depression in the absence of a robust sympathetic nervous system.[11]

Intubation of the trachea may be facilitated by the administration of succinylcholine or a nondepolarizing muscle relaxant; however, hypothyroid patients may be more sensitive to standard doses of nondepolarizing muscle relaxants because of coexisting muscle weakness and decreased hepatic metabolism and renal elimination of these drugs.[8] Maintaining muscle paralysis with minimal doses of muscle relaxants is an appropriate goal.

Supplemental perioperative cortisol should be considered in the patient with symptomatic disease, because there exists a potential for adrenal insufficiency with stress.[8]

In hypothyroidism, the number of β-receptors is diminished, and responses to inotropic drugs and sympathetic stimulation may be influenced by the altered β-receptor pool.

Body temperature should be monitored closely in hypothyroid patients, and mechanisms for warming the patient should be used during surgery. Box 33-10 summarizes the anesthesia implications for the patient with hypothyroidism.

Myxedema Coma. Myxedema coma is a rare syndrome that reflects the end stage of untreated hypothyroidism. The presence of coma is a marker of the patient's clinical deterioration rather than a primary effect of hypothyroidism. A critical insult (e.g., infection, surgery, cerebrovascular accident, pneumonia, gastrointestinal bleeding, cold exposure) can precipitate myxedema coma in a patient with hypothyroidism.[164]

Generally the patient is elderly, has severe clinical features of hypothyroidism, and is hypothermic, hypoventilating, and hyponatremic. The response to hypoxia and hypercapnia is measurably decreased, and mechanical ventilation may be required. The patient is typically lethargic or stuporous. The skin often is pale as a result of cutaneous vasoconstriction.[164]

Myxedema coma is a medical emergency with a mortality rate greater than 50%.[11] Therapeutic attention should be paid to body temperature, shock, and ventilatory failure. Treatment consists of hemodynamic and ventilatory support and the intravenous administration of levothyroxine (300 to 500 mcg), with continuous ECG monitoring for myocardial ischemia.[8] Supplemental cortisol is appropriate because the myxedematous patient may have adrenal atrophy and decreased adrenal reserve.[164] Because these patients may be vulnerable to water intoxication and hyponatremia, meticulous fluid replacement is important. Only lifesaving surgery should proceed in a patient with myxedema coma.[8,11]

BOX 33-10

Anesthesia Implications for the Hypothyroid Patient

- Delay elective surgery for the patient with severe symptomatic disease.
- Evaluate the airway closely.
- Monitor for exaggerated central nervous system depression with anesthetic agents.
- Titrate muscle relaxants carefully, considering possible coexisting muscle weakness.
- Consider decreased hepatic metabolism and renal elimination when dosing medications.
- Maintain normothermia.
- Monitor ventilation closely, considering blunted ventilatory response to hypercarbia and hypoxia.

SUMMARY

The number and variety of patients with endocrine disorders presenting to surgery remains a consistent challenge for the practicing anesthesia provider. Our ability to diagnose and treat these disorders continues to evolve. Several advances in imaging and genetic profiling have yielded improved preoperative diagnostics. The increase in knowledge of the pathophysiology associated with each patient's individual condition will result in better anesthesia management.

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34 CHAPTER Hematology and Anesthesia

◆ *Judith A. Franco and Mark H. Gabot*

When disruptions within the endothelial lining of blood vessels occur, the breach in vessel-wall integrity can be due to spontaneous plaque disruption, trauma, or iatrogenic reasons such as venous access or surgical intervention. Vessel-wall injury initiates an extraordinary chain of events that causes the cessation of bleeding with the formation of a clot, allowing the site of injury to heal. This event is followed by clot dissolution. *Hemostasis* is the process by which the body maintains the delicate balance between bleeding and clotting. Were it not for this balance, hemorrhage or thrombosis would ensue.

The focus of this chapter is to review the normal and abnormal processes of hemostasis, emphasizing: (1) the vessel wall, (2) platelets, (3) coagulation cascade, (4) emerging cell-based theory of coagulation, and (5) fibrinolytic system. An in-depth discussion surrounding the importance of hemostatic assessment and management during the perioperative period, with particular attention to transfusion practices and guidelines follows. A discussion concerning the patient with special hematologic circumstances concludes the chapter.

THE NORMAL VESSEL WALL

The normal blood vessel acts as a conduit to maintain a state of fluidity within the vascular system. Blood vessels are cylindrical and consist of three distinct layers—the intima, the media, and the adventitia (Figure 34-1).

The intima (the inner layer) is the lining separating the flowing blood from the vessel; it is made up primarily of endothelial cells. These endothelial cells play an important role in the modulation of hemostasis by synthesizing and secreting many procoagulants (initiators of coagulation), anticoagulants (inhibitors of coagulation), and fibrinolytics (to dissolve the clot) (Table 34-1). One of the important mediators, von Willebrand factor (vWF), is a necessary cofactor for the adherence of platelets to the subendothelial layer. Tissue factor (a cofactor from the coagulation cascade) activates the clotting cascade pathway when injury to the vessel occurs. Some mediators (e.g., thromboxane A_2, adenosine diphosphate [ADP]) control blood flow by influencing vasoconstriction. Other mediators (e.g., nitric oxide, prostacyclin) control blood flow by vasodilation of blood vessels. Endothelial cells also can suppress activation of the coagulation system by their expression of many coagulation inhibitors such as tissue factor pathway inhibitor.[1]

One of the most important yet simple functions of the endothelial lining is that of forming a barrier separating the fluid contents within the blood vessel (e.g., red blood cells, white blood cells, albumin, globulins, fibrinogen, platelets) from the highly thrombogenic material (e.g., collagen and procoagulants) that lies beneath, within the subendothelial space. The smooth endothelial lining physically repels the blood components away from the vessel wall, preventing activation of the clotting mechanism. When the endothelial wall is damaged, the above properties no longer apply.

The second layer of the vessel wall, the subendothelial layer, is extremely thrombogenic and very active. The subendothelial layer contains collagen, a potent and important stimulus for platelet attachment to the injured vessel wall. The subendothelial layer also contains fibronectin, which facilitates the anchoring of fibrin during the formation of a hemostatic plug.

The third layer, the adventitia, participates in the control of blood flow by influencing the vessel's degree of contraction. The endothelial cells produce nitric oxide and prostacyclin, which influence the adventitia. Nitric oxide affects platelet function by inhibiting platelet adhesion, aggregation, and the binding of fibrinogen between glycoprotein IIb/IIIa complex (GpIIb-IIIa) pseudopods. The ability of nitric oxide to influence and promote smooth-muscle relaxation results in vascular vasodilation. Once the vessel vasodilates, the increase in blood flow limits the activity of procoagulant mediators by simply washing the procoagulant mediators away. This metabolic reaction occurs within the endothelial lining (Figure 34-2). Under the influence of nitric oxide synthetase (NOS), L-arginine is converted to nitric oxide (NO). Nitric oxide then diffuses into the muscle cells and activates soluble guanylate cyclase, subsequently producing a second messenger, cyclic guanosine monophosphate, causing muscle relaxation.[1]

Prostacyclin is a lipid molecule produced in the endothelial cells from prostaglandin. A powerful vasodilator, prostacyclin also interferes with platelet formation and aggregation.

Platelets are an essential component of the thrombogenic response to bleeding. Platelets are round and disklike and circulate freely within the blood. They are formed in the bone marrow from megakaryocytes, maintain a concentration count of approximately 150,000 to 300,000/mm^3, and survive approximately 8 to 12 days.[2] Platelets are constantly working to "patch" thousands of minute vascular injuries that occur in perpetuity. Approximately 7.1×10^3 are used each day.[3]

The platelets flow along the vessel surface. Because they are smaller than some other constituents in fluid blood (e.g., red blood cells [RBCs], white blood cells [WBCs]), they tend to be pushed aside, strategically positioned near the vessel-wall surface where they can then "react" in the event of injury (Figure 34-3).

The membrane surface of the platelet serves as a physical barrier between platelet cytoplasm and the surrounding plasma. Platelets contain mitochondria in their cytoplasm, enabling them to participate in aerobic metabolism, and have glycogen stores that allow for anaerobic metabolism.[4] Platelets also contain contractile proteins, store large amounts of calcium and various enzymes, and require the use of their phospholipids' surface to promote cellular activity. Platelets contain alpha (α) granules that store proteins (e.g., vWF, fibrinogen, fibronectin, platelet factor 4, and platelet growth factor) and dense granules that store nonproteins (e.g., serotonin, ADP, adenosine triphosphate [ATP], histamine, and epinephrine).[2] Many of these granules synthesize

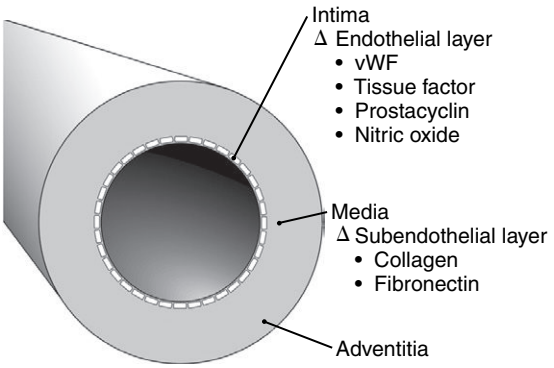

FIGURE **34-1** Schematic of vessel layers and some important mediators. *vWF*, Von Willebrand factor.

TABLE 34-1 Mediators Responsible for Procoagulant, Anticoagulant, and Fibrinolytic Activities

Property	Mediator	Function
Procoagulant	Coagulation factors	Coagulation
	Collagen	Tensile strength
	vWF	Adhesion
	Protein C	Degrades V and VII
	Protein S	Cofactor for protein C
	Fibronectin	Mediates cell adhesion
	Thrombomodulin	Regulates anticoagulant pathway
Anticoagulant	Antithrombin III	Degrades factors XII, XI, X, IX, & II
	Tissue pathway factor inhibitor	Inhibits tissue factor
Vasodilation	Nitric oxide	Vasodilates
	Prostacyclin	Vasodilates, inhibits aggregation
		Both promote smooth-muscle relaxation
Vasoconstriction	Thromboxane A_2	Vasoconstriction
	ADP	Vasoconstriction
	Serotonin	Vasoconstriction
Fibrinolytic	Plasminogen	Converts to plasmin
	tPA	Activates plasmin
	Urokinase	Activates plasmin
Antifibrinolytic	Plasminogen activator inhibitor	Inactivates tPa, urokinase
	α-Antiplasmin	Inhibits plasmin

ADP, Adenosine diphosphate; *tPA*, tissue plasminogen activator; *vWF*, vonWillebrand factor.

prostaglandins that enable the platelets to promote vascular and local tissue reactions.[2,4] Platelets also produce thrombin. In the platelet, thrombin's role is to activate some of the coagulation factors and to influence recruitment of platelets to the site of injury. All the contents in the cytoplasm of the platelet participate in regulating hemostasis. Platelets do not contain a nucleus, RNA (ribonucleic acid), or DNA (deoxyribonucleic acid), so they do not reproduce.[2]

Platelets are largely inactive unless they become activated as a result of vascular trauma. Adequate hemostasis is not possible in the absence of an adequate quality or quantity of activated platelets. It is important to note that platelets do not work independently to achieve hemostasis. They work in

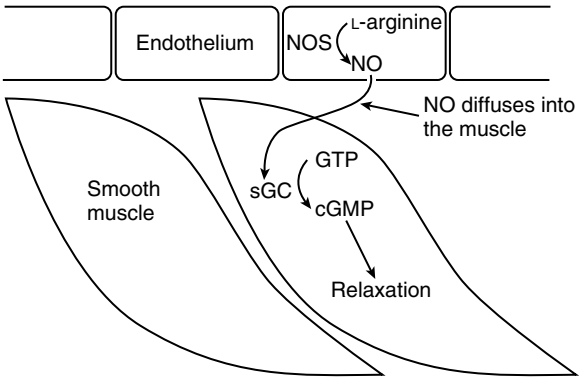

FIGURE **34-2** Nitric oxide influences vessel-wall vasodilation by causing muscle relaxation. *cGMP*, Cyclic guanosine monophosphate; *GTP*, guanosine triphosphate; *NO*, nitric oxide; *NOS*, nitric oxide synthetase; *sGC*, soluble guanylate cyclase.

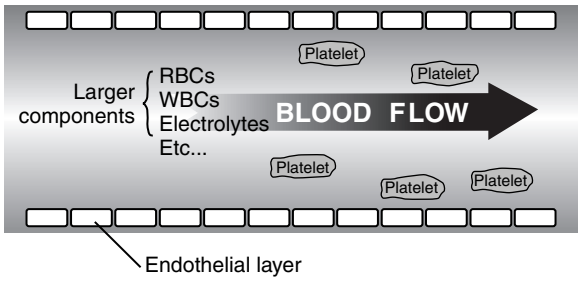

FIGURE **34-3** Position of platelets flowing in the blood vessel.

conjunction with plasma proteins of the coagulation cascade (see "Vessel Injury") to build a stable clot when injury to the vascular integrity occurs.

VESSEL INJURY

Clot formation in response to injury has traditionally been described to include the adherence of the platelet to the injured vessel wall and the response of the clotting cascade to form a stable clot and stop the progress of bleeding. When the endothelial lining is disrupted, as it might be by plaque dislodgement, surgical instrumentation, or trauma, an intricate process to maintain hemostasis and promote clot formation is initiated.

The vessel wall immediately contracts to cause a tamponade, decreasing blood flow. This contraction is a result of autonomic nervous system reflexes and the expression of thromboxane A_2 and ADP.[2,5] The area adjacent to the injury vasodilates and distributes blood to the surrounding organs and tissues. Contraction is followed by three separate stages in the formation of a primary plug: adhesion, activation, and aggregation.

In the adhesion stage, vWF mobilizes from within the endothelial cells and emerges from the endothelial lining. Glycoprotein Ib (GpIb) receptors emerge from the surface of the platelet (Figure 34-4). The purpose of GpIb is to attach to vWF and attract platelets to the endothelial lining; vWF makes platelets "sticky" and allows them to adhere to the site of injury.

Under the influence of tissue factor (a cofactor of the extrinsic clotting pathway), the platelet then undergoes a conformational transformation as it becomes activated (Figure 34-5). The once disklike structure swells and becomes oval and irregular. From the platelet surface, two other major glycoproteins, IIb and IIIa, project themselves outward. The purpose of the GpIIb-IIIa receptor complex is to link other activated platelets together in an effort to form a primary platelet plug. When this action is complete, the

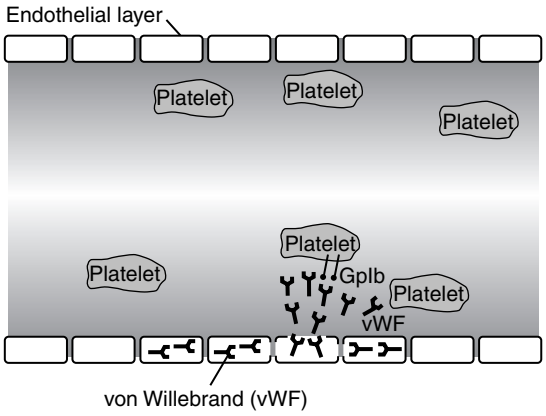

FIGURE **34-4** von Willebrand factor is responsible for adhesion of platelets.

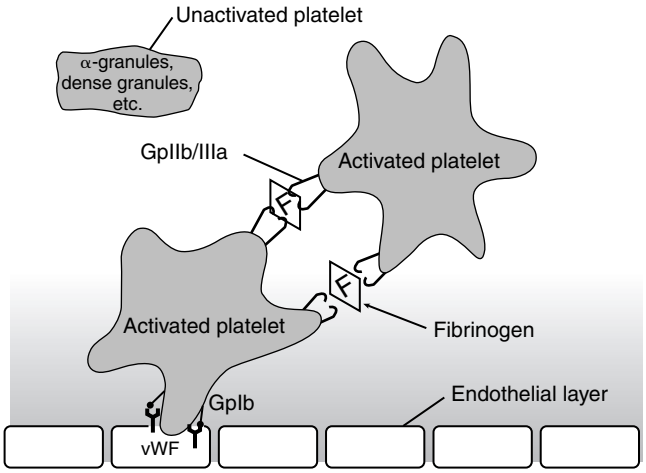

FIGURE **34-5** Glycoprotein IIb/IIIa complex (GpIIb-IIIa). Pseudopods link activated platelets together with fibrinogen to form a mound to "patch" injury to vessel walls. *VIII,* Factor VIII; *vWF,* von Willebrand factor.

platelets form a mound whose only goal is to seal and heal the site of injury within the blood vessel.

As platelets undergo this metamorphosis, they release the alpha and dense granules, the contractile granules, thrombin, and many important mediators into the blood in an effort to promote procoagulant activity. All these mediators are responsible for platelet aggregation to form a primary unstable clot. When injury is minute and less threatening, this primary plug is enough to maintain hemostasis. When the injury is large, activation of the coagulation clotting cascade is required for permanent repair to create and stabilize a secondary clot to cease bleeding.[2]

The coagulation cascade illustrates the activation of cofactors (also referred to as *zymogens*) and their role in this process of hemostasis. Most cofactors are enzymes, with some exceptions (e.g., factors V and VIII). The coagulation factors circulate as inactive cofactors until they are activated to assist in the process of coagulation (Table 34-2). Activation of cofactors results from either tissue or organ damage and sets in motion a process that terminates in stabilization of hemorrhagic conditions in the absence of pathology. The factors are identified with Roman numerals for ease of interpretation.

The clotting pathways are thought to be two separate and distinct pathways (extrinsic and intrinsic) that worked independently of each other but in conjunction with platelet activity and the common coagulation pathway (Figure 34-6). The extrinsic pathway (tissue factor pathway) became activated by the release of tissue factor when injury occurred outside the vessel wall (with organ trauma or crushing injuries). This section of the coagulation cascade consisted of factor III (tissue factor or thromboplastin) and factor VII (proconvertin).

When damage occurs outside of blood vessels, tissue factor (factor III) activates proconvertin (factor VII), changing it to activated (a) factor VII (VIIa). (When factor III activates factor VII, it is immediately inhibited by tissue factor pathway inhibitor, so only a predetermined amount of factor VII is activated.) Once factor VII is activated, it in turn activates factor X (Stuart-Prower) of the common pathway. Factor X forms a complex with factor V (proaccelerin, a prothrombinase complex), activating factor II (prothrombin), which when activated becomes factor IIa (thrombin). Thrombin in turn activates factor I (fibrinogen) to form activated factor I (Ia, fibrin).

The intrinsic pathway (contact activation pathway) is initiated when damage occurs to the blood vessels themselves. The intrinsic pathway is initiated by prekallikrein, high-molecular-weight kininogen (HMWK), and by the activation of factor XII (Hageman). With the help of calcium (factor IV), the coagulation pathway initiates a domino effect. Each factor, once activated, affects its subsequent factor. Factor XII (Hageman) activates factor XI (plasma thromboplastin antecedent), which activates factor IX (Christmas), which then activates factor VIII (antihemophiliac factor) and ultimately (similar to the extrinsic pathway) merges at the common pathway and activates factor X. The result is the generation of fibrin from the activation of prothrombin to thrombin.

Conversion of prothrombin to thrombin is an important reaction for both coagulation pathways. Thrombin assists in activating factors V, VIII, I, and XIII and influences the recruitment of platelets to the injured area. Enough thrombin must be present to activate adequate fibrin to form a stable clot.

Thrombin also behaves as an anticoagulant. It (1) prevents runaway clot formation by releasing tissue plasminogen activator (tPA) from endothelial cells, (2) stimulates protein C and protein S to inhibit clot formation, and (3) forms a relationship with antithrombin III to interfere with coagulation.[1] The common pathway is the terminal pathway of the coagulation cascade. In the common pathway, factor X has been activated by the intrinsic and extrinsic pathways. Factor X requires the help of factor V (proaccelerin) and calcium to convert factor II (prothrombin) to its active-state thrombin (IIa). Thrombin then activates factor I (fibrinogen) to its active form, Ia (fibrin). Factor XIII (fibrin-stabilizing factor) is required to ensure the platelet plug will hold. Factor XIII helps form a cross-linked mesh within the platelet plug, increasing its strength. Fibrin (factor Ia) in conjunction with factor XIII finally secures a stable secondary plug, and bleeding stops. Once a clot is made, it retracts, eliminating its serum. As it retracts, it weaves the edges of the vessel together, healing the site of injury.[2]

Most of the coagulation proteins are synthesized in the liver. Calcium, which is not a true factor, comes from diet; it is needed to "position" the coagulation factors on the surface of the platelet so clotting will ensue. Von Willebrand factor is synthesized in the endothelial cells, and factors II, VII, IX and X are dependent on vitamin K for utilization.

CELL-BASED THEORY OF COAGULATION

The cell-based theory is a newer concept for explaining the involvement of the platelet and clotting cascades in hemostasis. It hypothesizes *why* platelets and the extrinsic and intrinsic pathways of coagulation cascade do not work independently of one

TABLE 34-2 Coagulation Factors

Factor	Factor Name	Synthesized	Vitamin K Dependent	Action
I	Fibrinogen	Liver	No	Form a clot
II	Prothrombin	Liver	Yes	When in active form, activates I, V, VII, XIII, platelets, and protein C
III	Tissue factor or thromboplastin	Vascular wall and extravascular cell membranes; released from traumatized cells	—	Cofactor of VII
IV	Calcium	Diet	—	Promotes clotting reactions
V	Proaccelerin	Liver	No	Cofactor of X; forms a prothrombinase complex
VI	(Unassigned)	—	—	—
VII	Proconvertin	Liver	Yes	Activates IX and X
VIII	Antihemophiliac	Liver	No	Cofactor to IX
vWF	Von Willebrand	Endothelial cells	—	Mediates adhesion
IX	Christmas	Liver	Yes	Activates X
X	Stuart-Prower	Liver	Yes	Activates II, forms a prothrombinase complex with V
XI	Plasma thromboplastin antecedent	Liver	No	Activates IX
XII	Hageman	Liver	No	Activates XI
XIII	Fibrin stabilizing	Liver	No	Cross-links fibrin
Prekallikrein	Fletcher		—	Activates XII, cleaves HMWK
High-molecular-weight kininogen (HMWK)	Contact activation factor		—	Supports activation of prekallikrein, XII, XI

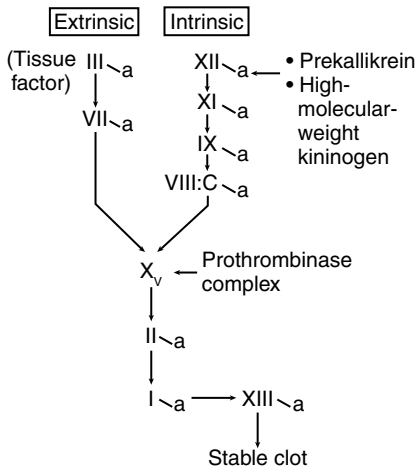

FIGURE **34-6** Schematic of the coagulation cascade (extrinsic, intrinsic, and common pathways). *a*, Active form.

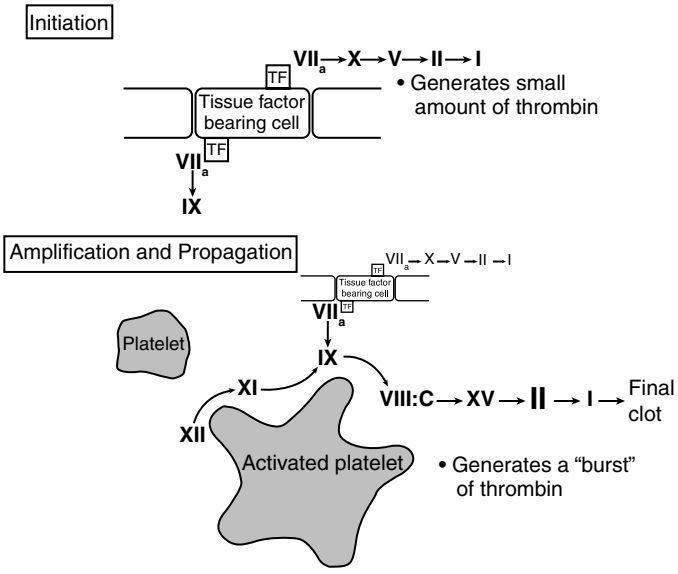

FIGURE **34-7** Cell-based theory of coagulation. (Adapted from Hoffman M, Monroe D. Coagulation 2006: a modern view of hemostasis. *Hematol Oncol Clin North Am.* 2007;21[1]:1-11.)

another but form a very interdependent relationship.[6] The theory posits that coagulation takes place on different "cell surfaces" that bear tissue factor (TF). These surfaces play a pivotal role in factor expression leading to hemostasis. The cell-based theory describes hemostasis as taking place in three phases: initiation, amplification, and propagation.

The initiation phase is triggered by injury to the endothelial surface (Figure 34-7). When injury occurs, TF is exposed at the site of injury. In its presence, the endothelial surface of the blood vessel changes, becoming acidic and making its phospholipid surface less repellent to platelets. TF down-regulates anticoagulants that reside in the subendothelial layer (e.g., antithrombin III, thrombomodulin) in an effort to promote coagulation.[7] This new medium enhances the many enzymatic processes that work to maintain hemostasis by encouraging aggregation and the activation of clotting factors to the site of injury. TF recruits platelets and activates factor VII.

In the cell-based theory, TF/VII reaction results in the activation of factors X (common pathway) *and* IX (intrinsic pathway). Factor X forms a complex with factor V, and together these two activated factors are able to generate a *small* amount of thrombin for clot formation.[8] Only a small amount of thrombin is created

because this reaction terminates almost immediately when tissue factor pathway inhibitor (TFPI) limits the amount of TF expressed. The activation of factor IX from the TF/VII complex does not participate in this initiation stage because IX does not act on TF-bearing cell surfaces.[7]

It is on the platelet cell surface that factor IX (generated from TF/VII) exerts its coagulation contribution to hemostasis. Factor IX attaches to the activated platelet cell surface and binds with a receptor, resulting in the activation of factor VIII, which in turn activates factor X. Additional thrombin is then produced.

As injury perpetuates and TF is expressed, platelets mobilize to the site of injury.[7] It is during the amplification phase that thrombin generation gains momentum, and acceleration and activation of clotting factors persists. Thrombin activates factors V, VIII, and IX.[6] Activated factor XI assists in generating even more factor IX on the platelet surface.[9] Von Willebrand factor promotes platelet aggregation through its adhesive properties with GpIb, and the expression of the GpIIb-IIIa pseudopods from the surface of platelets facilitates aggregation of additional platelets.

During the propagation phase, all coagulation factors are actively influencing one another, promoting coagulation and finally activating prothrombin, resulting in a large "*burst*" of thrombin. Remember, enough thrombin must be present to convert fibrinogen to fibrin to form a stable secondary hemostatic plug. This burst of thrombin does just that.

The cell-based theory is a means of providing a more thorough understanding and an innovative interpretation of coagulation. It explains how cell surfaces do not just express coagulation factors; these surfaces participate in conjunction with platelets and the coagulation cascade pathways to maintain hemostasis. This theory also explains why certain deficiencies fail to cause bleeding, despite changes in laboratory values such as the PT prothrombin time (PT) or activated partial thromboplastin time (aPTT), indicative of coagulation problems.[6]

FIBRINLOYTIC SYSTEM

Once a disrupted vessel is sealed, there is no longer a need for a hemostatic plug. A counterbalance mechanism, the fibrinolytic system, exists to degrade fibrin. Initially there is an increase in blood flow at the site of injury. This increase in blood flow washes away ADP and thromboxane A_2 and other procoagulant mediators, which were initially present to encourage hemostasis and limit the size of the clot. Thrombin, which initially behaved as a procoagulant, now acts as an anticoagulant and activates additional anticoagulant mediators. TFPI stops the action of TF. Protein C and protein S inhibit coagulation factors III, V, and VIII. Antithrombin III inhibits thrombin activity by sequestering factors XII, XI, IX, and X. Antithrombin III is a mediator that corrals some of the factors present in the clotting cascade and takes them out of the clotting equation (Figure 34-8). The clot manufactured is disrupted.

The process of fibrinolysis is highly regulated by plasma proteins (Figure 34-9). A clot is composed primarily of plasminogen, plasmin, fibrin, and fibrin degradation products. Plasminogen is an enzyme synthesized in the liver. It is stored like the clotting factors in an inactive form. While the clot is forming, plasminogen incorporates itself into the clot. With the assistance of the body's own tPA and urokinase, plasminogen is activated to plasmin. Plasmin then acts on the fibrin, causing fibrin to degrade into fibrin degradation products. The circulatory system removes the waste products of the clot. α-Antiplasmin and tissue plasminogen activator inhibitor are important fibrinolytic mediators that stop the process of fibrinolysis when the clot has been digested.

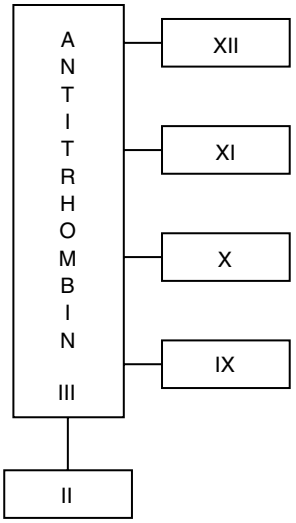

FIGURE **34-8** Antithrombin III corrals clotting factors XII, XI, IX, X. This influences factor II.

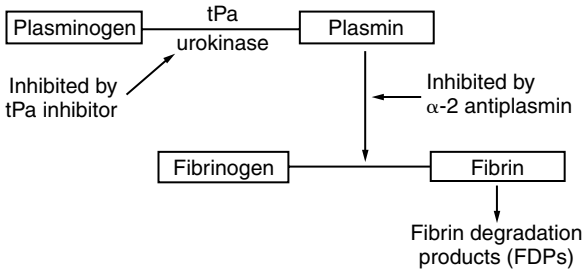

FIGURE **34-9** Schematic of the fibrinolytic system. *tPA*, Tissue plasminogen activator.

Platelets, coagulation cofactors, and the fibrinolytic systems are dependent on each other to ensure a person does not bleed to death or clot to death at any given moment. This system of checks and balances maintains hemostasis when a breach in vascular integrity occurs.

ANESTHETIC IMPLICATIONS

Preoperative Considerations

The preoperative interview is the ideal time for the anesthesia provider to gather detailed information regarding the patient's health status. A thorough history and physical is the best way to identify patients at risk for surgical bleeding or those patients with thrombopoietic tendencies.[10] It is also during the interview that additional laboratory tests can be ordered if necessary to identify potential defects in hemostasis and to guide the decision regarding whether to order and/or administer blood products.

During the preoperative interview, it is important to ask questions directly related to bleeding: (1) Does the patient experience unusual bleeding or bruising (e.g., bleeding gums, epistaxis, mucous membrane bleeding, bloody stools)? (2) Is there a history of previous bleeding with dental procedures? (3) Are there repeated spontaneous bleeding episodes or a history of excess bleeding that may have occurred after a minor procedure or childhood trauma? (4) Do familial bleeding tendencies exist? (5) Has there been a time when expected bleeding from a surgical procedure was more than anticipated?[4,11] These questions can reveal an undiagnosed inherited disorder of coagulation. Patients who have undiagnosed inherited coagulopathies may complain of hematomas, runaway bruising, and oozing, even after the most minor

injuries. An undetected preoperative bleeding tendency can lead to life-threatening blood loss during surgery.[4] Laboratory evaluation of platelets, coagulation, and fibrinolytic components can be screened with the commonly available coagulation tests.

When approaching the patient scheduled for surgery, a physical examination with a complete systems approach is necessary. The anesthesia provider must be alert to potential disruptions in hemostasis. Any overt physical sign of bleeding such as the appearance of bruising or petechial hemorrhages on the chest, abdomen, or upper extremities warrants further investigation. Small hemorrhages on the skin may indicate the presence of small hemorrhages on other organs as well. Remember, the questionable coagulopathy can be related to any number of disruptions in the hemostasis process: a platelet problem, a factor deficiency, an inherited disorder of coagulation, the presence of circulating anticoagulants, or a disturbance in the fibrinolytic system.

During the physical assessment, disorders of malnutrition or liver insufficiency suggesting a vitamin K deficiency may be revealed. These disorders can influence coagulation and explain increased bleeding, even for the simplest surgery. Vitamin K is created from bacteria in the gut and is necessary for the formation of factors II, VII, IX, and X. When illness such as liver insufficiency, cirrhosis, absorption problems, and failure to secrete bile are present, the patient will be unable to form and use these factors for effective coagulation.

Patients with preexisting inherited disorders of coagulation must undergo an adequate preoperative workup prior to surgery. Consultation with a hematologist or transfusion specialist is strongly recommended. Patients with preexisting coagulation disorders require considerable attention in the operating room. If general surgery is anticipated, special attention must be made to ensure no damage to soft tissues occurs. Damage to tissues may transpire during direct laryngoscopy, endotracheal intubation, peripheral or central line placement, and positioning or moving to and from the operating-room table.

The preoperative use of many medications—prescribed, over–the-counter, and herbal remedies—can interfere with normal platelet function and coagulation (Box 34-1). The anesthesia provider must ascertain whether the patient regularly ingests medications that might interfere with normal coagulation and when were the medications or herbals last taken. For example, many patients take aspirin for a number of reasons. Historically it has been recommended that aspirin be held for 7 to 10 days prior to surgery. Current recommendations are discussed in detail later in this chapter. Aspirin directly affects the life of the platelet by *irreversibly* inhibiting cyclooxygenase, resulting in decreased platelet function.[12] Nonsteroidal antiinflammatory drugs (NSAIDs) also inhibit cyclooxygenase, albeit *reversibly*, and the recommendation is to withhold NSAIDs for approximately 24 to 48 hours to avoid any bleeding effects in surgery[13,14] (Figure 34-10).

A preoperative discussion between the patient, surgeon, and anesthesia provider must occur regarding transfusion requirements during surgery. Informing patients about the safety, screening measures, and risks of blood administration cannot be ignored. A small percentage of patients will have to contend with the negative sequelae of transfusion therapy (e.g., hepatitis, human immunodeficiency virus, and bacterial transmission), despite careful screening and handling. In situations with emergent or trauma patients, many times a preoperative interview is unattainable, and the provider must rely purely on information supplied by family members (if present), physical assessment, and laboratory analysis.

Careful consideration must be given to the patient who refuses blood component therapy for personal or religious reasons.

BOX 34-1

Frequently Encountered Medications That Influence Coagulation

Anticoagulants
- Heparins
- Low-molecular-weight heparins
- Coumarin derivatives
- Direct thrombin inhibitors

Procoagulants
- Vitamin K

Antiplatelets
- Nonsteroidal antiinflammatory drugs
- Persantine
- Thienopyridine (Plavix and Ticlid)

Antifibrinolytics
- Amicar
- Tranexamic acid

Nonherbal Dietary
- Vitamin K
- Vitamin E
- Coenzyme Q10
- Zinc
- Omega-3 fatty acids

Herbal
- Garlic
- Ginger
- Ginkgo
- Feverfew
- Fish oil
- Flaxseed oil
- Black cohosh
- Cranberry

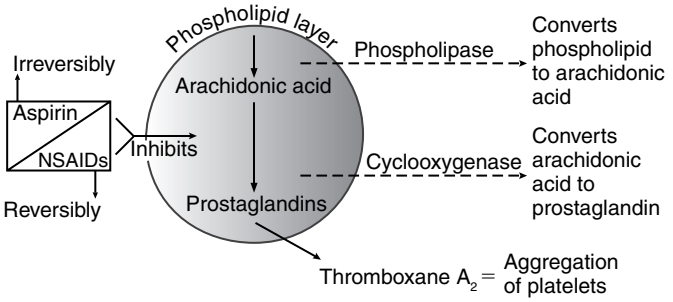

FIGURE **34-10** Schematic illustration depicting the mechanism and site of action of aspirin and nonsteroidal antiinflammatory drugs (NSAIDs).

This patient can be an ethical challenge to healthcare providers, especially when refusal may mean a greater chance for mortality because a high-risk procedure may incur greater blood loss. In these special situations, an inclusive discussion of potential or available options must be addressed. If the patient is a candidate, there are alternatives available such as erythropoietin administration, acute normovolemic hemodilution, cell salvage, recombinant factor VII or VIII, and topical coagulants. Pharmacologic alternatives (e.g., Amicar [aminocaproic acid], tranexamic acid) also can be a means of stabilizing coagulation when significant blood loss is anticipated.

Most anesthesia providers are familiar with the Jehovah Witness (JW's) population and their refusal of blood transfusion or derived components. However, it is important to consider that some JW's will accept certain fractions of primary blood components (e.g., albumin, leukocyte-depleted red cells, platelets, solvent-treated fresh frozen plasma [FFP], and recombinant products) or alternatives to allogenic transfusions, as long as blood remains continuous with the body.[15] Advice regarding available management options should be discussed, especially with high-risk blood-loss procedures.[16]

TABLE 34-3 Possible Causes and Treatment of Hemostatic Disorders

CLINICAL COAGULATION TESTS							
BL	**aPTT**	**PT**	**BT**	**PC**	**Fib**	**Possible Cause**	**Treatment**
	Abn					Factor VIII, heparin, "lupus anticoagulant," poor sample	No treatment
+	Abn					Factors XI, IX, VIII, heparin therapy	FFP, protamine
+	Abn	Abn				Factors V, X, II, dysfibrinogenemia, heparin, coumarins	FFP, cryoprecipitate, protamine
+		Abn				Factor VII	FFP
+	Abn		Abn			Von Willebrand disease	Desmopressin acetate, cryoprecipitate
+	Abn	Abn	Abn		Low	Hypofibrinogenemia	FFP, cryoprecipitate
+			Abn	Abn		Thrombocytopenia	Platelet concentrate (8-10 units)
+			Abn			Thrombocytopathy, aspirin, NSAIDs	Platelet concentrate
+	Abn	Abn	Abn	Abn	Abn	DIC, severe liver disease, dilutional coagulopathy	FFP, cryoprecipitate, platelet concentrate, whole blood

+, Increased clinical bleeding; *Abn*, abnormal result; *aPTT*, activated partial thromboplastin time; *BL*, bleeding; *BT*, bleeding time, *DIC*, disseminated intravascular coagulation; *FFP*, fresh frozen plasma; *Fib*, fibrinogen; *NSAIDs*, nonsteroidal antiinflammatory drugs; *PC*, platelet count; *PT*, prothrombin time.

TABLE 34-4 Coagulation Tests

Laboratory Test	Value*	Description
Bleeding time	3-7 min	Measures platelet function: adhesion, aggregation Not considered a routine test Modest prolongations do not predict surgical bleeding Altered by aspirin and NSAIDs*
Platelet count	150,000-350,000 mm^3	Thrombocytopenic: <100,000 mm^3 Surgical risk: <50,000 mm^3 Spontaneous bleeding: <20,000 mm^3
Prothrombin time (PT)	Normal: Control Average Normal: 12-14 sec	Value is reagent dependent Prolonged with: • Extrinsic pathway disorder • Common pathway disorder Altered by coumarin derivatives*
Activated partial thromboplastin time (aPTT) (intrinsic and common pathway)	Average normal: 25-32 sec	Prolonged with: • Intrinsic pathway disorder • Common pathway disorder Altered by heparin and Lovenox*
Thrombin time (common pathway)	8-12 sec	Measures fibrinogen-to-fibrin reaction
Activated clotting time (ACT)	80-150 sec	Guides anticoagulation dosing
Fibrinogen	>150 mg/dL; 200-350 mg/mL	Measures fibrinogen level
Fibrinogen (degradation products)	<10 mcg/mL	Measures by-products from clot dissolution
D-Dimer	<500 mg/mL	Measures degradation products secondary to fibrinolysis
Thromboelastogram		Measures global hemostasis
Antithrombin III	80%-120%	Measures antithrombin III levels; decreased level may explain subtherapeutic heparin Severely depressed in DIC

*Values may vary among laboratories.
DIC, Disseminated intravascular coagulation; *NSAIDs*, nonsteroidal antiinflammatory drugs.

Laboratory Tests

Routine laboratory tests must be evaluated preoperatively. They serve to guide the clinician in determining whether a coagulation disorder exists (Table 34-3). Laboratory tests should be ordered on an individual basis, considering the patient's history and planned surgical procedure.

The most frequently assessed tests are the bleeding time, platelet count, PT, and aPTT (Table 34-4). Together, these tests evaluate vascular contraction, platelet function, coagulation, and the fibrinolytic system. Results of these routine tests must fall within the normal range. If they are outside normal range, there must be a reasonable explanation, and adequate measures must be taken to correct or control hemostasis before bringing the patient into the operating room. For example, if the patient requires surgery but not emergently, vitamin K can be administered 4 to 6 hours prior to surgery. If the risk of bleeding is moderate, a type and crossmatch may be preferred to a type and screen. If the patient requires surgery emergently, ordering blood components such as packed red blood cells, FFP, platelets, and cryoprecipitate may be advisable.

The bleeding time evaluates the capability of microvascular contraction and the function of platelets. When vascular injury occurs, the initial response from the blood vessels is to contract, and the response of the platelets is to adhere to the site of injury. If either of these two processes is compromised, prolonged bleeding will occur, resulting in inadequate hemostasis.

The bleeding time was once thought to be the best indicator of bleeding risk. The use of a bleeding time test, however, is open to much scrutiny, and there are many reasons to question its use and interpretation.[17] In the absence of drug ingestion, a prolonged bleeding time suggests primary hemostasis abnormality, and further investigation is recommended. Although the bleeding time is a means of evaluating vascular integrity and platelet function, it is important to appreciate that a prolonged bleeding time is not a good predictor of bleeding or a sign that an abnormality is present.[18] In addition, an isolated prolonged value is not a reason to cancel or delay a surgical procedure.

The platelet count is the actual number of platelets present in blood per cubic millimeter. A normal platelet count does not imply normal platelet function exists, only how many platelets are present in plasma. It is used to evaluate patients who present with petechiae or unexplained spontaneous bleeding and to monitor thrombocytopenia (low platelet count). The platelet's primary role is to maintain vascular integrity, aggregate when a plug is necessary to stop bleeding, and help initiate the clotting pathways. A normal platelet count is 150,000 to 300,000/mm^3.[2] Patients are considered thrombocytopenic at counts less than 100,000 mm^3. There are varying degrees of thrombocytopenia that must be considered preoperatively. Platelet counts greater than 100,000 are sufficient for hemostasis. When the platelet count declines to 50,000/mm^3, spontaneous bleeding rarely occurs, but one should suspect prolonged bleeding under surgical conditions.[19] A platelet count less than 20,000 is considered a critical level, and spontaneous bleeding is likely to occur.[20,21]

The PT is used to evaluate the efficiency of the extrinsic factors (III and VII) and common coagulation pathway (factors X, V, II, I) in generating enough thrombin to form fibrin to create a stable clot. The PT is specific to the extrinsic pathway of the clotting cascade. It is the most commonly used test to monitor oral anticoagulant therapy (e.g., the coumarin derivatives). The PT will be prolonged when patients have abnormalities or are deficient in factors specific to the extrinsic and common clotting pathways (III, VII, X, IX, II, I).[5]

Despite the frequent assessment of the PT value preoperatively, this laboratory value has drawbacks. The PT is not a very sensitive test. The PT also fails to identify the specific factor defect in the hemostatic system. It only identifies an existing problem that may or may not cause bleeding.

The international normalized ratio (INR) evaluates the extrinsic and common pathway independently of various reagents used in different laboratory settings and in different areas of the world. The normal INR is 1.5 to 2.5. Many institutions report both PT and INR values.

The aPTT is a test used to evaluate the efficiency of the intrinsic coagulation pathway (factors XII, XI, IX, and VIII) and the common coagulation pathway (factors X, V, II, I, and ultimately XIII) to form fibrin and eventually a stable clot. The aPTT can identify abnormalities in all factors except III and VII. It is also used to monitor anticoagulation status when heparin therapy is used. The aPTT can be prolonged by abnormalities, deficiencies, or inhibitors of any intrinsic or common pathway defect. Factor concentration must be decreased 30% before evidence of a prolonged PT or an aPTT can be appreciated.[1,19]

Any factor deficiency in either limb of the clotting cascade can alter the PT and/or aPTT, but this does not imply that any prediction of an individual patient risk of bleeding can be anticipated.[7] For example, a decrease in factor XII will demonstrate an increase in aPTT but will not cause bleeding.[6] A decrease in factor XI may or may not cause abnormal bleeding. However, a decrease in either factor VIII or IX will definitely cause bleeding with injury. This is seen in hemophilia.

The activated clotting time (ACT) is a simple, quick test that can be used in surgery to monitor the ability of blood to clot. The ACT is also used to regulate heparin therapy. The normal ACT is 90 to 150 seconds. The ACT is not, however, a sensitive test.

The thrombin time is a screening tool for assessing the ending phase of coagulation. Because fibrinogen can be assessed directly, analysis of the thrombin time is less emphasized.

The thromboelastogram (TEG) measures the process of clot formation over time. The benefit of this test is its ability to evaluate (1) platelet reactions, (2) coagulation, and (3) fibrinolysis. A blood specimen is collected and placed in a machine that measures the speed at which a clot forms. The results of the TEG provide an indication of (1) clot strength, (2) platelet number and function, (3) intrinsic pathway defects, (4) thrombin formation, and (5) the rate of fibrinolysis. The results of this test can be used to guide blood component therapy and possibly decrease the amount of transfusion products administered.[2]

Laboratory tests are only as good as the individual interpreting them and many times will not adequately reflect the potential to bleed or thrombose. The use of coagulation tests is best interpreted when patients are without pathology, are not on any medications that could disrupt the laboratory value measured, and are assessed in conjunction with physical assessment and clinical judgment. It is prudent to consult with a hematologist when there is any suspicion of the potential for abnormal bleeding in surgery or if a coagulation disorder exists. Coagulation tests can be performed in the operating room; however, lengthy delay in reporting their values during a time of critical volume loss and coagulopathic alterations can render the value ineffective. Coagulation tests initiated in the operating room may nevertheless serve as a guide.

Intraoperative Period

One main focus of the surgeon and the anesthesia practitioner in the operating room is to recognize and efficiently control blood loss. Frequent evaluation of the patient's clinical status, surgical site, sponges, canisters, and the operating room floor cannot be overemphasized.[19] The surgeon and anesthesia provider are equally responsible in communicating that persistent oozing or frank bleeding is occurring. It is this open communication that helps the surgical team recognize problems and rapidly intervene by having blood components in the room, rechecking ABO compatibility, and anticipating the need for coagulation-factor replacement if transfusion therapy is necessary.

There are many potential adverse effects associated with the administration of blood component therapy. Despite the presence of screening tests, hepatitis and human immunodeficiency virus (HIV) transmission continue to influence patients' decisions about whether they wish to receive blood components. But the incidence of hepatitis and HIV is low when compared with the frequency of other adverse reactions to blood component therapy. Transfusion therapy is also associated with acute hemolytic transfusion reactions, nonhemolytic reactions, viral transmission, transfusion-related acute lung injury, parasite transmission, and bacterial transmission.

The most commonly transfused blood components are red blood cells, platelets, fresh frozen plasma, and cryoprecipitate (Table 34-5). The major reasons for transfusion therapy in the operating room are to replace volume and coagulation factors and

TABLE 34-5 Blood Components

Blood Component	Definition	Surgical Indications	Dose
PRBC	Red blood cells anticoagulated in plasma	Bleeding Increase O_2-carrying capacity	1 unit increases Hgb by 1 g/dL and Hct by 3%
FFP (all factors)	Plasma separated from RBC and platelets Contains ALL clotting factors Contains naturally occurring inhibitors Source of antithrombin III One bag = 200-250 mL Expires 12 months post-donation	Microvascular bleeding Coagulopathy due to factor deficiency PT/aPTT >1.5 normal Massive blood transfusions Reversal of warfarin Acquired coagulopathy von Willebrand disease unresponsive to DDAVP Antithrombin deficiency	10-15 mL/kg
Platelets	Obtain from whole blood or plateletpheresis donations Contain platelets only One bag = random volume One bag pheresis = 250-300 mL	Massive blood transfusion Active bleeding: <5000 = spontaneous hemorrhage 10,000-50,000 = variable bleeding risk >50,000 = spontaneous bleeding unlikely due to platelets	1 unit/10 kg body weight 1 unit increases platelet level 5000-10,000/mm^3
Cryoprecipitate	Protein fraction taken off the top of FFP when being thawed Then refrozen up to 1 year Contains factors I, vWF, VIII, fibrinogen, XIII One bag = 10-20 mL	Microvascular bleeding von Willebrand disease unresponsive to DDAVP	1 bag/5 mg body weight 1 unit raises fibrinogen by 50 mg/dL

aPTT, Activated partial thromboplastin time; *DDAVP*, 1-deamino-8-D-arginine vasopressin (desmopressin acetate); *FFP,* fresh frozen plasma; *Hct*, hematocrit; *Hgb*, hemoglobin; *PRBC*, packed red blood cells; *PT,* prothrombin time; *vWF*, von Willebrand factor.

improve oxygen-carrying capacity.[22] Each component carries its own concerns.

Packed red blood cells (PRBCs) are transfused to improve tissue oxygenation. Although the oxygen-carrying capacity of red cells decreases with the length of storage, it improves when 2,3 diphosphoglycerate (2,3 DPG) is regenerated once transfused. Platelets are provided to patients when a deficit is appreciated or when massive transfusion is required. Platelets can be given as a single-donor plateletpheresis pack or collected and pooled from multiple donors (random-donor platelets).

The recommended dose for platelet replacement is one plateletpheresis pack per each 10 kg of patient weight. This dose should increase the platelet count by approximately 5000 to 10,000 mm^3.[5,19] Whereas the normal life span of a platelet is 7 to 10 days, the life span of a donated platelet is only 4 to 5 days.[9]

The Anesthesia Task Force recommends (1) the use of platelets in the operating room for microvascular bleeding, regardless of platelet count, and (2) the use of clinical judgment based on the risk of bleeding and the length of the surgery when the platelet count falls between 50,000 and 100,000/mm^3. Prophylactic administration of platelets may not be necessary, especially when the cause of thrombocytopenia is destruction of platelets (e.g., heparin-induced thrombocytopenia, idiopathic thrombocytopenia purpura, thrombotic thrombocytopenia purpura) or when the count is greater than 100,000.[19,22] Although there are varying degrees of thrombocytopenia, if persistent bleeding or oozing occurs in the operating room, a transfusion might be considered despite a platelet count greater than 50,000. Compatible plateletpheresis is recommended, but when matched platelets are unavailable, unmatched platelets can be given; however, this incompatibility shortens the life span of the platelet.[3,23] When pooled platelets are administered to women of childbearing age, Rh sensitization can occur, and administration of RH_O(D) immune globulin may be necessary prior to discharge.

Platelets carry the greatest risk of bacterial transmission.[23,24] Platelets are stored for 4 to 5 days at room temperature, providing an excellent medium for the growth and reproduction of bacteria. Standard protocols for blood banks and transfusion services require that a method be in place to detect bacterial contamination of platelets.[23,25]

Fresh frozen plasma is the fluid portion of whole blood, separated then frozen to preserve coagulation factors and subsequently thawed on use. FFP contains all the clotting factors and naturally occurring inhibitors.[26] It does not provide platelet replacement. The average volume in a unit of FFP is 200 to 250 mL. FFP must be ABO plasma compatible whenever possible.

FFP is transfused (1) for microvascular bleeding, (2) when the concentration of coagulation factors is deficient, (3) to patients with an inherited coagulopathy, (4) for the reversal of warfarin administration, and (5) for a deficiency resulting from a dilutional coagulopathy[19,21,26] (assuming the patient's preoperative laboratory values were normal). Dilutional coagulopathies increase when blood is diluted to at least 30% or when a patient loses more than one volume of blood, indicating only a third of the coagulation factors are present.[27] This deficit is reflected in laboratory values. Laboratory analysis will reveal the need for FFP by a PT and aPTT prolonged more than 1.5 times normal. The use of FFP for volume replacement is contraindicated. Safety screening for FFP is the same as for RBCs.

Cryoprecipitate is the precipitate collected off the top of FFP as it is thawed. Cryoprecipitate is then refrozen and thawed on use. It is rich in fibrinogen and contains factors VIII, XIII, and fibronectin. The current guidelines recommend cryoprecipitate for (1) microvascular bleeding in conjunction with FFP, (2) patients with von Willebrand disease or hemophilia when concentrates are unavailable, (3) suspected factor deficiencies, and (4) prophylaxis when a fibrinogen defect is present.[21] Despite cryoprecipitate's ability to decrease factor deficiencies, more studies are required to ascertain the effectiveness of cryoprecipitate in clinical outcome.

It is preferable to transfuse platelets, FFP, and cryoprecipitate with adherence to ABO compatibility to avoid hemolytic

reactions, but there are times when this practice is impractical. When massive transfusion occurs, one should be alert to the risk of hemolytic reaction. In addition to viral screening for donor units, the institution of solvent detergents, psoralen derivatives, and methylene blue are being evaluated as a means to decreasing emerging viral contaminations, especially when blood products are pooled. The effect of these additives on platelets, FFP, and cryoprecipitate is still under investigation.[23,25]

Despite policies, procedures, and screening modalities, there may never be a time when blood component therapy will be without risk.[23,28] New illnesses and viruses emerge as quickly as the old ones are controlled. Additionally, human error influences the incidence of transfusion reactions. Nevertheless, blood component therapy is still often necessary in the operating room.

Transfusion Guidelines

There is no magic number or an absolute transfusion "trigger" for blood-component administration. There are few if any fixed guidelines or practice standards for transfusion therapy. There are, however, many suggested guidelines and protocols that vary among individual institutions. Past literature recommends a hemoglobin of 10 g/dL as an indicator for red-blood-cell transfusion, but transfusion delivery based on one isolated laboratory value without regard to the patient's overall health status is irresponsible.[29] A hemoglobin value of 8 g/dL and even 6 g/dL may be acceptable when ischemia or risk factors for cardiovascular disease are not evident.[19,22]

There are also alternatives available to reduce or allay allogenic component replacement: preoperative autologous donation (PAD), acute normovolemic hemodilution (ANH), blood-cell salvage (BCS), and recombinant factor VII.[30-32]

Recombinant factor VII was approved by the U.S. Food and Drug Administration (FDA) in 1999 for hemophilia A (factor VIII) and B (factor IX), inhibitor disorders of factors VIII and IX, factor VII deficiency, and as a universal hemostatic agent.[8,33-35] Its off-label use has successfully treated coagulation insufficiencies associated with platelet dysfunction, intracranial hemorrhage, prostate surgery, and trauma.[36]

The exact mode of action of factor VII is undetermined. Both the classic coagulation cascade and the cell-based theory agree that factor VII enhances thrombin generation by augmenting TF/VII at the site of vessel injury and on the surface of the platelet.[6,33,34] Administration ultimately boosts thrombin to form fibrin for clot stabilization. The recommended dose of factor VII for hemophilia is 90 to 120 mcg/kg. There is no definitive dose for use in the operating room for patients without prior coagulation disorders, but 20 to 45 mcg/kg has been suggested.[8]

Factor VII will reverse prolonged INR, but it fails to replace all the clotting factors.[33] The anesthesia provider must remain vigilant intraoperatively, providing interventions that would prevent acidosis and hypothermia, both of which can interrupt the efficacy of the drug.[33,34,37] Patients have experienced cerebrovascular accidents, myocardial infarctions, pulmonary emboli, and arterial and venous thromboemboli. Factor VII should be used cautiously in any patient predisposed to thrombosis. The indications for the use of factor VII remain limited and the treatment is very expensive.[19,26,35,36,38] An extensive discussion of transfusion management practices can be found in Chapter 20.

Postoperative Management

Patients should be reassessed in the postanesthesia care unit and again within 24 hours of surgery. Unrecognized bleeding can thus be identified and corrected before the patient deteriorates. Evaluations of (1) the patient's color and mentation, (2) trends in vital signs (with specific attention to tachycardia or hypotension), (3) urine output, (4) hypothermia, (5) hemodynamic values such as central venous pressure (CVP), (6) laboratory values, and (7) dressings and/or drain volume must be judiciously monitored.

SPECIFIC DISORDERS

Bleeding diathesis can result from any number of deficiencies in coagulation. A few disorders encountered in practice are described here, as well as points to consider when dealing with a patient requiring anticoagulant therapy.

Von Willebrand Disease

Von Willebrand disease (vWD) has traditionally remained the most common inherited coagulation diathesis. Von Willebrand factor (vWF) is a heterogeneous multinumeric glycoprotein that serves two main functions: to facilitate platelet adhesion and to behave as a plasma carrier for factor VIII of the coagulation cascade.[39] Synthesis of vWF takes place in the endothelial cells and megakaryocytes.[40] An acquired form of vWD is seen with lymphomyeloproliferative or immunologic disease states secondary to antibodies against vWF.[41]

Similar to many coagulopathies, vWD has varying degrees of severity—mild, moderate, and severe. In the milder or moderate forms, regular or spontaneous bleeding is not evident but is likely after surgery or when trauma occurs.[10] In the more severe form of vWD, spontaneous epistaxis and oral, gastrointestinal, and genitourinary bleeding can be relentless.

Most patients with vWD exhibit a prolonged bleeding time, a deficiency in vWF and factor VIII, decreased vWF activity measured by a ristocetin (an antibiotic) cofactor (RCoF) assay, and decreased factor VIII coagulant activity (VIII:C). The recommended treatment for vWD is supplementation with recombinant factor VIII-vWF concentrate preoperatively and during surgery to raise the levels of circulating factor VIII and vWF. Cryoprecipitate is another means of acquiring factor VIII; however, there is attendant risk of viral transmission. Desmopressin acetate (1-deamino-8-d-arginine vasopressin [DDAVP]), a synthetic vasopressin, is an excellent option for the milder forms of vWD and should not be overlooked. DDAVP helps increase plasma levels of vWF and augment aggregation.[42]

Hemophilia

Hemophilia is an X-linked hematologic recessive disorder characterized by unpredictable bleeding patterns. Patients are either deficient in factor VIII (hemophilia A) or factor IX (hemophilia B). Hemophilia affects males almost exclusively, although females carry the gene for the disease. Patients with hemophilia A are grouped as mild (excessive bleeding after trauma or surgery), moderate (rarely have extensive, unprovoked bleeding), and severe (absence of factor VIII in the plasma). Hemophiliacs exhibit spontaneous bleeding, muscle hematomas, and pain at joint sites. Continued joint bleeding often results in decreased range of motion and progressive joint arthropathy and often requires orthopedic surgical intervention throughout life.[43]

In the past, the life expectancy for the hemophiliac was short. Because hemophiliacs were deficient in factors VIII and IX, they required blood-component transfusion to replace the deficient or missing factors. The only factor components available were FFP and cryoprecipitate. Screening tests for donated blood units were unavailable, and patient mortality was high. Many hemophiliacs contracted transmissible diseases such as hepatitis and HIV and ultimately died from sequelae of blood transfusion therapy.[43]

Furthermore, hemophiliacs were termed "high risk" for most surgical procedures and often turned down for many elective procedures. Today, blood components undergo extensive screening, and newer and safer treatment modalities exist. Most surgeries are available to hemophiliacs, with little risk of uncontrolled bleeding.[44]

For patients with hemophilia or a family history of hemophilia, a preoperative assessment of hemostasis is imperative. Preoperative laboratory tests should include a platelet count and function, a coagulation panel (PT, aPTT, factor VIII, factor IX, and fibrinogen), as well as an inhibitor test.[44] If the hemophiliac was given a test dose of factor VII preoperatively, the response to the test dose should be evaluated. The patient should be typed and crossmatched, because even a low-risk procedure can be catastrophic for the hemophiliac.

A clearly defined anesthesia plan is essential for the hemophiliac; uncontrolled bleeding is certainly a possibility. Factor VIII concentrate can be given prior to surgery. Factor VII is administered intraoperatively to augment thrombin generation and deter bleeding. The dose should be precalculated and vial availability confirmed prior to going into the operating room. Desmopressin (0.3 mcg/kg) also can be administered to increase plasma levels of factor VIII and vWF for mild to moderate hemophiliacs.[39,45] There is no risk for viral transmission when either of these drugs is initiated.

OTHER CONSIDERATIONS

Perioperative Management of Patients Taking Antithrombotic Drugs

The advent of new antithrombotic medications within the last decade has garnered increasing interest regarding the perioperative management of these potent medications. Antithrombotic medications can be categorized based on their respective method of altering the normal physiologic process of hemostasis: antiplatelet, anticoagulant, and fibrinolytic medications (Figure 34-11). See Table 34-6 for common antithrombotic medications.[46-50] Selection, dosing, and monitoring of antithrombotic therapy should be adjusted based on the patient's primary diagnosis, comorbidities, type of therapy (e.g., treatment or prophylaxis), and renal impairment.

The preoperative management of antithrombotic therapy is currently a controversial topic in that the risk of perioperative bleeding must be weighed against the risk of disease exacerbation. Excessive bleeding may occur if the anticoagulation medications are continued before surgery. This may lead to potentially serious intraoperative and postoperative complications or the need for transfusion of blood products. In contrast, abruptly withholding anticoagulant medications places the patient at increased risk for myocardial infarctions, cerebrovascular accidents, arterial or venous thromboembolism, pulmonary embolism, or death.[46-49] Situation-specific considerations are leading to new

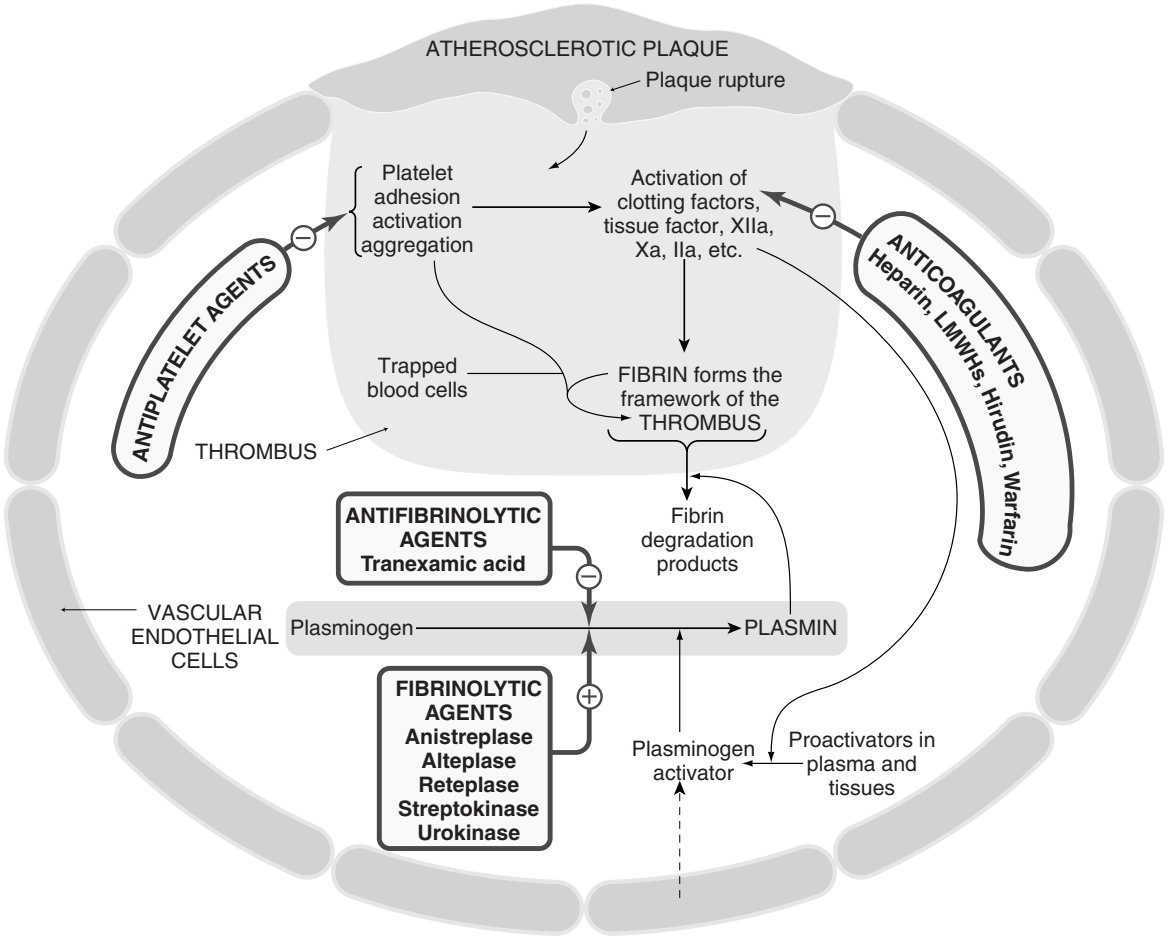

FIGURE **34-11** Pharmacodynamic properties of antithrombotic and antifibrinolytic medications. (From Rang HP, et al. *Rang and Dale's Pharmacology*. 7th ed. London: Churchill Livingstone; 2012:306.)

TABLE **34-6** Pharmacologic Properties of Common Antithrombotic Medications

Type	Name	Pharmacodynamic	Pharmacokinetic (Metabolism/ Plasma Half-life)	Clinical Indication(s)	Perioperative Management (Stop Before Procedure)	Reversal Methods
Antiplatelet	Aspirin	COX 1-2 inhibitor	Liver/20 min	Acute myocardial infarction and stroke	7 days	None
	NSAIDS (e.g., ketorolac and ibuprofen)	COX 1-2 inhibitor	Liver/2-7 hr	Pain and inflammation	24-48 hr	None
	Rofecoxib	COX 1 inhibitor	Liver/10-17 hr	Pain and inflammation	None	None
	Celecoxib	COX 1 inhibitor	Liver/10-17 hr	Pain and inflammation	None	None
	Clopidogrel	ADP receptor antagonist (pro-drug)	Liver/7 days	Coronary artery disease and peripheral vascular disease	7 days	None
	Ticlopidine	ADP receptor antagonist (pro-drug)	Liver/4 days	Coronary artery disease and peripheral vascular disease	7 days	None
	Prasugrel	ADP receptor antagonist	Liver/5 days	Acute coronary syndrome and percutaneous coronary intervention	2-3 days	None
	Ticagrelor	ADP receptor antagonist	Liver/2-3 days	Acute coronary syndrome and percutaneous coronary intervention	24-48 hr	None
	Dipyridamole	Inhibition of platelet uptake of adenosine diphosphate (e.g., phosphodiesterase antagonist)	Liver/40 min	Peripheral vascular disease	24-48 hr	None
	Abciximab	Glycoprotein IIb/IIIa receptor antagonist	Kidney/3 min	Acute coronary syndrome and percutaneous coronary intervention	72 hr	None
	Eptifibatide	Glycoprotein IIb/IIIa receptor antagonist	Kidney/2 hr	Acute coronary syndrome and percutaneous coronary intervention	24 hr	None
	Tirofiban	Glycoprotein IIb/IIIa receptor antagonist	Kidney/2 hr	Acute coronary syndrome	24 hr	Dialysis

Continued

TABLE **34-6** Pharmacologic Properties of Common Antithrombotic Medications—cont'd

Type	Name	Pharmacodynamic	Pharmacokinetic (Metabolism/ Plasma Half-life)	Clinical Indication(s)	Perioperative Management (Stop Before Procedure)	Reversal Methods
Anticoagulant	Warfarin	Vitamin K antagonist	Liver/2-4 days	Thromboembolism and thromboprophylaxis	2-4 days	Vitamin K, recombinant factor VII, prothrombin complex concentrate, fresh frozen plasma
	Heparin	Antithrombin III catalyst (e.g., activated factors II, IX, X, XI, and XII antagonism)	Liver/1-2 hr	Thromboembolism and thromboprophylaxis	6 hr	Protamine
	Low-molecular-weight heparin (e.g., dalteparin, enoxaparin, and tinzaparin)	Antithrombin III catalyst (e.g., activated factor II and X antagonism)	Kidney/4-5 hr	Thromboembolism and thromboprophylaxis	12-24 hr	Protamine (partial)
	Pentasaccharide (e.g., Fondaparinux)	Antithrombin III catalyst (e.g., activated factor X antagonism)	Kidney/14-17 hours	Thromboprophylaxis	4 days	None
	Rivaroxaban	Direct activated factor X antagonism	Kidney/5-10 hr	Thromboembolism and thromboprophylaxis	24-48 hr	None
	Apixaban	Direct activated factor X antagonism	Kidney/10-14 hr	Thromboembolism and thromboprophylaxis	24-48 hr	None
	Argatroban	Direct thrombin inhibitor	Liver/40-50 min	Heparin-induced thrombocytopenia Type II	4-6 hr	None
	Hirudin	Direct thrombin inhibitor	Kidney/1-2 hr	Heparin-induced thrombocytopenia Type II	8 hr	Dialysis and polymethyl methacrylate
	Bibalirudin	Direct thrombin inhibitor	Kidney/25 min	Percutaneous coronary intervention in patients with history of heparin-induced thrombocytopenia	2-3 hr	None
	Dabigatran	Direct thrombin inhibitor	Kidney/14-17 hr	Stroke prevention in non-valvular atrial fibrillation	1-4 days	None
	Drotrecogin alfa	Activated protein C	Liver/2 hr	Severe sepsis	12 hr	None
Fibrinolytic	Tissue plasminogen activator (t-PA)	Plasminogen to plasmin conversion	Liver/1-5 min	Acute myocardial infarction and pulmonary embolism	1 hr	Antifibrinolytics
	Streptokinase	Plasminogen to plasmin conversion	Liver/15-30 min	Acute myocardial infarction and pulmonary embolism	3 hr	Antifibrinolytics

ADP, Adenosine diphosphate; *COX*, cytochrome oxidase; *NSAIDs*, nonsteroidal antiinflammatory drugs.

BOX **34-2**

Procedures That May Be Performed Without Warfarin Discontinuation

Ophthalmic
- Cataract extractions
- Trabeculectomies

Dental
- Restorations
- Endodontics
- Prosthetics
- Uncomplicated extractions
- Dental hygiene treatment

Dermatologic
- Mohs micrographic surgery
- Simple excisions

Gastrointestinal
- Upper endoscopy and colonoscopy with or without biopsy
- Endoscopic retrograde cholangiopancreatography (ERCP) without sphincterotomy
- Biliary stent insertion without sphincterotomy
- Endosonography without fine needle aspiration
- Push enteroscopy

Orthopedic or Podiatric
- Joint and soft tissue aspirations and injections
- Nail avulsions
- Phenol matrixectomies

recommendations for perioperative management of patients on antithrombotic therapy.

A study by Dunn and Turpie demonstrates safety with uninterrupted administration of anticoagulant therapy, specifically warfarin, for *low*-risk procedures such as minor ophthalmic, dental, dermatologic, gastrointestinal, orthopedic, and podiatric procedures (Box 34-2). A thorough assessment of the patient history, diagnosis, and procedure must be made to weigh the risks of potential stroke, myocardial infarction, and thromboembolism for both cardiac and noncardiac surgeries. Complications of any kind translate into increased cost and prolonged hospitalizations.[11]

Antiplatelet Drugs and Noncardiac Surgery: Patients with Coronary Stents

Coronary stents are placed to improve coronary artery flow in patients with stable but symptomatic coronary artery disease or acute coronary syndromes, including unstable angina, non–Q wave myocardial infarction, and ST-elevation acute myocardial infarctions. Every year more than 2 million patients undergo percutaneous coronary intervention. Of these 2 million patients, greater than 90% will require at least one intracoronary stent. Furthermore, approximately 5% of these patients will undergo noncardiac surgery within the first year after stent placement, while many patients will continue to present for surgery thereafter.[47] The clinical efficacy of intracoronary stents is highly dependent on long-term antiplatelet therapy. As a result, anesthesia providers routinely manage patients with coronary artery disease who have had coronary stents placed and are typically receiving dual antiplatelet therapy with aspirin and thienopyridines (Figure 34-12).

There are two distinct complications associated with stent placement: acute stent thrombosis and in-stent restenosis. Acute

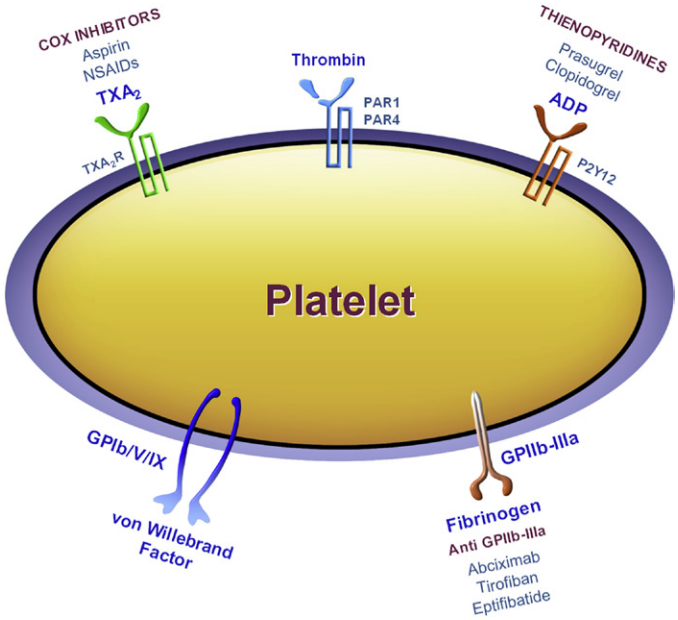

FIGURE **34-12** Main platelet receptors, glycoproteins, and common inhibitors. (From Albaladejo P, Samama CM. Patients under antiplatelet therapy. *Best Pract Res Clin Anaesthesiol.* 2010;24(1):41-50.)

stent *thrombosis* may lead to abrupt occlusion of the coronary artery and an acute coronary syndrome such as acute myocardial infarction. Acute stent thrombosis is a serious complication with a mortality rate of between 20% and 45%, or a myocardial infarction rate up to 64%. Stent thrombosis can occur anytime after stent implantation and anytime antiplatelet therapy is abruptly discontinued. Abrupt discontinuation of antiplatelet therapy can lead to a rebound effect, which is characterized by an inflammatory prothrombotic state. During this prothrombotic state there is increased platelet adhesion, platelet aggregation, and thromboxane A_2 activity.[49] Most events of acute stent thrombosis occur within the first 30 days after stent placement. In contrast, *restenosis* of a stent is a slowly developing occlusion directly related to excessive endothelial growth over time. In most cases, it peaks between 6 and 9 months after stent implantation. Symptoms of restenosis can be insidious and lead to symptoms of coronary insufficiency or be silent and lead to acute myocardial infarction.[46-48]

There are two types of stents available: bare-metal stents (BMS) and drug-eluting stents (DES). Bare-metal stents are made of a steel or cobalt alloy. Once the coronary stent is placed in the lumen of the coronary artery, the endothelialization process of the stent begins and takes approximately 2 to 4 weeks. For drug-eluting stents, the endothelialization process is significantly slower and in some cases may be incomplete. A polymer attached to the stent releases a drug designed to stop cell division and therefore excessive endothelial growth.[51] For both types of stent, patients typically receive dual antiplatelet therapy with aspirin and a thienopyridine (e.g., clopidogrel) to prevent acute stent thrombosis. The most common cause of acute stent thrombosis is premature discontinuation of dual antiplatelet therapy.[47] Current recommendations are to continue clopidogrel administration for 4 to 6 weeks for bare-metal stents and for at least 12 months for drug-eluting stents. Furthermore, aspirin is administered indefinitely. The risk of acute stent thrombosis is relatively low but may occur more commonly with DES because of the delayed or incomplete endothelialization process. Box 34-3 outlines additional risk factors for acute stent thrombosis. When considering discontinuing

BOX **34-3**

Additional Risk Factors for Acute Stent Thrombosis

Coronary Anatomy Factors
- Site of stent placement (e.g., bifurcation stenting, side branch occlusion)
- Left main coronary artery stent
- Long stent length (greater than 18 mm)
- Ostial stenting
- Overlapping stents
- Placement of multiple stents
- Small stent diameter (less than 3 mm)
- Suboptimal stent placement

Patient Risk Factors
- Advanced age
- Diabetes mellitus
- Gene polymorphism
- Hypercoagulable states (e.g., diabetes, malignancy, and surgery)
- Major cardiac adverse event within 30 days of percutaneous cardiac intervention
- Reduced left ventricular ejection fraction
- Prior brachytherapy
- Renal insufficiency

Stent Indication Factors
- Acute coronary syndrome
- Type C coronary lesion or total occlusion

Stent-Related Factors
- Type of stent placed
- Hypersensitivity to stent polymer

Pharmacologic Factors
- Abrupt discontinuation of antiplatelet therapy
- Diminished response or resistance to antiplatelet therapy

Adapted from Hall R, Mazer CD. Antiplatelet drugs: a review of their pharmacology and management in the perioperative period. *Anesth Analg.* 2011;112(2):292-318.

BOX **34-4**

Recommendations for Management of Patients with Drug-Eluting Stents

- Elective surgery with high risk of perioperative bleeding should be postponed until the appropriate course of thienopyridine therapy has been completed:
  - Bare-metal stent: 4-6 weeks
  - Drug-eluting stent: 12 months
- Elective noncardiac surgery is not recommended after stent placement when thienopyridine therapy or aspirin and thienopyridine therapy needs to be discontinued perioperatively. The prescribed period of thienopyridine therapy or aspirin and thienopyridine therapy is:
  - Bare-metal stent: 4-6 weeks
  - Drug-eluting stent: 12 months
- When surgery cannot be postponed and thienopyridine therapy must be interrupted, it is recommended that aspirin therapy be continued throughout the perioperative period and that thienopyridine therapy should be restarted as soon as possible after the procedure.
- Antiplatelet and anticoagulant medications with short half-lives may be used as perioperative bridging between discontinuation of antiplatelet therapy and surgery. In contrast, evidence is lacking in the use of warfarin, antithrombins, or glycoprotein IIb/IIIa agents as perioperative bridging after discontinuation of oral antiplatelet agents.
- Consideration should be given to the following patients:
  - Continuation of dual antiplatelet therapy beyond the recommended timeframe in patients at high risk for stent thrombosis
  - Continuation of aspirin antiplatelet therapy perioperatively in patients with drug-eluting stents

Modified from Grines CL, et al. Prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents: a science advisory from the American Heart Association, American College of Cardiology, Society of Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, with representation from the American College of Physicians. *J Am Coll Cardiol.* 2007;49(6):734-739.

or modifying antiplatelet therapy, it is prudent to involve a multidisciplinary team including a cardiologist, surgeon, and anesthetist for guidance regarding preoperative and postoperative management of antiplatelet therapy.

This patient population requires special attention preoperatively. Important information should include the date of stent implantation, the type of stent deployed, and antiplatelet therapy if applicable. Additional points to consider are the type of operation planned and the risk of bleeding. The current medication regimen must be assessed because many patients have discontinued their antiplatelet medications preoperatively, whereas others continue them at the request of their cardiologist. Surgery in which the risk of bleeding is low may not require discontinuation of antiplatelet therapy. Patients who require emergent surgery should be evaluated on a case-by-case basis, weighing the risks of bleeding against the risks of thrombosis. Due to the lack of prospective studies and guidelines, a wide variety of potential approaches to the perioperative management of BMS, DES, and antiplatelet therapy have been proposed. In 2007 the American Heart Association/American College of Cardiology (AHA/ACC) released their guidelines for management of patients with drug-eluting stents (Box 34-4).

Outpatients Requiring Noncardiac Surgery

The Eighth American College of Chest Physicians (ACCP) provides guidelines for the perioperative management of antithrombotic therapy and thromboembolism (Table 34-7).[52] When determining the perioperative management of anticoagulation therapy, consideration must be given to the risk of bleeding as related to the type of surgery (see Table 34-7), as well as the patient's risk for thromboembolism (Table 34-8). To date there lacks sufficient prospective, double-blind, randomized controlled studies to evaluate perioperative bridge therapies. Recent trials suggest that the bleeding risk using perioperative unfractionated heparin or low-molecular-weight heparin (LMWH) may be higher than previously thought. For these reasons, bridging anticoagulation should be approached cautiously, using patient input once risks and benefits have been discussed.

Disseminated Intravascular Coagulation

Disseminated intravascular coagulation (DIC) is a systemic coagulation disorder characterized by activation of systemic inflammation and coagulation process as a result of an underlying pathologic condition. Clinical presentation of DIC may include thrombosis, hemorrhage, or both. Multiorgan system failure and hemorrhage is the result of widespread thrombotic microangiopathy and depletion of procoagulant factors (e.g., consumptive coagulopathy), respectively[53] (Figure 34-13).

The diagnosis of DIC is usually secondary to an underlying pathologic process (Box 34-5). Coagulation activation ranges from mild thrombocytopenia and prolongation of clotting times to acute DIC characterized by extensive bleeding and thrombosis.[54] Systemic activation of coagulation results in (1) intravascular deposition of fibrin, (2) thrombotic microangiopathy, (3)

TABLE 34-7 Bleeding Risk Associated with Invasive Procedures and Recommendations for Perioperative Management

Bleeding Risk (Category)	Invasive Procedures	Recommendations
High	Cardiac surgery, abdominal aortic aneurysm repair, neurosurgery, most cancer surgery, bilateral knee replacement, TURP, kidney biopsy	*Low-risk thromboembolism:* Stop warfarin 5 days before surgery and allow INR to return to near normal Restart warfarin 12-24 hr after surgery Use prophylactic dosages of LMWH or unfractionated heparin if procedure predisposes to thrombosis *Intermediate-risk thromboembolism:* Stop warfarin therapy 5 days before surgery Consider no bridging versus starting prophylactic LMWH or unfractionated heparin 2 to 3 days before surgery After surgery, restart warfarin and prophylactic LMWH or unfractionated heparin Alternatively follow bridge protocol *High-risk thromboembolism:* Follow bridge therapy protocol Await hemostasis before restarting LMWH; consider using therapeutic dosages of LMWH or unfractionated heparin
Intermediate (surgical)	Abdominal surgery, hemorrhoidal surgery, axillary node dissection dilation and curettage, hydrocele repair, orthopedic surgery, pacemaker insertion, internal cardiac defibrillator insertion, endarterectomy or carotid bypass surgery, noncataract eye surgery (complex lid, lacrimal, orbital), extensive dental surgery (multiple tooth extractions)	*Low-risk thromboembolism:* Stop warfarin 4 to 5 days before surgery and allow INR to return to near normal Restart warfarin after surgery Use prophylactic LMWH or unfractionated heparin if procedure predisposes to thrombosis *Intermediate-risk thromboembolism:* Stop warfarin 4 to 5 days before surgery Consider no bridging versus starting prophylactic LMWH or unfractionated heparin 2 to 3 days before surgery After surgery, restart warfarin and prophylactic LMWH or unfractionated heparin Alternatively follow bridge therapy protocol *High-risk thromboembolism:* Follow bridge therapy protocol Await hemostasis before restarting LMWH; consider using therapeutic dosages of LMWH or unfractionated heparin
Intermediate to low (nonsurgical)	Coronary angiography with or without percutaneous coronary intervention, noncoronary angiography, upper endoscopy with endosphincterotomy, colonoscopy with polypectomy, bronchoscopy with or without biopsy, biopsy (e.g., prostate, bladder, thyroid, breast, lymph node, pancreas)	*Low-risk thromboembolism:* Stop warfarin 5 days before surgery and allow INR to return to near normal Restart warfarin after surgery Use prophylactic dosages of LMWH or unfractionated heparin if procedure predisposes to thrombosis *Intermediate-risk thromboembolism:* Stop warfarin therapy 5 days before surgery Consider no bridging versus starting prophylactic LMWH or unfractionated heparin 2 to 3 days before surgery After surgery, restart warfarin within 12 to 24 hr, and/or prophylactic LMWH or unfractionated heparin Alternatively follow bridge protocol *High-risk thromboembolism:* Follow bridge therapy protocol Await hemostasis before restarting LMWH; consider using therapeutic dosages of LMWH or unfractionated heparin
Low to minimal	Arthrocentesis, general dental treatment (e.g., hygiene, restorations, endodontics, prosthetics, minor periodontal therapy, and uncomplicated extractions), ophthalmic procedures (e.g., cataract, trabeculectomy, vitreoretinal), TURP with laser surgery, upper and lower gastrointestinal endoscopy with or without mucosal biopsy	*All risks of thromboembolism:* Continue warfarin therapy Continue aspirin therapy Check INR the day of or the day before surgery to be sure not supratherapeutic

From du Breuil AL, Umland EM. Outpatient management of anticoagulation therapy. *Am Fam Physician*. 2007;75(7):1031-1042; Geerts WH, et al. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. 8th ed. *Chest*. 2008;133(suppl 6):381S-453S.

INR, International normalized ratio; *LMWH*, low-molecular-weight heparin; *TURP*, transurethral resection of the prostate.

TABLE 34-8 Suggested Risk Stratification for Perioperative Thromboembolism

	INDICATION FOR VKA THERAPY		
Risk Stratum	**Mechanical Heart Valve**	**Atrial Fibrillation**	**VTE**
High	• Any mitral valve prosthesis • Any caged-ball or tilting disc aortic valve prosthesis • Recent (within 6 months) stroke or transient ischemic attack	• $CHADS_2$ score of 5 or 6 • Recent (within 3 months) stroke or transient ischemic attack • Rheumatic valvular heart disease	• Recent (within 3 months) VTE • Severe thrombophilia (e.g., deficiency of protein C, protein S, or antithrombin; antiphospholipid antibodies; multiple abnormalities)
Moderate	• Bileaflet aortic valve prosthesis and one or months of the of following risk factors: atrial fibrillation, prior stroke or transient ischemic attack, hypertension, diabetes, congestive heart failure, age > 75 years	• $CHADS_2$ score of 3 or 4	• VTE within the past 3-12 months • Nonsevere thrombophilia (e.g., heterozygous factor V Leiden or prothrombin gene mutation) • Recurrent VTE • Active cancer (treated within 6 months or palliative)
Low	• Bileaflet aortic valve prosthesis without atrial fibrillation and no other risk factors for stroke	• $CHADS_2$ score of 0 to 2 (assuming no prior stroke or transient ischemic attack)	• VTE > 12 months previous and no other risk factors

$CHADS_2$ = congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, and stroke or transient ischemic attack; *VKA* vitamin K antagonist; VTE venous thromboembolism

Modified from Douketis JD, et al. Perioperative management of antithrombotic therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e326S-50S.

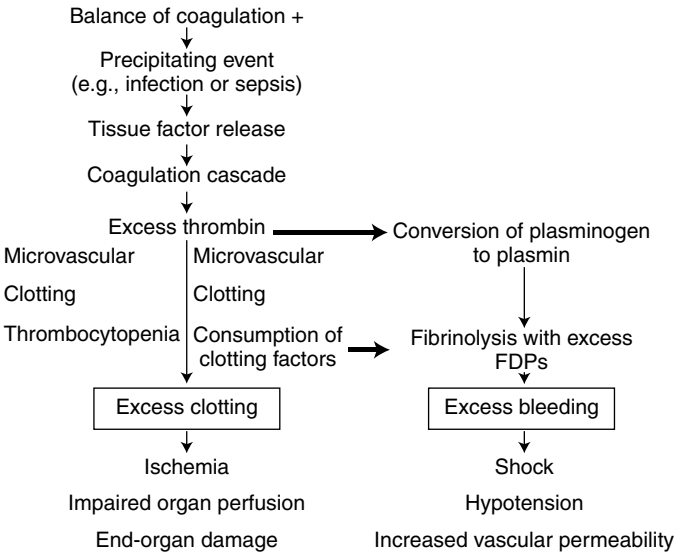

FIGURE 34-13 Pathophysiology of disseminated intravascular coagulation (DIC).

compromised blood supply to organs, and (4) multiorgan system failure. Systemic activation of coagulation also promotes the use and subsequent depletion of platelets and coagulation factors, which may induce severe bleeding from multiple sites.

Several factors play an important role in the pathogenesis of DIC. Tissue factor release is considered to play a central role in the development of hyperthrombinemia in DIC. Under normal conditions, mediators such as antithrombin and tissue factor pathway inhibitor (TFPI) regulate the process of coagulation. During specific conditions such as septicemia, liver impairment, capillary leakage, and the release of endotoxins and proinflammatory cytokines, the actions of these regulatory mediators are adversely altered. Experimental models of septicemia have shown increased fibrinolytic activity related to the acute release of tPA from the endothelium. The initial increased fibrinolytic activity is followed by the release of plasminogen activator inhibitor type 1 (PAI-1), which in turn impairs fibrinolysis and leads to accelerated thrombus formation in DIC. Finally, activated protein C mediates the release of inflammatory cytokines such as tumor necrosis factor and interleukins from endothelial cells. Complement activation and kinin generation increase the coagulation response, leading to subsequent vascular occlusion.[55]

Diagnosis of DIC is made by evaluation of the patient's clinical presentation in conjunction with laboratory tests such as platelet count, aPTT, PT, fibrin-related markers (e.g., fibrin degradation products, D-dimer), fibrinogen, and antithrombin. Additionally, a scoring system developed by the International Society of Thrombosis and Haemostasis (ISTH) assists with the diagnosis[56] (Box 34-6). Acute (overt) DIC is characterized by ecchymosis, petechiae, mucosal bleeding, depletion of platelets and clotting factors, and bleeding at puncture sites. A score of 5 or greater indicates overt DIC. Chronic (nonovert) DIC is characterized by thromboembolism accompanied by evidence of activation of the coagulation system. A score less than 5 suggests nonovert DIC.

The management and treatment of DIC depends on identification of the underlying pathologic condition. In obstetric catastrophes, DIC may resolve as a result of prompt delivery. Treatment of sepsis with antibiotic therapy may halt the progression of DIC. Restoration of physiologic anticoagulant pathways with activated protein C in the treatment of sepsis with overt DIC holds promise.[54] Activated protein C inactivates factors Va and VIIIa, resulting in decreased thrombin formation. Its use in treating DIC patients with severe sepsis has been approved by the FDA. For individuals requiring surgery who are bleeding or at risk for active bleeding, correction of coagulopathy with platelets, FFP, and/or cryoprecipitate must be used. Continued replacement of blood products should be based on the clinical presentation and reassessment of laboratory results.[5]

The use of antithrombotics for DIC remains controversial, especially in a patient who is prone to bleeding. Antithrombin III concentrates may prove effective in inhibiting coagulation; however, their use is still under investigation.[55]

Sickle Cell Disease. Sickle cell disease is a common hereditary hemoglobinopathy. Under normal circumstances, the beta-globin gene on chromosome 11 codes for the production of the beta-globin chains of the protein hemoglobin A. However, in

BOX 34-5

Clinical Conditions Associated with Disseminated Intravascular Coagulation

Respiratory
- Acute respiratory distress syndrome

Cardiovascular
- Fat embolism
- Hypovolemia
- Vascular disease
  - Kasabach-Merritt syndrome (i.e., giant hemangioma)
  - Large-vessel aneurysm (i.e., aortic aneurysm)

Neurologic
- Traumatic brain injury

Hematologic
- Hemolytic transfusion reaction
- Massive transfusion
- Thrombotic thrombocytopenic purpura

Gastrointestinal
- Fulminant hepatic failure

Pharmacologic
- Illicit drug use (i.e., methamphetamine overdose)

Other Considerations
- Immune-mediated disorders
  - Adult Still's disease
  - Allergic reactions
  - Lupus erythematosus
  - Transplant rejection
- Malignant disease
  - Cytotoxic chemotherapy
  - Myeloproliferative malignancy (i.e., acute promyelocytic leukemia)
  - Pancreatic carcinoma
  - Solid tumors (e.g., metastatic adenocarcinoma)
  - Trousseau syndrome (i.e., chronic compensated DIC)
  - Tumor lysis syndrome
- Massive trauma and shock states
  - Extensive burns
- Obstetric complications
  - Amniotic fluid embolism
  - HELLP syndrome (i.e., hemolysis, elevated liver function tests, and low platelets)
  - Placenta previa
  - Placental abruption
  - Retained dead fetus or products of conception syndrome
  - Septic miscarriage or abortion
- Sepsis
  - Fungal
  - Gram-negative and gram-positive bacteria
  - Helminthic
  - Malaria
  - Protozoan
  - Rocky Mountain spotted fever
  - Viral
- Systemic toxins
  - Snake venom

DIC, Disseminated intravascular coagulation.

BOX 34-6

International Society of Thrombosis and Haemostasis Scoring System for Disseminated Intravascular Coagulation

1. Risk assessment: Does the patient have an underlying disorder known to be associated with overt DIC?
   If yes, proceed; if no, do not use this algorithm.
2. Order global coagulation tests (e.g., platelet count, prothrombin time, fibrinogen, soluble fibrin monomers, or fibrin degradation products).
3. Score global coagulation test results.
   _____ Platelet count
   (>100, 0; <100, 1; <50, 2)
   _____ Elevated fibrin-related marker (e.g., soluble fibrin monomers/fibrin degradation products)
   (no increase, 0; moderate increase, 2; strong increase, 3)
   _____ Prolonged prothrombin time
   (<3 sec, 0; >3 sec but <6 sec, 1; >6 sec, 2)
   _____ Fibrinogen level
   (>1.0 g/L, 0; <1.0 g/L, 1)
4. Calculate score
5. If 5 or more, compatible with overt DIC; repeat scoring daily. If less than 5, suggestive (not affirmative) for nonovert DIC; repeat next 1 to 2 days.

Adapted from Bakhtiari K, et al. Prospective validation of the International Society of Thrombosis and Haemostasis scoring system for disseminated intravascular coagulation. *Crit Care Med*. 2004; 32(12):2416-2421.
DIC, Disseminated intravascular coagulation.

sickle cell disease, an autosomal recessive genetic abnormality of the beta-globin gene codes for the production of the variant hemoglobin, hemoglobin S. Patients may present with sickle cell trait or sickle cell disease. The sickle cell trait is a heterozygous disorder observed in 10% of African Americans.[39] Hemoglobin S levels are between 30% to 50% and erythrocyte sickling is observed with a P_{O_2} of 20 to 30 mmHg. In contrast, sickle cell disease is a homozygous disorder observed in 0.5% to 1.0% of African Americans. The majority of the hemoglobin molecule is hemoglobin S, and sickling is observed with a P_{O_2} of 30 to 40 mmHg. A sickle cell crisis may be triggered by a hypoxemia, hypothermia, infection, dehydration, venous stasis, and acidosis. Sickle cell crisis may be characterized by chronic hemolytic anemia, recurrent episodes of intermittent vasoocclusion, severe pain, and end-organ damage. Although previous studies of sickle cell disease cite a perioperative morbidity and mortality greater than 50%, perioperative mortality has diminished steadily, which is attributed with overall improvements in anesthetic care.[57] Suggestions for intraoperative management of patients with sickle cell disease are given in Box 34-7.

There is no universal method for caring for patients with a sickle cell disorder. The optimal percentage of hemoglobin S in patients receiving regular blood transfusions remains to be established, with clinical studies citing a range between 30% to 50%.[58,59] Providing preoperative transfusion supplementation always carries a risk of increasing the blood viscosity and causing end-organ damage. A conservative transfusion regimen has been shown to be as effective as an aggressive regimen in preventing perioperative complications and was associated with fewer transfusion-related adverse events.[8] Anesthesia management for a patient with sickle cell disease includes providing adequate hydration, promoting adequate oxygen saturation,

BOX **34-7**

Intraoperative Management of Patients with Sickle Cell Disease

- Standard monitors and invasive monitoring, as appropriate
- Selection of anesthetic technique appropriate for surgical procedure and clinical status of the patient
- Provide adequate hydration (e.g., monitor hemodynamic status, urine output, central venous pressures when available)
- Transfusion of cross-matched red blood cells to replace surgical blood loss (e.g., avoid increasing the Hgb greater than 10-11 g/dL)
- Avoid hypoxemia
- Maintain normothermia
- Maintain normal acid-base status
- Provide adequate perioperative pain management

From Firth PG. Anesthesia and hemoglobinopathies. *Anesthesiol Clin*. 2009;27(2):321-336.

ensuring normothermia, maintaining acid-base balance, and providing proper patient positioning, and supplying adequate analgesia may interrupt intraoperative and postoperative sickle cell crisis.[60]

Heparin-Induced Thrombocytopenia. Heparin-induced thrombocytopenia (HIT) is recognized as the most important immunologic complication of heparin therapy and remains one of the few absolute contraindications for heparin use. Heparin continues to be used clinically because of its rapid onset, easy reversibility, and moderate therapeutic window with relatively few side effects. In the United States, approximately 30% of hospitalized patients or about 12 million people a year receive heparin. Approximately 5% of patients receiving heparin or low-molecular-weight heparin (LMWH) will develop immune reactions characteristic of HIT; of these patients approximately 50% or about 300,000 people will have clinically significant HIT thrombosis.[61]

The classic clinical presentation of HIT includes thrombocytopenia, resistance to heparin anticoagulation, thrombosis, and positive assay tests indicative of HIT. There are two classifications of HIT; Box 34-8 describes defining characteristics of each type. Of the two classifications, type II is associated with the greatest clinical morbidity and mortality. HIT type II is caused by the formation of immunoglobulin G antibodies directed against heparin-platelet factor 4 (H-PH4) immune complexes. The immunoglobulin G antibody fixes to complements with H-PH4 and subsequently activates platelets via the Fc receptor causing platelet aggregation[62] (Figure 34-14). Traditionally a 30% decrease in the platelet count was considered significant for HIT. Despite thrombocytopenia, patients clinically do not present with bleeding tendencies (e.g., spontaneous bleeding, hemorrhage, petechiae). Rather, HIT type II induces a clinically relevant hypercoagulable state with clotting and thrombus formation causing serious sequelae. Amputation and mortality associated with HIT type II is estimated to be 20% and 30%, respectively.[61]

Diagnosis and treatment of HIT should be based on clinical presentation and laboratory findings. Thrombocytopenia, cutaneous abnormalities (e.g., skin necrosis, ecchymosis, hematoma, purpura, blistering), and tachyphylaxis after heparin administration may indicate developing HIT. The use of physiologic testing (e.g., serotonin release assay, heparin-induced platelet aggregation assay) and antibody detection (e.g., enzyme-linked immunosorbent assay) has been used to confirm the diagnosis of HIT. Anesthesia providers are the primary providers of heparin perioperatively. During the preoperative period, it is imperative that the anesthesia provider review current laboratory tests and medications. If HIT is suspected after heparin administration, a hematologist should be consulted. Treatment of HIT includes discontinuation of all sources of heparin (e.g., medications, heparin-coated invasive lines), administration of direct thrombin inhibitors (e.g., argatroban or hirudin).[61] Arterial or venous thrombosis that compromises perfusion to distal sites may require prompt surgical intervention (e.g., embolectomy or vascular bypass).

BOX **34-8**

Heparin-Induced Thrombocytopenia (HIT) Type I and Type II

Type I

- Thrombocytopenia is mediated by direct heparin-induced platelet aggregation (e.g., nonimmune mediated)
- Onset is typically 1 to 4 days after start of heparin therapy
- Mild thrombocytopenia (e.g., less than 100,000 per microliter)
- Thrombocytopenia often resolves spontaneously even with continued administration of heparin
- Typically occurs with high-dose heparin administration
- Not associated with thrombosis and serious clinical sequelae

Type II

- Thrombocytopenia is mediated by the actions of the heparin, platelet factor 4, and immunoglobulin G expression (e.g., immune mediated)
- Onset is typically 5 to 14 days after start of heparin therapy
- Severe thrombocytopenia (e.g., less than 60,000 per microliter)
- Thrombocytopenia does not resolve spontaneously, therefore heparin administration must be discontinued
- Occurs with any heparin dose and route
- Associated with thrombosis and serious clinical sequelae

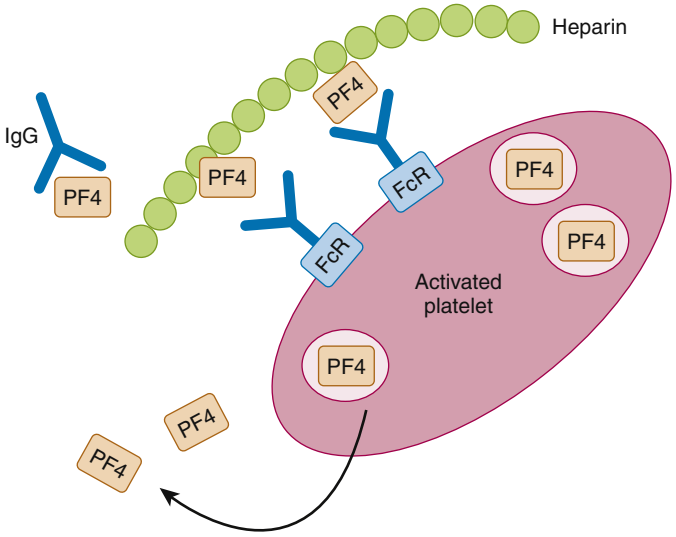

FIGURE **34-14** Pathophysiology of heparin-induced thrombocytopenia (HIT) type II.

SUMMARY

Each time patients consent to undergo a surgical or diagnostic procedure, the hemostatic system is challenged. An understanding of the normal hemostatic system, methods to prevent bleeding and decrease transfusion requirements, alternatives to blood transfusions, and an understanding of hemostatic pharmacology can only enhance patient care and safety when providing anesthesia care.

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35 CHAPTER Thermal Injury and Anesthesia

◆ *Valdor L. Haglund*

The American Burn Association's National Burn Repository of 2011 estimates approximately 450,000 individuals a year with burn injuries visited emergency departments in the United States (between 2001 and 2009).[1] Of these, approximately 45,000 individuals were hospitalized for acute burn injuries and a little more than half were admitted to one of 126 specialized burn centers around the country. These burn centers undergo a rigorous review by the American Burn Association (ABA) and the American College of Surgeons (ACS) to become verified. The verification process insures the facility provides high-quality, specialized care of burned patients, maintaining the necessary resources and medical services mandated by ABA guidelines.[2]

There has been a decline in the incidence of burn injury the past 2 decades. This is in part due to an increased focus on burn prevention including increased use of smoke detectors, fire and burn prevention education, decreased smoking, water temperature regulations, and regulation of consumer products and occupational safety. An improvement in all aspects of medical care of these patients has played a major role in improving survival. These include increased access to emergency medical care, advanced ventilation and treatment of inhalation injuries, improved infection control practices, enhanced nutritional support, early burn wound excision and grafting, and the treatment of the hypermetabolic response. The development of evidence-based practice guidelines and multidisciplinary care models available at regional burn care centers have also contributed to improvements.[3]

Nonetheless, during the period 2001 to 2010 in the United States, more than 1.25 million people sustained burn injuries annually with 450,000 receiving medical treatment.[4] Approximately 3500 die from the burn injury—3000 from residential fires and 500 from motor vehicle or aircraft crashes.[5] Approximately 75% of deaths occur at the scene of the accident or during initial transport.[6] Roughly 35% of all burn victims are younger than 17 years of age, with more than 15,000 children requiring hospitalization as a result of their burn injuries. Scald injuries predominate among small children, with a progressive increase in the frequency of thermal-related burns in the elderly. Major causes of death in burn patients are multiple organ failure and infection. Major risk factors for death are older age and a higher total percentage of burned surface area, as well as chronic diseases. The main causes of early death (less than 48 hours after injury) are shock and inhalation injury. Multiorgan failure and sepsis were the most frequently reported causes of death. Death after a burn injury is not related to the toxic biologic effects of thermally injured skin but to shock associated with metabolic and infectious consequences of a large open wound, sepsis, inhalation injury, and extensive malnutrition, which cumulatively set the stage for life-threatening bacterial sepsis.[7,8]

CLASSIFICATION OF BURN INJURY

Burn injuries, regardless of their etiology, are classified according to the depth and extent of skin and tissue destruction, as well as the total body surface area (TBSA) involved. First-degree (superficial) burns are limited to the epidermis, the outermost layer of skin. The epidermis is thin and avascular, usually healing spontaneously and seldom requiring medical intervention. Second-degree burns, also known as deep and superficial *partial-thickness burns*, extend to the dermis. In contrast to the epidermis, the dermis is very vascular and contains numerous blood vessels and nerves. Thus severity of the type of burn varies, depending on the amount and depth of the dermal tissues involved. If the epithelial basement membrane of the dermis is intact, the skin will regenerate, and grafting may not be required. Third-degree burns, or *full-thickness burns*, extend to the subcutaneous tissue lying below the dermis. The entire skin thickness is destroyed with third-degree burns.[9] Skin grafting is required for these types of burns because the epithelium and the dermal appendages are destroyed. A fourth-degree burn classification is used by some to describe structures burned below the dermis, such as muscle, fascia, and bone. Table 35-1 classifies burns according to depth of skin layers affected, and Figure 35-1 illustrates the layers of burn injury.

The burn team assesses the extent of a burn and plans initial resuscitation efforts. Burn wounds can be readily quantified, but estimation of the burn size remains subjective and assessor related. The most widely used estimation is the "rule of nines," which was first described by Lund and Browder (Figure 35-2). The body is divided into regions that represent 9% or a multiple of 9% of the TBSA. Specific modifications apply to children because the surface areas of their heads and trunks are proportionally larger than their extremities.[10] The rule of nines is a quick method to visually estimate burn size; however, it may not be all inclusive. The extent of burn injury can be more specifically quantified using the Lund and Browder chart. Figure 35-3 demonstrates this method, which is more accurate in determining a burn victim's injury but is also more time-consuming to use. This method is often used when determining the extent of burn in the pediatric patient.

According to the ABA's injury severity grading system, a *major burn* is (1) a second-degree burn involving more than 10% of the TBSA in adults or 20% at extremes of age, (2) a third-degree burn involving more than 10% of the TBSA in adults, (3) any electrical burn, or (4) a burn complicated by smoke inhalation. Associated mortality estimates follow a burn formula derived from the National Burn Registry: if the age of the patient plus percentage TBSA of burn exceeds 115, the mortality is greater than 80%. Additionally, clinical observations estimate the mortality of a burn victim is doubled if inhalation injury is sustained in conjunction with a thermal burn.

ETIOLOGIES OF BURN INJURIES

On admission to a burn unit, the team determines the etiology of the burn injury and the circumstances surrounding the injury. This is especially important because specific pathophysiologic sequelae can be expected after an electrical burn, and still others after a thermal burn. An individual burned in a contained space, such as in a house fire, should be suspected of having an inhalation injury as well. There are four types of burn injuries: chemical, electrical, thermal/heat (also referred to as *flame* or *scald*), and inhalation. Chemical burns commonly occur in a laboratory setting or industrial environment. These chemical burns occur when a noxious chemical substance comes into contact with the skin. Tissue damage and destruction result from the reaction of the chemical with tissue proteins and cellular components. Skin disruption will continue until the chemical irritant is removed or neutralized. Initial treatment is application of copious amounts of water or normal saline irrigation. Chemical burns are uncommon in children.

Electrical burns can be the most damaging to skin and surrounding tissues. The extent of the burn depends on the amount of thermal energy conducted through the skin, based on the voltage and duration of contact with the electrical source. Significant tissue disruption can occur where electric current is most concentrated—at points of entry and exit, although two wounds are not always evident. Initially, the extensiveness of skin and underlying tissue involvement may be hard to diagnose, because surface damage may not reflect all tissue damage, and the entrance wounds may appear superficial. Electrical burns can cause severe damage to bones, blood vessels, muscle, and nerves. If the amount of muscle damaged from the conducted electric current is significant, myoglobin can be released into the circulation. Myoglobinemia places the patient with an electrical burn at great risk for developing renal failure secondary to myoglobinuria, which affects nephron and renal tubular function.

Thermal burns, or burns sustained from any heat source, commonly occur in and around the home. Approximately 70% of burns sustained by those up to the age of 4 years old are the result of scald injuries, whereas flame burns are the most common pattern among children 5 years and older. In general, younger children are at higher risk for sustaining burn injuries, and abuse or neglect may account for as much as 15% to 20% of these cases.[3]

Inhalation burn injuries often accompany thermal burns and should be suspected until aggressively ruled out.[11-13] Inhalation injury can be classified into three types, based on anatomic location. The first type includes upper-airway injuries caused primarily

TABLE 35-1 Degrees of Burn Injury

Classification	Tissue Level Involvement	Outcome and Treatment
First-degree burn (Superficial)	Epidermis	Skin appears red and slightly edematous; heals spontaneously; mild pain and no scarring; barrier preserved; sunburn or flash flame
Second-degree burn (Partial-thickness)		
Superficial dermal burn	Epidermis and upper dermis	Heals spontaneously; red and edematous; appears wet, hyperemic, and blistering; heals in 7-10 days; scar uncommon
Deep dermal burn	Epidermis and deep dermis	Requires excision and grafting for rapid return of function; heals in 2-8 weeks; probable scar without surgery
Third-degree burn (Full-thickness)	Destruction of epidermis and dermis	Epidermal and complete dermal loss; wound excision and grafting required; limitation of function and scar formation; waxy white leathery appearance; no pain due to nerve damage
Fourth-degree burn	Skeletal muscle, fascia, bone	Complete dermal loss with injury down to tendon or bone; complete excision, limited function; muscle necrosis; electrical injuries; limb loss common

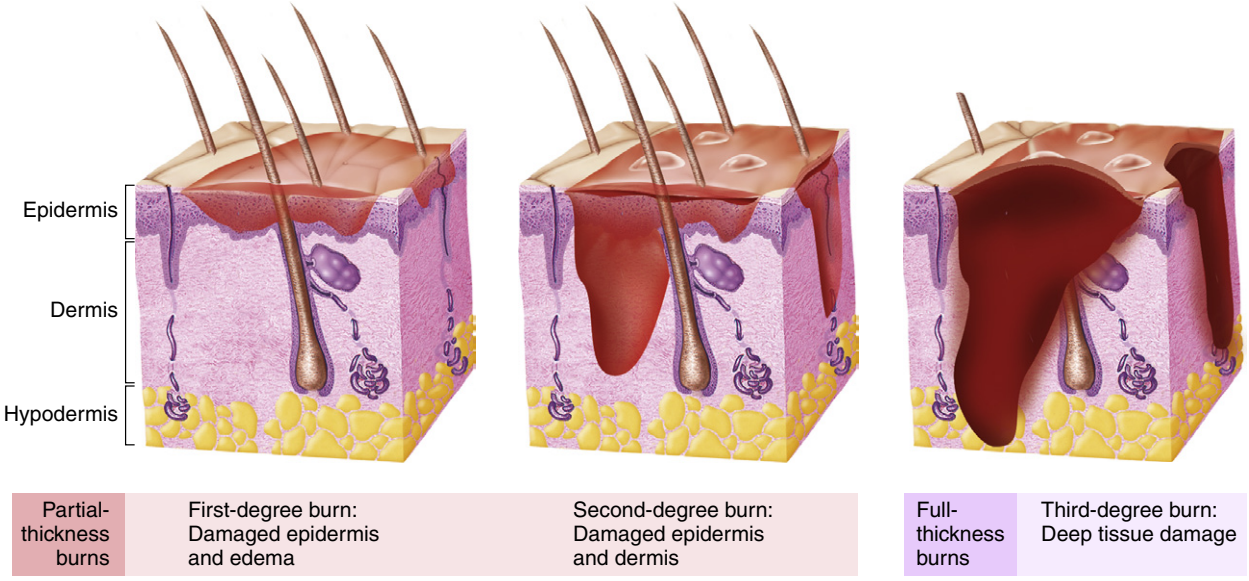
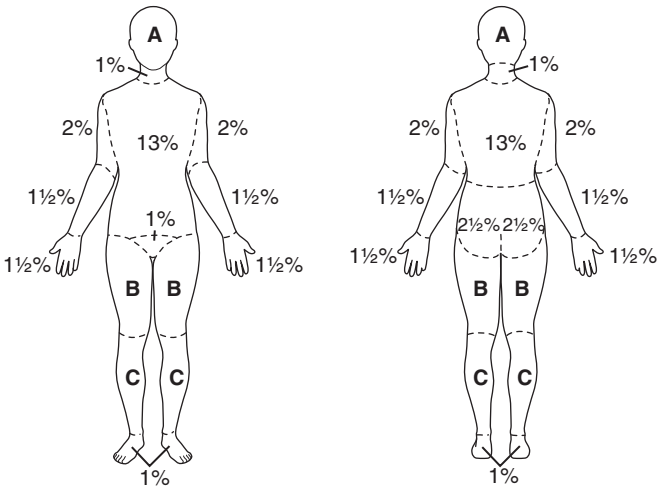


FIGURE 35-1 Classification of burns. Partial-thickness burns include first- and second-degree burns. Full-thickness burns include third-degree burns. Fourth-degree burns involve tissues under the skin, such as muscle or bone. (From Patton KT, Thibodeau GA. *Anatomy & Physiology*. 8th ed. St. Louis: Mosby; 2013:193.)

by thermal injury to the mouth, oropharynx, and larynx. The second type includes lower airway and parenchymal injuries to the trachea, bronchioles, and alveoli caused by chemical and particulate constituents of smoke. Inhalation injury usually means injuries of this type. The third type includes metabolic asphyxiation in which certain smoke constituents such as carbon monoxide or hydrogen cyanide impair oxygen delivery or use by the tissues. All three types may coexist in a given patient.

Damage to the airway can vary, depending on whether the upper airway or lower airway is affected. Upper airway injuries result from inhalation of superheated air or steam and toxic compounds found in smoke.[15] Brief exposure of the epiglottis or larynx to either dry air at 300° C or steam at 100° C can lead to massive edema and rapid airway obstruction.[16] The addition of an inhalation injury to a cutaneous burn doubles the mortality rate[17] and is a greater determinant of death than size of the burn wound. Inhalation of heated air can result in direct injury to the face, oropharynx, and upper trachea, while sparing the lower airway. It is speculated that heat entrained is readily dissipated in the upper airway, and there is reflex closure of the vocal cords effectively protecting the lower airway from heat-related injury. However, true thermal injury from exposure to live steam can occur in the lower respiratory tract because heat-exchange mechanisms of the airway are unable to cool the gas sufficiently as it is inhaled. Obstruction of the upper airway is due to excessive edema, macroglossia, and swelling of the pharyngeal soft tissue. Lower airway injuries more commonly arise from the inhalation of soot particles and/or chemicals produced by a fire. In the lower airway, inhaled toxins react with the airway mucosa forming acidic and alkali substances. Capillary permeability is increased. Extensive alveolar and epithelial damage can occur, with the trachea and bronchi becoming necrotic. Warning signs of respiratory injury include hoarseness, sore throat, dysphagia, hemoptysis, tachypnea, the use of accessory muscles, wheezing, carbonaceous sputum, and elevated carbon monoxide levels.[14,18,19]

Treatment of the burn patient involves three distinct phases: the resuscitative phase, debridement and grafting, and the



Area	Age 0	1	5	10	15	Adult
A - ½ of head	9½%	8½%	6½%	5½%	4½%	3½%
B - ½ of one thigh	2¾%	3¼%	4%	4¼%	4½%	4¼%
C - ½ of one leg	2½%	2½%	2¾%	3%	3¼%	3½%

FIGURE **35-3** Lund-Browder chart. (From National Association of EMTs. *PHTLS: Prehospital Trauma Life Support*. 7th ed. St. Louis: Mosby/JEMS; 2011.)

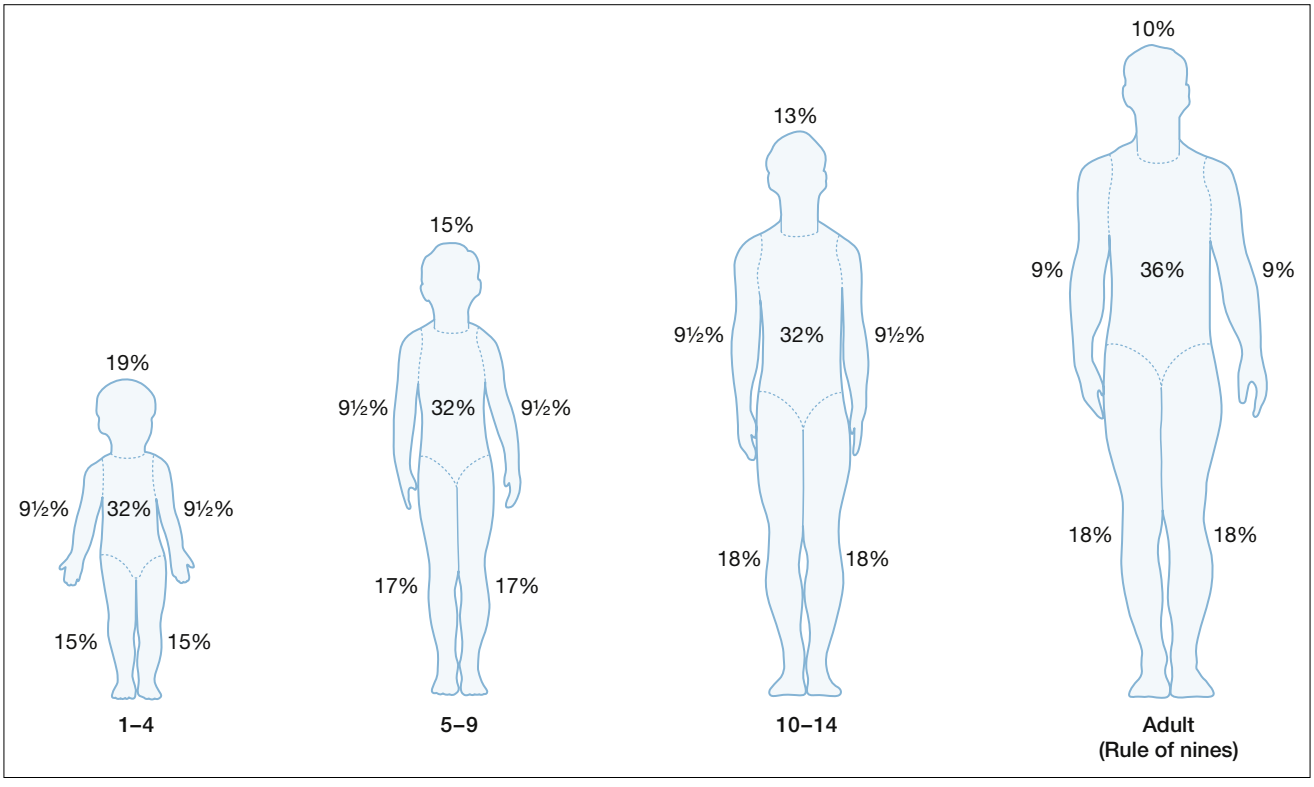


FIGURE **35-2** Burn assessment chart with body proportions. Numbers under figures indicate age; other numbers indicate percent body surface. (From Herndon DN. *Total Burn Care*. 4th ed. Edinburgh: Saunders; 2012:407.)

reconstructive phase. Each phase has its own unique set of challenges the anesthesia provider must consider when developing an anesthetic plan.

TREATMENT OF THE BURN PATIENT

Resuscitative Phase

As with any trauma patient, initial treatment of the burn patient should involve attention to the airway, breathing, circulation, and coexisting trauma. All burn patients must be considered at risk for pulmonary compromise, especially if the percentage of TBSA involved is significant, and signs of inhalation injury are present.

Airway Injury

It is essential to aggressively rule out upper airway injury in patients at risk (e.g., involving a fire that occurred in a closed space or the development of unconsciousness or stupor that prevented the patient from protecting his or her airway). Diagnosis is made by history, the circumstances surrounding the burn injury, and physical examination. Above the oropharynx, thermal injury can produce significant inflammation, occluding the airway. Heat rarely causes damage below the vocal cords because it is effectively dissipated. The other components of smoke such as particulate materials, systemic toxins, and respiratory irritants trigger a cascade of events, resulting in pulmonary edema and a ventilation/perfusion $\dot{V}/\dot{Q}$ mismatch.[20] Airway examination is best accomplished by direct visualization of the airway with a laryngoscope or fiberoptic bronchoscopy.[21] Fiberoptic bronchoscopy is the gold standard for the diagnosis of the severity of inhalation injury. Table 35-2 has a commonly used classification of fiberoptic injury findings and associated mortality.[22] The chest radiograph is usually normal in the early phase of inhalation injury (unless aspiration of gastric or pharyngeal contents occurred during the accident), becoming abnormal once pulmonary edema or infiltration develops. Treatment of upper airway injury involves *early* endotracheal intubation, even if the burn patient is not yet demonstrating signs of airway decompensation. Even in the absence of an inhalation injury, the lungs are at risk for compromise if the burn area is large.

Thermal damage to soft tissues of the respiratory tract and trachea can make intubation an incredibly difficult task because of the malalignment of structures, swelling, and bleeding of the tissues involved. Intubation of the trachea is much easier to perform earlier rather than later, when there may be glottic or facial edema, which worsens after fluid resuscitation.[18-25] In the pediatric population, intubation should be performed with an uncuffed endotracheal tube, usually one size smaller than expected according to age and weight. Fiberoptic-assisted or laryngeal airway mask (LMA) guided intubation techniques are useful. The use of a retrograde wire, light wand, or GlideScope video-assisted techniques have all been used successfully.[26] Nasotracheal intubation in children may be preferred because it is better tolerated, and tube displacement with movement is less likely. Cuffed endotracheal tubes are traditionally used for pediatric patients younger than 8 years old. They are commonly used in pediatric burns because of the added flexibility of not requiring replacement that can be necessitated by decreasing edema and air leaks, which is the case with uncuffed tubes.[3,26]

In the absence of an airway abnormality, early tracheal intubation can usually be achieved using a rapid-sequence technique with an intravenous (IV) induction agent and a rapidly acting muscle relaxant. There is general agreement that succinylcholine administration to patients more than 24 hours after burn injury is unsafe,[27,28] although some authors extend this safe period to slightly longer.[29] Receptor up-regulation occurs after a burn injury, with proliferation of acetylcholine receptors throughout the muscle membrane. Succinylcholine can cause potassium (K^+) release from the entire muscle membrane rather than from discrete end-plate junctions, leading to hyperkalemia and possibly cardiac arrest.[30] The magnitude of K^+ elevation appears to be related to the size of the burn. This process of receptor up-regulation takes days to develop, allowing an initial 24-hour window of safety. It is wise to avoid the use of succinylcholine in a burn patient more than 24 hours after injury.[31]

Intubation with a nondepolarizing relaxant or without a relaxant via the techniques mentioned above allow for safe airway control. Several factors converge to produce an increased dose requirement of nondepolarizing relaxants in burn patients. These include up-regulation of acetylcholine receptors, massive fluid shifts producing significant changes in volume of distribution, and a qualitative decrease in receptor sensitivity. Plasma protein-binding alterations do not effect relaxants clinically because they are not highly bound. Rocuronium, for example, is only 30% protein bound. Both the dose administered and the serum concentrations required in the burn patient may be increased three- to five-fold to achieve the desired paralysis with a nondepolarizer.[32-34]

With an abnormal airway or upper airway obstruction, the safest way to secure the airway is with the patient awake. Key actions include effective topical anesthesia, patient positioning, and supplemental oxygenation. Incremental doses of ketamine or dexmedetomidine infusion along with topical anesthesia and avoiding relaxants allow the patients to continue to breath spontaneously with airway reflexes relatively intact while the airway is secured. Administration of sedatives may worsen airway obstruction and should be given judiciously. However, IV opioid administration may be appropriate for the alert patient in pain. Methods to secure the airway include flexible fiberoptic bronchoscopy, direct laryngoscopy, LMA-assisted intubation, blind nasal intubation, retrograde wire, light wand, or GlideScope video-assisted techniques. When the upper airway is badly damaged and endotracheal intubation is not possible, a direct surgical approach such as tracheotomy is indicated.

For the most part, after airway management, the burn patient is taken to the intensive care unit and placed on ventilatory support.[35] Inspired gases should be humidified to aid clearing of tracheobronchial debris and prevent drying of secretions. The endotracheal tube must be kept in place until the surrounding laryngeal edema has subsided. A progressive air leak around the endotracheal tube, especially in uncuffed pediatric sizes, may be an indication that edematous tissue is returning to normal.[14,18-20,36]

TABLE 35-2 Grading Scheme for Fiberoptic Bronchoscopy Findings in Inhalation Injury

Grade	Findings	Mortality (%)
0	Normal (no inhalation injury)	0
B	Positive based on biopsy only	0
1	Hyperemia	2
2	Severe edema and hyperemia	15
3	Severe injury: ulcerations and necrosis	62

Adapted from Chou SH, et al. Fiber-optic bronchoscopic classification of inhalation injury: prediction of acute lung injury. *Surg Endosc*. 2004;18(9):1377-1379; Cancio LC. Airway management and smoke inhalation injury in the burn patient. *Clin Plast Surg*. 2009, 36(4):555-567.

Administration of nebulized heparin and *N*-acetylcysteine with massive burn and smoke inhalation injury results in a decreased incidence of re-intubation for progressive pulmonary failure, decreased atelectasis, and reduced mortality. The Shriners Burns Hospital formula includes 5000 units of heparin and 3 mL of a 20% solution of *N*-acetylcysteine aerosolized every 4 hours for the first 7 days after the injury.[20]

Carbon Monoxide Poisoning

Any burn victim rescued from an enclosed-space fire should be considered at high risk for carbon monoxide poisoning. It is estimated that 50% to 60% of all fire victims die from carbon monoxide poisoning.[37] Symptoms depend on the carboxyhemoglobin level, although it is actually the tissue carbon monoxide level that determines the toxicity of carbon monoxide (Table 35-3).

Carbon monoxide binds to the hemoglobin molecule with 200 times greater affinity than oxygen, leading to a fall in oxyhemoglobin saturation as tissues become unable to extract oxygen.[14] The end result is a disruption in mitochondrial oxidative phosphorylation, which produces metabolic acidosis at the cellular level. Analysis of blood gases reveals a normal arterial oxygen tension but a decreased total oxygen content, indicating that the hemoglobin oxygen saturation is markedly reduced. Carbon monoxide increases the stability of the oxyhemoglobin molecule, decreasing the release of oxygen to the tissues and producing a leftward shift in the oxyhemoglobin curve (see Figure 17-6). Pulse oximeters do not detect carboxyhemoglobin (CoHgb) in blood and give falsely elevated readings for oxygen saturation in its presence. The diagnosis of carbon monoxide poisoning requires measurement of arterial CoHgb levels using a co-oximeter. The half-life of CoHgb is variable. In patients treated with 100% oxygen, it ranged from 26 to 148 minutes.[38] Treatment continues with 100% oxygen until the CoHgb level is less than 5% or for 6 hours.[39] A co-oximeter measures concentrations of all hemoglobin moieties (i.e., oxyhemoglobin, deoxyhemoglobin, carboxyhemoglobin, and methemoglobin).[40]

Hyperbaric oxygen therapy (HBOT) is an alternative treatment and may be helpful if the CoHgb level exceeds 25% or if clinical signs of toxicity are evident. Hyperbaric oxygen accelerates the clearance of carbon monoxide beyond that achieved using 100% oxygen at 1 atmosphere. The main rationale for its use is prevention of delayed neurocognitive syndrome. It can be difficult to transport and care for patients in the chamber, and debate continues over its effectiveness.[41]

TABLE 35-3 Carbon Monoxide Poisoning

Carboxyhemoglobin (%)	Symptoms
0-10	Normal
10-20	Headache, confusion
20-40	Disorientation, fatigue, nausea, visual changes
40-60	Hallucination, combativeness, convulsion, coma, shock state
60-70	Coma, convulsions, weak respiration and pulse
70-80	Decreasing respiration and stopping
80-90	Death in less than 1 hour
90-100	Death within a few minutes

From Herndon DN. *Total Burn Care*. 4th ed. Edinburgh: Saunders; 2012:411.

Cyanide Poisoning

Hydrogen cyanide (HCN) poisoning is another toxicity seen with fires. It is produced by the combustion of materials such as plastics, foam, paints, wool, and silk. Cyanide poisoning produces tissue hypoxia by blocking the intracellular use of oxygen. Cyanide binds to the terminal cytochrome on the electron transport chain, causing hypoxia, lactic acidosis, and elevated mixed venous oxygen saturation. The half-life of HCN is approximately 1 hour. Signs and symptoms of poisoning include loss of consciousness, dilated pupils, seizures, hypotension, tachypnea followed by apnea, and high lactate levels. Cyanide has several antidotes, with differing mechanisms of action and diverse profiles. Hydroxocobalamin (vitamin B_{12}a) actively binds cyanide by forming cyanocobalamin, which is directly excreted via the kidney.

Hydroxocobalamin has a rapid onset of action, neutralizes cyanide without interfering with cellular oxygen use, and has a good safety profile. It is safe for use with smoke-inhalation victims, easy to administer, and is the preferred antidote to this type of cyanide poisoning. A hydroxocobalamin dose of 50 mg/kg is recommended. In addition, aggressive stabilization of cardiopulmonary function augments the hepatic clearance of cyanide via rhodanase, and can resolve cyanide poisoning (blood levels, 5.6-9 mg/L), without the use of antidotes.[14,20,42]

Hypovolemic Shock Associated with Thermal Injury

After the airway has been secured and other life-threatening injuries have been managed, the burn patient must be resuscitated with large volumes of fluid. Aggressive fluid administration and restoration of blood volume are critical for improving chances of patient survival and preventing renal failure. Burns cause a form of hypovolemic shock. These changes are reflected in loss of circulating plasma volume, hemoconcentration, massive edema formation, decreased urine output, and depressed cardiovascular function.[25,43] Fluid losses are greatest in the first 12 hours after burn injury and then begin to stabilize after 24 hours. Fluid losses occur secondary to direct transudation of plasma and plasma proteins from the wound and from diffuse capillary leakage that shift fluid from the intravascular space to the interstitium of unburned tissue. Capillary leak results from a loss of endothelial integrity and from reduction of intravascular oncotic pressure as plasma proteins are lost through the burn wound and incompetent capillary beds. The end result of changes in microvasculature caused by thermal injury is disruption of normal capillary barriers separating intravascular and interstitial compartments and rapid equilibration of these compartments. This causes severe depletion of plasma volume and a marked increase in extracellular fluid, clinically manifested as hypovolemia and burn-induced edema.[10,25,43]

Inflammatory mediators are released from burned tissues after injury, causing localized inflammation and burn-wound edema. Localized mediators include oxygen radicals, arachidonic acid metabolites, histamine, prostaglandins, leukotrienes, products of platelet activation, and the complement cascade.[23,37,44] Most edema occurs locally at the burn site and is maximal at 24 hours after injury. The edema itself results in tissue hypoxia and increased tissue pressure with circumferential injuries. Aggressive fluid therapy can correct the hypovolemia but will accentuate the edema process. In minor burns, the inflammatory process remains sequestered in the wound itself. However, in major burn insults, this local injury signals the release of systemic circulatory mediators resulting in a systemic response.

Fluid Resuscitation

Within seconds after an acute burn injury, massive fluid shifts begin to occur. Therefore, fluid resuscitation and airway management

are the hallmarks of initial therapy and should be instituted by the first-response emergency medical providers. There are many formulas for calculating a burn patient's initial fluid resuscitation requirements. Crystalloid resuscitation often provides substantial volumes of fluid, often in excess of that predicted by current formulas, resulting in numerous edema-related complications. This phenomenon is coined "fluid creep," and fluid therapy after the initial 24 hours is constantly being refined. In most centers, two formulas are accepted as guidelines for the resuscitation of severely burned patients, the Parkland and modified Brooke formulas.[45,46] The need for blood transfusion is usually not a major concern during the immediate resuscitation phase in acutely burned patients unless other coexisting trauma exists. Transfusion management is a prominent issue during subsequent surgical intervention.

The current ABA consensus formula for fluid resuscitation and urine output in burn patients is given in Box 35-1. Table 35-4 lists other suggested fluid protocols. Common to all of these formulas is the patient's weight in kilograms and the percentage of TBSA involved. The American College of Surgeons Committee on Trauma has advocated that only crystalloid formulas be used for all burn resuscitation. Colloid solutions are not advocated in the first 24 hours because capillary permeability remains enhanced, and colloids administered will not remain in the intravascular space. Isotonic crystalloid is the most commonly used fluid for resuscitation in U.S. burn centers. The most popular fluid resuscitation regimen, the Parkland formula, uses isotonic crystalloid solutions and estimates the fluid requirements in the first 24 hours to be 4 mL/kg/% TBSA burned. Crystalloid solutions generally provide adequate volume resuscitation, but the large volumes that are needed result in substantial tissue edema and hypoproteinemia. Consequently, complications of over-resuscitation, including abdominal compartment syndrome, pleural effusions, pulmonary edema, fasciotomies, and conversion of partial-thickness lesions to full-thickness lesions are more frequently observed.[46] It is important to remember that formulas for fluid guidelines are only that—guidelines. Individual factors also must be taken into account. It is crucial to resuscitate the patient with fluids according to patient response, hemodynamic variables, sensorium, and urinary output (0.5 to 1 mL/kg/hr in adults and 1 mL/kg/hr in children weighing less than 60 pounds),[44] instead of by a fixed formula.[23] Fluid resuscitation in children requires extreme precision, owing not only to their size but also their limited physiologic reserve. Because infants and small children have high volume-to-surface-area ratios, formulas that base fluid requirements on surface area burned and weight may underestimate need. The ABA recommends that to counteract the rapid use of glycogen stores and prevent the development of hypoglycemia, a dextrose-containing IV solution be administered for maintenance purposes in burned children in the immediate postburn period.[47,48] Some clinical criteria to indicate adequate fluid rescuscitation are noted in Box 35-2.

Intraabdominal hypertension (IAH) and abdominal compartment syndrome (ACS) are increasingly recognized as causes of significant morbidity and mortality in critically ill burn patients. These are the most dangerous and frequently reported adverse outcomes of fluid creep in massive burn resuscitation. IAH is a continuum of progressively worsening organ dysfunction, whereas ACS is an "all or none" phenomenon resulting when IAH remains either unrecognized or untreated. IAH and ACS impact end-organ function within not only the abdominal cavity (e.g., kidneys, liver, intestine) but also throughout the body (e.g., brain, lungs, heart). The most recent Consensus Guidelines define IAH as an intraabdominal pressure (obtained by transduction of bladder pressure) greater than or equal to 12 mmHg, and ACS as an intraabdominal pressure greater than 20 mmHg with evidence of new organ dysfunction. New organ dysfunction typically manifests as oliguria, impaired mechanical ventilation with high peak airway pressures, worsening metabolic acidosis, and hemodynamic instability. ACS is fatal without treatment. Treatment includes the use of neuromuscular relaxants and increased sedation in mechanically ventilated

BOX 35-1

Consensus Formula for Fluid Resuscitation and Urine Output in Burn Patients (American Burn Association)

Adults: Lactated Ringer's 2-4 mL × kg body weight × percent TBSA burned
Children: Ringer's lactate 3-4 mL × kg body weight × percent TBSA burned*†

Formulas for Minimum Urinary Output in Burn Patients
Adults: 0.5-1.0 mL/kg/hr
Children weighing less than 30 kg: 1 mL/kg/hr
Patients with high-voltage electrical injuries: 1-1.5 mL/kg/hr

From Pham TN, et al. American Burn Association practice guidelines burn shock resuscitation. *J Burn Care Res*. 2008;29(1):257-266.
*One half of the estimated volume of fluid should be administered in the first 8 hours after the burn. The remaining half should be administered over the subsequent 16 hours of the first postburn day.
†Infants and young children should receive fluid with 5% dextrose at a maintenance rate in addition to the resuscitation fluid noted above.
TBSA, Total body surface area.

TABLE 35-4 Fluid Resuscitation Formulas for Burn Patients

Formula	First 24 Hours	Second 24 Hours
Modified Brooke		
Crystalloid	2 mL LR/% burn per kg ½ in first 8 hr ½ in next 16 hr	D_5W maintenance
Colloid	None	0.5 mL/% burn per kg
Parkland		
Crystalloid	4 mL LR/% burn per kg ½ in first 8 hr ½ in next 16 hr	D_5W maintenance
Colloid	None	0.5 mL/% burn per kg

D_5W, 5% dextrose in water; *LR*, lactated Ringer's solution.

BOX 35-2

Criteria for Adequate Fluid Resuscitation

- Normalization of blood pressure
- Urine output (1-2 mL/kg/hr)
- Blood lactate (<2 mmol/L)
- Base deficit (<−5)
- Gastric intramucosal pH (>7.32)
- Central venous pressure
- Cardiac index (CI) (4.5 L/min/m^2)
- Oxygen delivery index (DO_2I) (600 mL/min/m^2)

From Woodsen LE, et al. Anesthesia for burned patients. In: Herndon DN, ed. *Total Burn Care*. 4th ed. Edinburgh: Saunders; 2012:180.

TABLE 35-5 Summary of the Main Effects of Various Pharmacologic Interventions to Alter the Hypermetabolic Response to Burn Injury

Drug	Inflammatory Response	Stress Hormones	Body Composition	Net Protein Balance	Insulin Resistance	Hyperdynamic Circulation
rhGH	Improved	No difference	Improved	No difference	Hyperglycemia	No difference
Insulin-like growth factor-1	Improved	No difference	Improved	Improved	Improved	No difference
Oxandrolone	Improved	No difference	Improved	Improved	No difference	No difference
Insulin	Improved	No difference	Improved	Improved	Improved	No difference
Fenofibrate	No difference	No difference	No difference	No difference	Improved	No difference
Glucagon-like peptide-1	Unknown	Unknown	Unknown	Unknown	Improved (indirect)	Unknown
Propranolol	Improved	Improved	Improved	Improved	Improved	Improved
Ketoconazole	Unknown	Improved	Unknown	Unknown	Unknown	Unknown
rhGH and propranolol	Improved	Improved	Improved	Improved	Improved	Improved
Oxandrolone and propranolol	Improved (preliminary)	Improved (preliminary)	Improved (preliminary)	Improved (preliminary)	Improved (preliminary)	Improved (preliminary)

From Williams FN, Herdon DN, Jeschke MG. The hypermetabolic response to burn injury and interventions to modify this response. *Clin Plast Surg.* 2009;36(4):583-596.
rhGH, Recombinant human growth hormone.

patients; extension of escharotomies on any anterior trunk burns, judicious use of diuretics, and decompressive laparotomy.[49,50-54]

Invasive hemodynamic monitoring (central venous pressure, pulmonary artery catheter) is indicated in patients who do not respond to fluid resuscitation, have preexisting cardiopulmonary disease, or are at risk of IAH and ACS. Catheters should be removed as quickly as possible to minimize the risk of local and systemic infection.

Hypermetabolic/Hyperhemodynamic Phase

Severe thermal injury with burns over 40% of a patient's total body surface area (TBSA) is followed by a pronounced hypermetabolic response that persists for up to 1 to 2 years. During this phase, there are significantly increased metabolic rates, multiorgan dysfunction, muscle protein degradation, blunted growth, insulin resistance, and increased risk for infection. The initial stress response to severe injury lasts for the first 2 to 3 days postburn. The subsequent phase is characterized by an increase in metabolism and hyperdynamic circulation. When left untreated, physiologic exhaustion ensues, and the injury becomes fatal.

Catecholamines and corticosteroids are the primary mediators of the hypermetabolic response after severe burns. There is a 10- to 50-fold surge of plasma catecholamine and corticosteroid levels that last up to 9 months postburn. Glucagon levels are also increased. Burn patients have increased resting energy expenditures, increased cardiac work, increased myocardial oxygen consumption, marked tachycardia, severe lipolysis, liver dysfunction, severe muscle catabolism, increased protein degradation, insulin resistance, and growth retardation.[55-57] Numerous efforts to control this response have been studied. Early burn wound excision and complete wound closure, prevention of sepsis, the maintenance of thermal neutrality for the patient by elevation of the ambient temperature, and graded resistance exercises during convalescence are simple, nonpharmacologic effective treatment goals. Several pharmacologic interventions and their efficacy are noted in Table 35-5.[55,58]

Pathophysiologic Changes

As with any disease entity, certain pathophysiologic alterations occur after an acute burn injury (Table 35-6). It is important for the anesthetist to understand the basis for these changes because many of these changes must be managed intraoperatively and reflected in the anesthetic plan.

Cardiovascular System. The cardiovascular system is greatly affected in the burn patient. Almost immediately after an acute burn injury, intravascular fluid losses begin. Etiologies for this include the loss of vascular and endothelial integrity and the release of circulating mediators described earlier. The loss of plasma proteins from within the intravascular compartment (due to disruption of the endothelium) persists for up to 36 hours after the initial burn injury. Hypovolemia results, with subsequent hypotension and circulatory compromise. The size and extent of the burn determine the magnitude of this development. Hence, burn victims can develop "burn shock" within the first 24 to 36 hours after an acute burn injury. A reduction in cardiac output is a hallmark of burn shock and appears to occur within minutes after the injury. It is initially preserved via catecholamine responses—tachycardia and vasoconstriction. However, with the progressive loss of intravascular fluids and proteins, left ventricular filling declines, leading to a reduction in cardiac output. Additionally, cardiac output is thought to be depressed from the release of myocardial depressant factor or proteins from burned tissues. The cardiovascular response to catecholamines is attenuated after burn injury as the result of reduced adrenergic-receptor affinity and decreased secondary-messenger production. Coronary blood flow can be reduced, further decreasing myocardial function. Systemic vascular resistance increases.

Aggressive fluid resuscitation administered over the first 24 to 36 hours aims to restore intravascular volume and cardiac function. What is seen is a systemic inflammatory response syndrome, characterized by increased cardiac output, tachycardia, and a reduction in systemic vascular resistance. The patient becomes hypermetabolic, with an increase in oxygen consumption and carbon dioxide production.[59]

Children with extensive burn injuries can become quite hypertensive weeks after their injury. Heart rate, cardiac output, and cardiac index remain significantly increased in burned children for up to 2 years when compared with normal ranges indicating vastly increased cardiac stress. Aggressive treatment of the hyperdynamic cardiac response may improve long-term morbidity.[60]

TABLE 35-6 Pathophysiologic Effects of Major Burns

System	Considerations
Respiratory	
Upper airway	Thermal damage to soft tissue and respiratory tract requires early endotracheal intubation Decreased chest wall compliance, functional residual capacity, and restricted chest wall expansion
Carbon monoxide poisoning	Considered in all victims of enclosed fires; treatment with 100% oxygen by mask, endotracheal intubation strongly advised until status can be evaluated
Neurologic	
Encephalopathy, seizures, increased intracranial pressure	Ongoing neurologic assessment mandatory because status frequently changes
Hematology	
Anemia, thrombocytopenia, and coagulopathies	Coagulopathies, transfusion reactions, and infection are common
Cardiac	
Burn shock phase (0 to 48 hr)	Hypovolemia is a major concern; fluid resuscitation mandatory; expect impaired cardiac contractility, initial myocardial depression, and decreased cardiac output
Hypermetabolic phase (after 48 hr)	Increased blood flow to organs and tissues; manifested by hyperthermia, tachypnea, tachycardia, increased oxygen consumption, and increased catabolism
Renal	
Early	
Reduced renal blood flow and glomerular filtration rate	Secondary to hypovolemia and decreased cardiac output; adequate fluid resuscitation and diuresis prevents renal failure; myoglobinuria and hemoglobinurea common, which alters urine-concentrating ability
Electrical burns and muscle necrosis damage renal tubules	Careful fluid resuscitation, renal function monitoring, and possible diuretic administration
Late	
Increased renal blood flow	Variable drug clearance
Nutrition	
Increased caloric requirements	Tight nutritional support mandatory
Hepatic	
Early	
Decreased function and drug clearance	Hepatomegaly; hypermetabolism and enzyme induction during hypermetabolic phase; sepsis common
Pharmacokinetics	
Decreased albumin	Altered volume of distribution, protein binding Highly protein-bound drugs have a higher free fraction and thus a larger volume of distribution
Increased α_1-acid glycoprotein	Usually minimal clinical effects of drugs in spite of the changes in protein levels
Denervation phenomenon with spreading of acetylcholine receptors	Succinylcholine avoided 24 hours after injury
Increased nicotinic acetylcholine receptors and decreased function	Requires a two-fold to three-fold increased concentration of nondepolarizer for paralysis
Skin Integrity	
Vulnerable to nosocomial infections	Strict adherence to aseptic individual patient rooms; wound care, including topical antimicrobial agents and early excision/grafting of the burn wound

Pulmonary System. Like the cardiovascular system, the pulmonary system can be significantly impacted in burn patients. Pulmonary function may decrease significantly even in the absence of inhalation injury. For example, functional residual capacity (FRC) is reduced, and lung and chest-wall compliance decrease, especially when the chest wall is circumferentially burned. With progressive fluid shift and interstitial edema formation in those with eschar formation, the inability to adequately expand the lungs impairs ventilation. In some cases, escharotomies are performed to alleviate the constrictive pressure in the tissues to improve oxygenation and ventilation. The oxygen gradient between alveoli and arterial blood increases with minute ventilation increasing to as much as 40 L/min from what is normally 6 L/min.

As previously mentioned, the lungs are at risk for compromise even without an inhalation injury. There are several mechanisms involved, including the effect of released mediators on the lung. In addition, plasma oncotic pressure is greatly reduced after burn injury, owing to the loss of plasma proteins in burned and nonburned tissues. Impaired vascular and capillary permeability, combined with the amount of fluid resuscitation necessary, sets the stage for pulmonary edema.

Mechanical ventilation is often required after major burn injury, especially when the patient has concomitant inhalation injury. The term "acute lung injury" (ALI) is used to designate the acute onset of impaired oxygen exchange that results from lung injury, and the condition is characterized by a Pa_{O_2}/Fi_{O_2} ratio of less than 300. Severe cases of ALI, categorized as acute respiratory distress syndrome (ARDS), are common as well. The risk for mortality from ALI and ARDS is due to respiratory failure and hypoxia, or may result from associated multisystem organ failure or ventilator-associated pneumonia. New strategies for mechanical ventilation are currently being used to support burn patients who have respiratory insufficiency, ALI, and ARDS. These strategies include changes in traditional mechanical ventilation paradigms (such as the use of low-tidal-volume ventilation) and the use of alternative modes of ventilation. Current practice is to use low-volume lung-protective ventilation to reduce overinflation and barotrauma.[61,62] This involves using tidal volumes of less than 7 mL/kg of measured ideal body weight and plateau pressures of less than 31 cm of water. Using ideal body weight is an important consideration in patients who have a major burn injury because they often have vast increases in body weight due to massive fluid

resuscitation. Modest permissive hypercapnia is allowed.[63] Several nonconventional modes of ventilation have been proposed for the treatment of severe ARDS in patients who have burn injury, including airway pressure release ventilation (APRV) and high-frequency oscillatory ventilation.[64,65]

Immune System. The burn-injured victim is particularly susceptible to infection. Because the normal protective function of the skin has been breached, the stage is set for microbial invasion. Within hours after an acute burn, altered immunologic responses are present. Leukocyte activity is depressed, as well as humoral and cellular responses. Burn eschar is a prime medium for bacterial growth. Colonization of gram-negative bacteria increases mortality. Patients often become septic and are vulnerable to pneumonia, particularly when prolonged endotracheal intubation is required. Strict asepsis is therefore required. Of those patients who die after sustaining a burn, infection is the leading cause of death in up to 100% of children and 75% of adults.[3,26,59]

Renal System. Renal function may decrease soon after burn injury as a result of myoglobinuria and hemoglobinuria. Myoglobinuria is most common after electrical injury, whereas hemoglobinurea is common after severe cutaneous burns of about 40% or greater. Acute kidney injury (AKI) is a common complication following major burn injuries and the incidence of maybe as high as 40%. The development is dependent on the size and severity of the burn and the presence of inhalation injury and is a poor prognostic indicator. AKI is divided into early and late categories. Early AKI was defined as occurring within 5 days of burn injury and results from hypotension and myoglobinuria. AKI occurring after 5 days of injury was defined as late and sepsis is the most common cause.[46] Patients may exhibit an inability to concentrate the urine. Elevated levels of stress hormones (e.g., aldosterone, angiotensin, catecholamines, and plasma renin) also contribute to renal dysfunction observed in the early post-burn period. Several burn centers are using the RIFLE criteria to assess the acute kidney injury (AKI). Rifle is an acronym for risk (R), injury (I), failure (F), loss (L), and end-stage kidney disease (E). (see Chapter 29). It is often used for patients with renal disease to identify the risk factors for occurrence of AKI, as well as to analyze the progression between stages of the RIFLE classification and the impact of progression of AKI on morbidity and mortality.[66,67]

Decreases in renal blood flow alter glomerular filtration. This is usually due to intravascular depletion, hypovolemia, decreased cardiac output, and increased levels of circulating plasma catecholamines. The renin-angiotensin-aldosterone system and the release of antidiuretic hormone are stimulated to conserve sodium and water.[68] Subsequently, alterations in electrolyte balance take place. Hourly urine output measurements remain the gold standard for assessing adequate fluid replacement and resuscitation (see Box 35-1). Delayed renal failure in children is rare.[69]

Gastrointestinal System/Nutrition. Aggressive nutrition support is mandatory after a severe burn injury. Metabolic rates may be increased up to twice normal secondary to the hypermetabolic state. Whole-body catabolism, muscle wasting, and severe cachexia occur with inadequate nutrition. Failure to meet the increased substrate requirements may result in impaired wound healing, multiorgan dysfunction, increased susceptibility to infection, and death.[70,71] In patients with extensive burns and a pronounced hypermetabolic response, carbohydrate is more effective than fat in maintaining body protein.[72] The burn-injured patient is resistant to the action of insulin in the liver and skeletal muscle, thus ongoing assessment of blood glucose, with administration of insulin in a tight control protocol, is necessary.

The necessity for continued adequate caloric intake during the preanesthetic evaluation period cannot be ignored. It is therefore unwise to arbitrarily discontinue enteral feedings the evening before a scheduled surgical procedure. This action can result in an excessive loss of calories, especially if the patient is to undergo extensive burn excision and debridement. Preoperative *nil-per-os* (NPO) guidelines must be considered at a safe minimum to prevent the patient from reverting to a catabolic state. For example, intubated patients do not need enteral feedings discontinued before surgery, whereas unintubated patients may remain on nutritional support up to 4 hours before a scheduled surgical procedure.[73] This practice maintains preoperative nutrition without increasing the risk for aspiration. Upon admission to the operating room, a non-intubated patient's nasogastric tube should be suctioned and general anesthesia induced to ensure rapid protection of the airway. If the patient is not receiving enteral feedings, but rather parenteral feedings through a central venous catheter, the parenteral nutrition line should not be used for administering fluids or drugs during the course of the anesthetic. Parenteral hyperalimentation and lipid infusions should be continued intraoperatively. Monitoring of glucose levels in these patients is advised. The use of infusions pumps is recommended in children to avoid over or under infusions.[26]

Burn patients also demonstrate a decrease in overall gastrointestinal function. When the percentage of TBSA involved is greater than 20%, the development of ileus is common.[74] Other gastrointestinal sequelae include acute ulcerations of the gastric and/or duodenal mucosa known as *Curling ulcers*. Treatment of these stress ulcers includes the administration of acid suppressive therapy (AST) including H_2 blockers, proton pump inhibitors, and antacids.[23] Fortunately, with the use of AST, these ulcers are rare.[75]

Hepatic effects of burn injury are variable. There may be an increase in liver function during the hypermetabolic phase followed by hypertrophy, hepatomegaly, and impairment in protein synthesis. Hepatic dysfunction also may result from drug toxicity, sepsis, or blood transfusions. Preoperative assessment of liver function is advised.[76,77]

Burn Management: Debridement and Grafting

The goal of burn therapy is to rapidly restore skin integrity. After thorough cleansing, the burn wound is typically treated with antimicrobial agents as early as possible to limit bacterial proliferation on the wound surface and to avoid bacterial wound invasion. Wounds have been shown to re-epithelialize more rapidly with less pain and inflammation when they are covered and a thin layer of wound fluid is maintained in contact with the surface. Subsequent treatment involves surgical procedures such as amputation, grafting, and multiple debridements.[78] Early removal and excision of the dead burn tissue with rapid closure of the burn wound has now become the standard in management of a severe burn. The early reestablishment of a physical skin barrier provides protection from bacteria, mechanical trauma, and insensible water loss and improves long-term outcomes.[79]

Because most patients with extensive burns require multiple procedures, limiting a single procedure to 20% excision of body surface has been suggested; however, larger areas may be excised depending on the patient's preoperative and perioperative hemodynamic stability and coagulation status. Other surgical end-points include a time of 2 to 3 hours if the patient's core temperature decreases to 35° C or if there has been blood loss requiring 10 units or more of packed red blood cells.[80] Generally, the burn patient may require surgical treatment every 2 to 3 days, with staging of

burn wound excisions until full grafting has been completed. Significant blood loss during burn surgery continues to be a challenge. Implementation of blood-conserving protocols can decrease blood component requirements. Several options include tumescent epinephrine, thrombin, fibrin, and other systemic hemostatic agents. The best hemostatic protocol must be individualized.[81]

In patients with extensive burns and limited donor sites, the wound coverage may require a combination of skin grafts, cultured skin, and skin substitutes. Several temporary and permanent skin substitutes are available.[82]

Anesthetic Implications

To facilitate a safe and effective anesthetic, a thorough preoperative plan must be developed in consultation with the entire burn team.

Preoperative Evaluation. The burn patient requires a thorough and complete preoperative assessment. Medical history, including laboratory studies, and physical examination with lung auscultation, assessment of chest compliance, and inspection of the neck and oral cavity to determine potential difficulties with airway management, should be implemented. In addition, the clinician should be aware of any underlying trauma, mechanism of burn (electrical, inhalation), percentage of TBSA injured, location of the burn sites, and the type and extent of the planned procedure. This information may impact the selection of agents, appropriate monitoring, positioning, vascular access, and blood-product requirements. A review of prior surgical procedures and anesthetics can be helpful in determining one's anesthetic plan. This is quite often possible as these patients tend to have multiple procedures.

The Set-Up and Preparation. A successful anesthetic that facilitates surgical excision and grafting of a burn wound requires planning and preparation of all necessary equipment (Box 35-3). There are specific anesthetic interventions that should be considered prior to patient arrival in the operating room. Perioperative challenges in the acute burn patient are noted in Box 35-4.

Intraoperative Management

Equipment and Monitoring. Burn patients require all standard monitors intraoperatively, although this otherwise routine consideration may be challenging. Electrocardiogram (ECG) leads are often difficult to place due to a lack of intact skin. Alternatives include stapling lead electrodes to the skin, use of needle electrodes or an atrial pacing-type esophageal stethoscope used for its ECG monitoring capability. Ideally, blood pressure cuffs should be placed on the unaffected limb or at a nonsurgical site. If the extent of surgical debridement is extensive or if movement of the patient's extremities intraoperatively limits accuracy of noninvasive cuff readings, the placement of an arterial line for blood pressure monitoring may be warranted, even in healthy patients. Large burns (i.e., greater than 20% to 30% TBSA) may necessitate invasive blood pressure monitoring after induction of anesthesia, if not in place preoperatively. Rapid and significant blood loss, potential for hemodynamic swings, and the need to verify intraoperative laboratory values more than validate this requirement.

Standard sites for monitoring pulse oximetry may not be available. Alternative sites include the nose, nasal alae or septum, ear, cheek, tongue, or toes. Any preexisting invasive monitors such as an arterial line, central venous catheter, or pulmonary artery catheter should be continued in the operating room. Noninvasive monitors for cardiac output, index, and stroke volume are also available.[83] Accurate temperature monitoring is essential because burn patients can become extremely hypothermic intraoperatively. Skin temperature devices are highly inaccurate in these patients, and there may not be a suitable area to apply them. Temperature measurements are obtained from a properly positioned esophageal stethoscope (i.e., distal third of the esophagus). Because many of these patients are in intensive care units, they may already be benefiting from a urinary drainage catheter that supports bladder temperature monitoring.

Critically ill burn patients are usually transported by the anesthesia provider directly to the operating room from the burn intensive care unit (and vice versa, postoperatively). These patients are typically intubated or have a tracheostomy, are on continuous infusions of pharmacologic agents, and have invasive lines in place. Astute monitoring of the patient's vital signs during transport is, of course, mandatory. Extreme care and diligence should be taken during transport so that any of these do not become dislodged. Portable oxygen delivery system is another component of required transport equipment. Careful handling and vigilant guarding of the airway is crucial. Amnestic and analgesic drugs should be administered as needed to facilitate moving the patient.

Airway Management. Acute airway problems are usually addressed immediately upon the patient's entry into the emergency department or once in the burn unit. In the nonintubated

BOX 35-3

Preoperative Anesthesia Planning for the Burn Patient

- Warm the operating room ahead of time (should not exceed 95° F).
- Check availability of blood products and order more if needed (based on preoperative hemoglobin value, the size of the burn, and extent of the planned debridement).
- Have blood products immediately available in the operating room as surgical debridement is initiated. This is particularly critical in the pediatric patient.
- Have at least one blood warmer primed, plugged in, and turned on. If the burn is large, have two.
- Make sure that you have adequate IV access before the surgeon begins debriding the burn.
- Have an adequate supply of narcotics and muscle relaxants.
- Know and plan ahead of time if invasive lines are needed.
- Plan for airway management and ventilation both intraoperatively and postoperatively as needed.
- Have a plan but be willing to modify it if necessary.

BOX 35-4

Perioperative Challenges in the Acute Burn Patient

- Compromised airway
- Pulmonary insufficiency
- Altered mental status
- Associated injuries
- Limited vascular access
- Rapid blood loss
- Impaired tissue perfusion due to:
  - Hypovolemia
  - Decreased myocardial contractility
  - Anemia
- Decreased colloid osmotic pressure
- Edema
- Dysrhythmia
- Impaired temperature regulation
- Altered drug response
- Renal insufficiency
- Immunosuppression
- Infection/sepsis

From Herndon DN. *Total Burn Care*. 4th ed. Edinburgh: Saunders; 2012:174.

patient without an inhalation injury and whose airway is essentially normal, induction and intubation of the airway can proceed as with any other anesthetic with the exception of avoiding succinylcholine as discussed previously. The use of a videolaryngoscope or the other airway methods discussed earlier may be considered if securing the airway is judged to be potentially difficult.

If the patient is already intubated, vigilance must be maintained to insure the trachea does not become accidentally extubated. Edema of airway structures may make re-intubation difficult, if not impossible. Thus securing an endotracheal tube in these patients can be most challenging because tape does not readily stick to burned skin. Some clinicians have used soft straps, nasal septal ties, or sutures to secure the endotracheal tube. Cloth ties encircling the patient's head are frequently used as well.

Temperature Regulation. Depending on the percentage of TBSA affected by a burn, temperature regulation can be problematic. There is a high risk for development of hypothermia secondary to evaporative heat loss and the body surface area exposed intraoperatively. The temperature in the operating room should be above 28° C.[37,84] Intravenous solutions and skin preparations should be warmed. All methods of heat conservation should be employed while the patient is in the operating room. The use of inline circuit heat moisture exchangers or lower gas flows will reduce evaporative respiratory tract heat loss. Forced-air warming blankets are effective, but their use can be limited. Over-body heating lamps have been used but need to be at a safe distance from the patient to prevent further burning. Plastic bags also can be helpful to insulate exposed body parts not requiring surgical access.

It has been suggested that keeping a patient warm is more beneficial than rewarming. When hypothermia ensues, deleterious effects of vasoconstriction occur, which may hinder any subsequent warming efforts. Moreover, slow rewarming in the postoperative period can lead to an increase in mortality.[85] If a patient becomes hypothermic despite efforts at prevention, the surgeon should be advised to conclude the procedure as quickly as possible.

Fluid and Blood Replacement. Surgical burn debridement procedures may be extraordinarily bloody operations. Surgical blood loss depends on the area to be excised (cm^2), time since injury, type of excision planned, and the presence of infection. Surgical wound management involves removal of the eschar layer until brisk bleeding of the dermis is observed. The surgical team may remove eschar so rapidly that it becomes difficult to replace blood and IV fluid in a manner that parallels the loss, giving way to hypovolemia and hypotension. Some institutions have suggested stopping the surgical procedure after 2 hours if more than two blood volumes have been lost or if the body temperature falls to 35° C or by greater than 1.5° C from baseline.

There are several formulae to approximate the extent of potential blood loss for a burn patient undergoing debridement. These vary from 200 to 400 mL of blood loss for each 1% of BSA excised and grafted to as high as 4% to 15% of the patient's blood volume for every percentage of skin debrided.[26,37] After excision and debridement, several hemostatic therapies may be used including tumescent epinephrine, phenylephrine thrombin, fibrin, and other systemic hemostatic agents. Gauze soaked in a vasoconstrictor preparation applied to the wounds may result in systemic absorption causing an undesired change in vital signs.[81] Table 35-7 lists a method for predicting surgical blood loss. A complete discussion of transfusion management can be found in Chapter 20.

Preoperative anemia is another indicator for transfusion and is commonly seen in thermally burned patients with greater than 10% TBSA involvment.[86-88] There are several reasons for its development. The inflammatory process gives way to destruction of red blood cells that accumulate in thrombosed microcirculation of burned tissues, leading to an erythrocyte loss up to 18% in full-thickness burns greater than 15% TBSA.[89] Thus bone-marrow suppression leads to a reduction in the production of erythropoietin after burn injury. Lastly, patients with extensive burns generally undergo numerous surgical procedures, resulting in blood loss and further anemia.

Adequate vascular access is critical before the initiation of surgical debridement. The size and extent of planned debridement will determine how much access is needed. One large-bore intravenous catheter is adequate for the induction of anesthesia in many burned patients, but at least two large-bore intravenous catheters are necessary before beginning a major excision. Obtaining sufficient IV access can be challenging and time consuming, depending on the extent and location of the burn. Critically ill patients or those with limited peripheral sites for IV access will often have a central venous catheter already in place. A large-bore catheter or a central line with multiple ports should be used whenever administration of large amounts of IV fluid and blood products is anticipated.

Availability of blood products should be confirmed before the patient is taken to anesthesia and operation. Ideally, blood products should have been checked and ready for administration at the outset of the procedure. This is particularly important in pediatric patients. Indeed, some clinicians initiate blood transfusion before the beginning of surgical debridement and apply compression dressings after excision and grafting.

Careful planning is essential when managing hemorrhage and potential complications associated with massive transfusion (e.g., citrate toxicity, loss of clotting factors) during debridement. Visual estimation of blood loss is subjective at best and prone to miscalculation. Surgical suction is often not used during debridements and surgical sponges are difficult to assess. Blood may leak onto the floor, be covered in the surgical drapes, or ooze beneath the patient. Thus proper monitoring of the patient's urinary output, hemoglobin, hematocrit, coagulation, and hemodynamic status is crucial during and after the surgical procedure.

The Anesthesia Management

Induction. No single agent is preferred for IV induction of general anesthesia in the burn patient. As with all anesthetics, plans should be individualized and based on the patient's preoperative status and medical history. The acutely burned patient seldom comes to the operating room immediately after injury; generally the patient is admitted and stabilized in the burn unit first. If the patient requires immediate surgery, he or she can be expected to be extremely labile within the first 24 hours of injury. The effects of the anesthetic agents can be exaggerated, especially if fluid resuscitation is not adequate or has not been fully completed. The loss of intravascular volume coupled with the potential for

TABLE 35-7 Calculation of Expected Blood Loss

Surgical Procedure	Predicted Blood Loss
<24 hr since burn injury	0.45 mL/cm^2 burn area
1-3 days since burn injury	0.65 mL/cm^2 burn area
2-16 days since burn injury	0.75 mL/cm^2 burn area
>16 days since burn injury	0.5-0.75 mL/cm^2 burn area
Infected wounds	1-1.25 mL/cm^2 burn area

From Woodsen LE, et al. Anesthesia for burned patients. In: Herndon DN, ed. *Total Burn Care*. 4th ed. Edinburgh: Saunders; 2012:175.

depressed myocardium can result in a hemodynamically unstable patient under general anesthesia. Careful, slow titration of anesthetic agents is vital. Appropriate premedication of stable patients with benzodiazepines or an opioid decreases anxiety and makes transfer to the operating room (OR) tolerable. Anxiety, depression, and pain are interrelated in patients with burns.[90,91] Induction of general anesthesia can be performed with the patient in the bed so that subsequent movement onto the OR table provokes little discomfort.

Regional anesthesia has been used for procedures confined to small areas, an extremity, or for surgery during the reconstructive phase. Advantages include prolonged postoperative analgesia, but variables in this patient population restrict its more general use. Performing a regional technique that requires passing a needle through burned tissue should be avoided due to the potential for spread of infection. The hypotension (hypovolemia) and vasodilation (with or without sepsis) that often accompanies spinal or epidural anesthesia makes this choice suspect until the burn wound has closed. In addition, coagulopathy and cardiorespiratory instability may be reasons to avoid a regional anesthetic technique. The greatest limitation to the use of regional anesthesia is the topographic extent of the surgical field where the anesthetized region must include both the area to be excised and the area to be harvested for skin graft.

In children, regional anesthesia is sometimes a viable option for postoperative analgesia. Caudal or epidural techniques have been used for debridements of the lower extremities or skin harvesting from the buttocks or thighs. Catheters can be used to extend the regional block for postoperative infusion analgesia.

All commonly used anesthetic induction drugs are acceptable. Propofol can be given if the patient is stable. Ketamine is an excellent alternative in unstable patients. Low doses of ketamine produce adequate amnesia and analgesia for the debridement of superficial burns; higher doses may be administered for more extensive procedures such as eschar excisions.[92] Postoperative emergence reactions can be minimized with the administration of benzodiazepines in small doses, and an anticholinergic prevents excessive pharyngeal and tracheobronchial secretions. In the pediatric burn patient, an inhalation induction with sevoflurane is certainly acceptable if the child does not have intravenous access prior to induction of general anesthesia and if the airway is otherwise normal.

Anesthesia in the burn patient can be maintained with an opioid and/or inhalation agents because the hemodynamic status of the patient permits. Volatile agents have been shown to be safe and effective, allowing rapid adjustment of anesthetic depth while permitting high oxygen concentrations. These patients may be sensitive to the cardiovascular depressant effects of inhaled anesthetics, especially if acute fluid resuscitation is incomplete. Inhaled agents do not provide analgesia in the postoperative period. Intubated burn patients who require intraoperative ventilation with specialized critical-care ventilators (e.g., percussive ventilators) where a standard anesthesia machine ventilators cannot be used, may require a total intravenous technique.[93]

As discussed previously, succinylcholine should be avoided after the first 24 hours. The patient will exhibit resistance to nondepolarizing muscle relaxants, and higher and more frequent redosing is usually necessary. Several factors including up-regulation of acetylcholine receptors, massive fluid shifts producing significant changes in volume of distribution, and a qualitative decrease in receptor sensitivity are responsible.[94]

Pain Management. The necessity of proper pain management is well understood because almost every patient encounter may be associated with psychologic distress and physical pain. Establishment of pain treatment protocols for burn patients that address their anxiolytic and analgesic needs is essential. Intravenous (patient-controlled analgesia) is preferred early in the course of burn care, because the absorption from intramuscular sites may be erratic or slow for rapid control of pain.

Opioids are an important adjunct in the care of burn patients. Pain from skin harvest sites frequently exceeds that from burned, debrided, and grafted areas. Morphine, fentanyl, and sufentanil all provide intra- and postoperative analgesia and are acceptable choices. Remifentanil, a short-acting opioid, may be used for dressing changes. Oftentimes, infusions of opioid will be used in the burn unit for pain control and/or sedation. One option is to continue these infusions during the operative procedure with bolus supplementation. Narcotic-based anesthetics provide the advantage of minimal cardiac depression. In addition, postoperative analgesia must be a vital constituent incorporated into the anesthetic plan.

Nonsteroidal antiinflammatory agents can be effective analgesics for smaller superficial burns. In larger burn injuries, the anticoagulant effects can lead to problems with hemostasis.

Painful procedures include dressing changes, debridements, nursing care, hydrotherapy, physiotherapy, and surgical procedures. The intensity of pain associated with treatments, together with the fact that they are inflicted repeatedly (sometimes twice a day or more) over long periods of time, explains the unique patient medication requirements in this population.[90,91]

Emergence from Anesthesia. The postoperative period should likewise be planned in advance. Critically ill and intubated burn patients should remain intubated postoperatively and transported directly to the burn unit. The anesthetist should safeguard the airway and be respectful of the patient's need for sedation and analgesia during this terminal phase of the anesthetic.

If extubation of the trachea is anticipated, opioids for postoperative analgesia can be titrated according to the need.

Reconstructive Phase

It is important to address the ongoing impact a burn injury can have on the individual. After numerous skin grafting and surgical procedures and some degree of healing has taken place, scarring may remain. To optimize function and prevent contractures and deformity, physical and occupational therapy are important considerations for these individuals. Months to years after hospital discharge, victims of major burns may return for reconstructive procedures to remove or reduce scar tissue. These procedures improve cosmetic and functional outcomes. Burn patients often experience anxiety, stress, and depression from prolonged hospital stays. The most important anesthetic concern is management of the airway, particularly if contractures of the face and neck are present. There are several options for airway management as mentioned previously from standard laryngoscopy, use of videolaryngoscope, or awake intubation using a fiberoptic technique.

Invisible scars may remain as well in the patient who has suffered a burn injury. Psychologic issues should be explored while the patient is still in-hospital. This is especially important when dealing with children. Recreational therapists can help them work through their feelings and fears. Once the child is home and physically healed, group settings such as burn camps can offer opportunities to be with other children who have suffered similar injuries. In such an environment, the child can experience freedom from judgment and not feel ashamed of their burn scars.

SUMMARY

Anesthetic implications for the burn patient are plentiful and can be extraordinarily challenging. As burn centers continue to evolve and improve in their ability to extend life after a severe burn injury, the likelihood of an anesthesia provider being involved in the care of a patient with thermal injury increases. Clinicians should remember these patients are challenged physically and emotionally. For many, the road to recovery is long and painful. As providers of anesthesia care and as patient advocates, it is important we take into account the unique aspects of the burn patient's overall care. As anesthetists, we can play a small but significant role in helping these patients in their difficult journey to recovery and healing. It is a role that comes with many rewards.

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CHAPTER 36

Trauma Anesthesia

◆ *Matthew D'Angelo*

ETIOLOGY OF TRAUMATIC INJURY

Traumatic injury is a unique condition. Unlike other diseases that have a biologic basis, trauma is a result of an external force that ultimately disrupts normal structure and function of the body. In most situations, the initial cause of injury is not a result of genetics or environmental exposure, but circumstance and misfortune. Traumatic injury is a disease of human behavior. Although improvements to automobile safety and development of public policy have successfully reduced the annual number of traumatic injuries caused by motor vehicle collisions (MVCs), falls, and firearms by nearly a third, traumatic injury still remains the leading cause of death for Americans under the age of 40.[1] This translates to 180,000 deaths in the United States alone, or more simply put, one death every 3 minutes.[2] The mortality of injury is striking; however, it represents only a small fraction of those affected by trauma.

There is no absolute number that can precisely quantify the toll and cost of trauma. Although figures vary by author, it has been estimated that the cost for medical care and lost productivity in the United States was more than $400 billion in 2005—of that amount, nearly $100 billion resulted from MVC alone.[1,3] These figures, while staggering, account only for expenses and do not account for the burden that injury places on utilization of scarce medical resources.[2] Mortality is only the tip of the iceberg. Trauma accounts for nearly 30 million emergency care treatments per year in the United States, a tenth of which will require hospital admission and possibly surgical intervention.[2,3,4]

Some progress in improving these statistics has clearly been made in the United States, but prevention and treatment of trauma outside of the United States has lagged. Globally, injury is increasing in developing nations.[5] The World Health Organization (WHO) demonstrated in the year 2000 that 1.6 million people died as a result of trauma.[6] Although half of these deaths were a result of suicide, the remainder were due to homicide or combat-related violence.[6] The WHO estimates that injury will be the leading cause of death worldwide by 2020.[1] If the prediction is true, the morbidity and mortality of injury—a manmade illness—will far surpass that of infectious diseases. This change will represent a true paradigm shift in global health.

COORDINATED MANAGEMENT OF CARE

The acute management of a trauma patient presents unusual challenges. In many instances, trauma warrants immediate surgical intervention. Mechanism of action, multisystem injury, and preexisting medical conditions create complexities that are unusual when compared with routine perioperative management.

Time is a luxury and often a scarce resource when managing the critically unstable trauma patient. In many cases, surgical care cannot be postponed to acquire a battery of preoperative exams. Patient medical history may be unknown or incomplete at best. Patients are often unable to provide competent medical history. The patient's inability to provide a history may be a result of the injury or of concurrent acute intoxication. Regardless of the cause, this gap in information leaves many preoperative questions unanswered. Although every attempt should be made to ascertain a thorough history, it should not be done at the expense of delays in care.

Management of trauma in the United States has historically occurred at the municipal level, between the emergency medical system (EMS) and community hospital. Coordination between these stakeholders has varied widely across the United States, resulting in a range of outcomes. The evolution of modern trauma systems has challenged the community level care model—integrating prehospital, tertiary care providers, and public policy in the effort to direct trauma care—a multivariate phenomenon.

The implementation of the modern trauma system has resulted in significant improvement in patient outcomes. Pioneering examples of this paradigm shift can be seen throughout many cities in the United States and around the world; the impact of this shift on patient morbidity and mortality was formally recognized in 1998. The Skamania Symposium (Skamania Lodge, Oregon; Academic Symposium to Evaluate Evidence Regarding the Efficacy of Trauma Systems) was the first academic group to evaluate the efficacy of a trauma system.[7] This group systematically evaluated published data to determine the impact of trauma systems. Their findings were that care in a trauma center (versus a nontrauma center) was associated with fewer unnecessary deaths and less disability.[7,8] These findings have been supported by several other groups in the United States. Risk of death is considerably lower among patients who require early operative intervention if they are treated at a designated Level I trauma center. These outcomes are not a result of more rapid assessment and intervention alone, and emphasize the complex factors that contribute to the survival benefit of trauma center care. Studies in the United States show that mature, statewide trauma systems dramatically reduce unnecessary deaths from greater than 30% to less than 5%, compared with nontrauma system care.[9-12]

Organization of trauma systems varies across the United States. Even though systems are not the same and may vary widely, the American College of Surgeons (ACS) Committee on Trauma has developed standards to which all trauma systems must adhere to become accredited.[13] Through these standards, a level (Level I, Level II, etc.) can be assigned to a particular center that designates the resources the center can provide to care for an injured

The views expressed in this chapter are those of the author, and do not reflect the official policy or position of the Uniformed Services University of the Health Sciences, the Department of Defense, or the United States government.

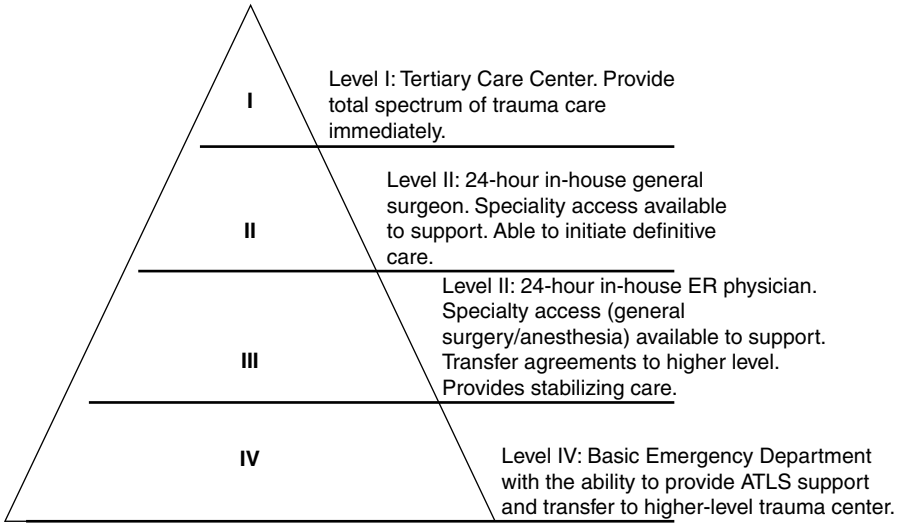

FIGURE **36-1** The levels of trauma care as described in Advanced Trauma Life Support. Lower echelons of care provide stabilizing measures, and care sophistication increases with increasing levels.

patient. Figure 36-1 describes the characteristics of the modern trauma system, its resources, and the levels of trauma care. What we can take away from the conclusions of the Skamania Symposium and guidance of the ACS Committee on Trauma is that positive outcomes in patient care are directly related to experience and development of a trauma system. Trauma can no longer be considered an *offshoot* skill where the paradigm involves massive fluid resuscitation, but a specific clinical expertise in which management and therapy directly impacts patient outcome. In short, experience and proficiency matter.

EARLY EVALUATION OF THE TRAUMA PATIENT AND COMMON INJURY PATTERNS

Immediate Admission of the Trauma Patient

The Advanced Trauma Life Support (ATLS) course developed by the American College of Surgeons provides a framework for the initial management and evaluation of the trauma patient from the prehospital setting through the hospital phase.

Prehospital

The prehospital management of trauma patients has a deliberate pathway. The primary goals revolve around ensuring a patent airway and adequate ventilation, as well as controlling external bleeding. Patients may be intubated in the field or treated with some other method of airway manipulation before arrival at the trauma center. There remains some controversy over the efficacy of rapid sequence induction in the prehospital setting; however, ensuring adequate oxygenation *is* essential. All patients should arrive at the hospital with some degree of supplemental oxygen in place.

In most cases, urgent airway management is not required in the prehospital setting. Occult hemorrhage and its ensuing pathology, on the other hand, is the greatest cause of early death from trauma.[14] Blood leaving the circulatory system can spill into cavities throughout the body (e.g., thorax, abdomen, retroperitoneum [the pelvis], or fascial planes of long bones) and/or bleed into the environment (i.e., the street). Classically, hemorrhage was met with intravenous (IV) access and volume resuscitation in the prehospital setting. This practice, however, is going through a renaissance of sorts in an effort to determine what is best practice and management.

As will be discussed later in the chapter, early fluid resuscitation in the absence of surgical hemostasis may not be beneficial because it will likely increase bleeding and may worsen patient outcome. Without hemostasis, mortality increases. The concept of "injury first" has been greatly developed in the wars in Iraq and Afghanistan. Tactical Combat Casualty Care has replaced the "ABC" acronym (airway-breathing-circulation) with "CABC" (catastrophic bleeding-airway-breathing-circulation), emphasizing the immediate application of direct pressure or tourniquets to control exsanguinating hemorrhage. The logic behind this change in priority is that if bleeding is not controlled, the patient will face certain death. Although civilian centers may not have to contend with the limited resources seen in austere environments, this change in approach exemplifies the important role hemorrhage control plays in hemorrhagic shock outcomes.

Primary Survey

Upon admission to the hospital or trauma center, ATLS guidelines provide a logical and sequential treatment strategy for rapidly assessing the patient. This process is commonly referred to as the *ABCDE's* of trauma care[15]:

*A*irway
*B*reathing
*C*irculation
*D*isability (neurologic status)
*E*nvironment/Exposure (undress the patient to fully assess)

The goal of the primary survey is to identify and rapidly manage life-threatening conditions or injuries. This sequence of events will be abbreviated and discussed individually from the anesthesia perspective shortly. Generally, however, the primary assessment involves a rapid assessment using physical examination techniques and American Society of Anesthesiologists (ASA) standard monitors. In addition, ultrasound and radiography are used to examine body cavities with the initial goal of determining the extent of injury. During this time, initial blood samples and IV access are obtained. All aspects of the primary survey are done simultaneously, thereby coordinating the efforts of surgical and anesthesia teams to prepare for potential surgical intervention. In the event the injuries are beyond the scope of the initial receiving facility, the primary survey provides the emergency team with enough information to stabilize and prepare the patient for transfer to a higher-level facility.

Secondary Survey

The secondary survey begins after the completion of the primary survey and resuscitative and stabilization efforts have been initiated. The secondary survey is a complete head-to-toe assessment that includes a neurologic examination.

BLUNT VERSUS PENETRATING TRAUMA

Blunt Trauma

Direct impact, deceleration, continuous pressure, shearing, and rotary forces may all contribute to the resulting *blunt trauma* a patient has incurred. These factors are associated with high levels of energy, and result from high-speed collisions and falls from substantial heights. Newton's first law can explain how most traumatic injuries occur: an object tends to remain in motion until it is affected by an outside force. Abrupt deceleration creates negative gravitational forces. When the outside "shell" of the human body decelerates abruptly, the internal organs, which in a sense are separate from the exterior of the body, continue forward at the original velocity and are torn from their attachments by way of rotary and shearing forces. These forces often cause disruption of connective tissue, blood vessels, and nerves.

Motor Vehicle Collision Trauma

Blunt trauma is most closely associated with motor vehicle collisions and falls. Blunt trauma tends to produce effects bodywide. The five types of *motor vehicle collisions* are classified as head-on, rear impact, side impact, rotational impact, and rollover. Injuries can be categorized as those above and those below the waist. The upper portion of the body may collide with the dashboard, steering wheel, or windshield, resulting in injuries of the head, neck, chest, abdomen, and upper extremities. Below the waist, injuries to the knees and femurs occur because of direct contact with the vehicle and lower dashboard. Acetabular fractures are typically a result of tensing the leg when bracing for impact. Blunt trauma rarely occurs in isolated body systems. As such, all blunt trauma victims, including those ultimately without high-risk mechanisms of cervical spine injury, should be suspected of and treated as if they have an unstable cervical spine until proven otherwise.[15]

Thoracic Trauma

Blunt chest trauma is the third leading result of injury—closely following traumatic brain injury and extremity trauma. Patients with blunt thoracic trauma present a unique series of concerns. These patients represent some of the most severely injured—with multisystem involvement—accounting for nearly 25% to 50% of all trauma deaths.[16,17] In developed nations, thoracic trauma is most often associated with motor vehicle collisions.

Blunt thoracic trauma often results when drivers who are not wearing safety belts impact the steering wheel during a motor vehicle collision. Penetrating and blunt trauma to the chest may injure several structures and thus compromise optimal resuscitation. Possibly injured structures include the chest wall, the lungs and airways, the heart and pericardium, and the great vessels of the thorax. Injuries to these structures also compromise anesthesia care by affecting gas exchange and cardiac output.

Pneumothoraces are present in as many as 40% of all blunt thoracic injuries.[16] The size and location of the pneumothorax may vary throughout the lung field. Although the etiology and management of pneumothoraces is somewhat commonplace to providers, the presence, or in many cases the assumed absence, of a pneumothorax should not be minimized. It is estimated that as many as 50% of pneumothoraces are not detected on initial radiography.[17] This occurrence presents several clinical intraoperative issues and may alter an anesthetic plan. Nitrous oxide should be avoided in patients with suspected thoracic trauma.

A number of life-threatening injuries, described below, require immediate interventions in patients with thoracic/chest trauma.

Tension Pneumothorax. *Tension pneumothorax* develops when the lung is punctured within the thoracic cavity, creating a one-way valve that traps air between the layers of the pleura. With each breath, more and more air becomes trapped in this space, increasing intrapleural pressure to the point that it eventually exceeds all other intrathoracic pressures. The enlarging pleural cavity then collapses the ipsilateral lung and shifts structures of the mediastinum (e.g., trachea, great vessels, heart) into the opposite hemithorax, thereby compressing the contralateral lung. The size of a pneumothorax will rapidly increase during positive-pressure ventilation, especially if nitrous oxide is used.

Patients with a pneumothorax often present with hypotension, subcutaneous emphysema of the neck or chest, unilateral decrease in breath sounds, diminished chest wall motion, hyperresonance to percussion of one hemithorax, distended neck veins, or tracheal shift. An upright expirational chest radiograph cam provide definitive information if the problem is significant.

Massive pneumothorax can result in reductions in cardiac output and ultimately cardiovascular collapse. Under emergent situations, a large-bore intravenous catheter (needle chest decompression) can be inserted into the second intercostal space just above the third rib, along the midclavicular line. Release of pressure should restore cardiac function. Initially, the catheter can be temporarily attached to an intravenous line extension tube and placed under water seal by putting it in a bottle of sterile water positioned beneath the level of the patient until proper chest tube thoracostomy can be performed. See Chapter 26 for a complete discussion of the diagnosis and management of a pneumothorax.

Pericardial Tamponade. *Pericardial tamponade* that restricts filling of the cardiac chambers during diastole and produces a fixed low cardiac output is also a life-threatening emergency that requires immediate correction with pericardiocentesis. Care should be taken when inducing anesthesia in patients with cardiac tamponade because cardiovascular collapse can occur. Ketamine has been recommended as an induction agent in these patients.

Massive Hemothorax. *Massive hemothorax*, which can be caused by bleeding from the heart and great vessels, is treated immediately. Adequate fluid resuscitation is accomplished before placement of chest tubes. Chest tubes allow drainage of blood from the pleural cavity but can lead to more extensive bleeding and hypotension.

Cardiac Rupture. Patients with *cardiac rupture* who are not treated with pericardial tamponade seldom survive because exsanguination is extremely rapid in this situation.

Traumatic Aortic Rupture. *Traumatic aortic rupture*, if complete, is usually fatal, but with an intimal tear with a dissecting aneurysm, the patient can be saved if the diagnosis and repair are performed promptly with concurrent well-managed fluid resuscitation and anesthesia care. Management of these cases requires rapid and accurate assessment and appropriate surgical and anesthesia intervention.

Tracheal Injuries. Airway injuries represent a devastating and potentially lethal event after blunt thoracic trauma. The relative infrequency of airway injury upon admission to a trauma center (0.2%-8.0%) is likely due to high victim mortality at the scene of injury.[16,17] *Partial disruption of the trachea or major bronchi* often is mangaged through securing of the airway (by intubation or tracheostomy) and surgical correction. *Total disruption of the trachea* is often fatal unless rapid surgical retrieval of the distal disrupted

airway segment is accomplished to allow lifesaving mechanical ventilation. The majority of thoracic airway injuries are found below the carina and are often visible only during bronchoscopy or computed tomography (CT) examination.

Penetrating Trauma

Penetrating injuries can range from a simple pinprick to high-velocity projectile injury. Damage depends on three interactive factors[18]:

1. The type of wounding instrument (e.g., knife; missile, such as a bullet; or fragment, such as a piece of shrapnel)
2. The velocity of the missile at time of impact
3. The characteristics of tissue through which it passes (e.g., bone, muscle, fat, blood vessels, nervous tissues, and organs)

Lower-velocity wounds (i.e., stab wound) inflict injury by lacerating and cutting tissue. Moderate- to high-velocity injuries (i.e., bullet) occur as a result of the deceleration of the object as it passes through tissue, causing kinetic energy to transfer to the surrounding tissue. In either situation, low- or high-velocity penetration, it ultimately results in disruption of normal anatomy and physiology. Velocity of the projectile is the most significant determinant of wound potential. In other words, penetrating bullet wounds have a greater potential to inflict serious injury when compared with a knife or other handheld projectile.

Damage Control Surgery

Surgical management for the severely traumatized patient is often a multistep process. In many cases, patients present to the trauma center with surgical emergencies. Early repair is often simply a life-saving measure and is not intended to be a definitive repair but rather a stabilizing measure, intended to reduce operating room (OR) time and morbidity.[19,20] After stabilization, patients will be transported for further evaluation (secondary survey) or additional resuscitation measures in the intensive care unit (ICU). Often patients will be returned to the OR several times because the surgical course involves several phases. This staged approach to surgical management is commonly known as *damage control surgery* (DCS).

Damage control surgery is a concept that developed in the early twentieth century. Its use fell in and out of favor until the 1970s and 1980s. Its utility in modern trauma care was rediscovered as advances in surgical technique, critical care medicine, and technology converged. DCS correlates with current concepts in trauma care that include damage control resuscitation with rapid surgical correction of bleeding and the prevention of the lethal triad of acidosis, hypothermia, and coagulopathy. It also involves limitation of crystalloid administration and application of high ratios of plasma and platelets to packed red blood cells.[21,22] DCS is used in various surgical disciplines, from packing the abdomen after abdominal trauma to using external fixators to set complex orthopedic injuries.[23]

Abdominal Trauma

Blunt abdominal trauma is a leading cause of morbidity and mortality among all age groups. Although diagnosis and treatment of penetrating trauma is easily determined, occult bleeding in blunt abdominal injury is often misdiagnosed.[24,25] Abdominal sonography, Focused Assessment with Sonography for Trauma (F.A.S.T.), computed tomography (CT) scan, magnetic resonance imaging (MRI), or angiography may help in the diagnosis of specific injuries and various treatment modalities. Extremely unstable patients, however, will require immediate surgery. It is essential that large-bore intravenous access be in place, above the diaphragm, prior to opening the abdomen in the event of massive hemorrhage as a result of liver or other organ injury.

THE ABCD'S OF TRAUMA ANESTHESIA

Although the ATLS curriculum provides an organized framework for the management of traumatic injury, it is not specific to any one discipline. The following sections discuss the implications of the *ABCD's* of trauma anesthesia and provide an approach to clinical management. It cannot be overstated; anesthesia must facilitate rapid surgical management. Trauma anesthesia and surgery is not elective. It should be the goal of the anesthesia team to rapidly move the patient to the OR. Perfusion of tissue (or lack thereof) is directly related to time.

Airway

Endotracheal intubation is a routine procedure of anesthesia practice. Despite its regular use during general anesthetics, intubation poses significant risk and may be extremely challenging when caring for the acutely injured patient. Difficult tracheal intubation is the third most common respiratory-related event leading to death and brain damage as reported in the ASA Closed Claims analysis.[26] Although certainly not all trauma patients will have a difficult airway, the anesthetist likely will not have the opportunity or time for a full airway examination because of several variables such as facial injuries and/or hypoventilation and apnea. As such, the provider must anticipate the worst-case scenario.

Emergent intubation in the trauma patient follows the general pathway of the ASA difficult airway algorithm.[27] Three assumptions should be made when approaching this type of patient. First, there is no turning back. Intubation is not routinely elective for these patients. Therefore, once induction begins the patient must end up with a controlled airway. In addition to requiring a secured airway, trauma patients are assumed to have delayed gastric emptying and a full stomach. As such, they are at increased risk for aspiration. Finally, any patient with blunt trauma or with penetrating injuries to the neck and face must be considered for cervical spine instability.

Rapid sequence intubation (RSI) is the standard method for traumatic airway management. This practice involves several steps often not used during standard induction. One of the greatest differences between routine induction and RSI is the use of a muscle relaxant before knowing whether the patient can be mask ventilated. Although daunting, and a deviation from the norm, muscle relaxation is associated with the highest overall rate of successful airway management and provides the greatest possibility for rapidly securing the airway.[28]

Steps to RSI

RSI begins with appropriate planning and team practice. Sufficient personnel must be on hand to (1) provide manual in-line stabilization of the cervical spine after removing the front of the cervical collar; (2) provide cricoid pressure (the Sellick maneuver); (3) oxygenate the patient with bag-valve-mask ventilation and then perform direct laryngoscopy; and (4) administer medications.

Direct laryngoscopy during manual in-line stabilization of the cervical spine is a safe and effective procedure in patients with potentially unstable necks.[29,30] Cricoid pressure is applied and intended to prevent both gastric insufflation during bag-valve-mask ventilation and passive reflux of gastric contents. Although caution is appropriate, both cervical spine injury and aspiration during intubation are moderately low-risk events when compared with the possible risks and injury from hypoxia. Therefore, it must be remembered that airway management is the priority. In-line

stabilization and cricoid pressure should be relaxed if they are interfering with successful intubation.

Whenever RSI is undertaken, the need for an emergent surgical airway is always a possibility; appropriate surgical resources should be immediately available in the event of the need for a surgical airway.

Common Indications for Airway Management

Patients with traumatic injury present in varying degrees of injury and may require emergent airway management. The most common indications for endotracheal intubation include: (1) inadequate oxygenation/ventilation; (2) loss of airway reflexes; (3) decreased level of consciousness (Glasgow Coma Scale [GCS] less than 8); and occasionally, (4) the need for pain management and the ability to safely provide deep sedation during painful procedures. Once it is deemed that the patient requires airway management, it should be done using RSI.

RSI is a procedure that is conducted to rapidly control a patient's airway, while reducing the likelihood of gastric aspiration. RSI consists of five primary components: (1) preoxygenation, (2) cricoid pressure, (3) induction/muscle relaxation, (4) apneic ventilation, and (5) direct laryngoscopy. Each of these steps is discussed in detail below.

Preoxygenation. Adequate preoxygenation is likely the best asset for the anesthetist managing a trauma patient. Preoxygenation provides the greatest amount of time before occurrence of hypoxemia. Preoxygenation is accomplished using 100% high-flow (10-15 L) oxygenation via a nonrebreather facemask or bag-valve facemask. Although there is some debate in the literature, four to eight tidal volume breaths appear to provide superior preoxygenation when compared with 3 minutes of tidal breathing.[31]

Preoxygenation is challenging in regard to patients who are unable to deep breathe or follow commands when obtunded. In these circumstances, it is appropriate to provide *controlled* positive pressure bag-valve-mask ventilation throughout induction. An increased oxygen reservoir in the lung will benefit the patient more than the (theoretic) increased risk of aspiration caused by ventilating through cricoid pressure.

Cricoid Pressure. Cricoid pressure was first described by Sellick in 1961.[32] The goal of this maneuver is to reduce the risk of pulmonary aspiration of gastric contents by compressing the esophagus with the continuous ring of the cricoid cartilage.[33] Cricoid pressure is maintained throughout the RSI and is not released until endotracheal tube (ETT) placement has been confirmed. Determining the appropriate pressure to apply to the cricoid ring has been the subject of debate. Vanner and Pryle[34] have determined that 30 Newtons (approximately 10 lbs of pressure) adequately occludes the esophagus.

Induction Agents. Anesthetic induction for RSI can be achieved by a variety of agents. At this time no literature is available to support the superiority of one agent over another. All induction agents will cause dose-dependent decreases in blood pressure in the hypovolemic, hemorrhaging patient. Dose-dependent hemodynamic instability can likely be attenuated by reductions in the induction dose. Although no formula can precisely predict the dose for a hemodynamically unstable patient, some authors suggest a dose that is one tenth to one half of the normal induction dose of propofol.[35] Ketamine can always be considered as an alternative trauma induction drug.[36,37] Etomidate use is discouraged due to the suppression of adrenal function. Recall during induction, an undesirable consequence, is a secondary concern when urgently managing an unstable trauma patient.

Succinylcholine (1.5 mg/kg) provides favorable and rapid muscle relaxation to facilitate intubation. It is generally the preferred agent for RSI for any patient who has no specific contraindication to its use. Succinylcholine administration may cause lethal hyperkalemia in patients with neurologic deficits from spinal cord injury, but not until 24 to 48 hours after injury.[38]

Rocuronium (1.2 mg/kg) and vecuronium (0.2 mg/kg) also can be used for RSI. The onset time for high-dose rocuronium (1.2 mg/kg) is similar to that for succinylcholine with only a slight delay in achieving complete relaxation.[39] Although these nondepolarizing agents may produce adequate intubating conditions, their use may influence what care can be provided. Prolonged paralysis will require sedation and will make any subsequent neurologic assessment more difficult.

Apneic Ventilation. Apneic ventilation is the concept of pulmonary ventilation using high-flow oxygen. Its purpose is to reduce the potential risk of gastric distension and pulmonary aspiration from positive pressure ventilation. The principle of apneic ventilation is based on Boyle's law in which gas leaves the facemask, fills the lungs, and exchanges in the lungs based upon the concentration gradient of gases in the alveoli. To work appropriately, apneic ventilation assumes that the airway is patent and that a high concentration of oxygen can be reliably administered.

Apneic ventilation remains controversial for practitioners. RSI for the trauma patient is intended to reduce the risk of aspiration in the case of a potentially full stomach, yet many trauma patients who present are unable to take a deep breath prior to induction, resulting in a reduced functional residual capacity and pulmonary reserve. Traditionally, with RSI, the practitioner is taught to refrain from positive pressure ventilation during induction. This practice, however, is commonly being modified by clinicians.

To avoid potential hypoxemia or in the event of an already hypoxemic patient, clinical modifications have been made to RSI that include bag-valve-mask ventilation through cricoid pressure—often termed "modified RSI." This method is actually the technique described by Sellick in 1961.[32,40] To date, there does not appear to be any increase in aspiration by bag-valve-mask ventilation through cricoid pressure.

Direct Laryngoscopy. No evidence indicates that a particular laryngoscope blade or size is optimal for RSI. The choice is likely provider dependent. The provider should use the equipment with which he or she is most comfortable.

Successful endotracheal tube placement is immediately confirmed by capnometry. If unsuccessful, a second direct laryngoscopy should be attempted, incorporating some change in technique (e.g., different laryngoscopist, blade, or patient position). There are a variety of adjunct tools available in the event of an unplanned difficult intubation. These include the basic and inexpensive, such as the intubating stylet or bougie, to the more advanced fiberoptic equipment.

If intubation is again unsuccessful (third attempt), the next step should be an airway adjunct to support oxygenation. These adjuncts range from the Combitube to the laryngeal mask airway (LMA). In the situation of "cannot intubate and inadequate facemask ventilation," LMA insertion should be the immediate next step.[41]

Airway Management of Cervical Spine Injuries

Cervical spine injury remains a significant concern when facing airway management of the trauma patient. The incidence of cervical spine injury after trauma is relatively rare at 2% to 3% of all trauma and approximately 6% to 10% for patients with traumatic brain injury.[42] Cervical spine injury should be assumed until proven otherwise. Immobilization of the neck is essential. To that

end, in-line stabilization is essential because it allows for removal of the front of the cervical collar, allowing more area for jaw and mouth movement, while limiting the risk for further injury.

The management and intubation of patients with suspected cervical spine injuries remains clinically controversial. Despite common belief, there is no evidence to suggest that fiberoptic intubation provides safer patient outcomes when compared with direct laryngoscopy with in-line stabilization.[43-45] As such, management of a cervical spine injury may be done so with the concepts of "emergent" which involves in line stabilization and RSI versus "controlled" which involves an awake fiberoptic technique. Figure 36-2 describes a logical management strategy for these two situations.

Breathing (and Ventilation)

Regardless of the need to manage the airway, the adequacy of breathing and ultimately patient oxygenation is essential to survival. Pulse oximetry is a commonly used noninvasive method to continuously monitor oxygen saturation. Pulse oximetry is often used as a surrogate measure of status. Although pulse oximetry provides a wealth of clinical information, it should be realized that this measurement is not ideal and that the data may provide a false sense of security. For instance, an otherwise healthy patient breathing room air oxygen (21%) will have a Pa_{O_2} level of approximately 100 mmHg and an Sa_{O_2} of 100%. If the patient is placed on a high-flow, nonrebreather mask of 100% oxygen, then the Pa_{O_2} could be expected to be approximately 500 mmHg and Sa_{O_2} would remain at 100%. Patients who experience declining pulmonary function will have a Sa_{O_2} of 100% over a wide range of Pa_{O_2} readings. It must be recognized that supplemental oxygen, although necessary, can mask pulmonary injury and in some cases respiratory decompensation. It should not be concluded that a saturation of 100% equates to a stable patient or the health of the pulmonary (breathing/ventilation) system.

Pulmonary contusions represent the most common lung injury. It is reported that as many as 70% of patients with blunt thoracic trauma present with some degree of pulmonary contusion.[17] Pulmonary contusions are injuries to the alveoli without gross disruption of pulmonary architecture. This injury is essentially a *bruise* to the lung tissue resulting in protein-rich fluid leaving ruptured pulmonary capillaries and settling into the alveolar membrane and interstitial space. Due to the widening of the pulmonary membrane, pulmonary contusions result in varying degrees of reduced gas diffusion that may be clinically relevant. Pulmonary contusions can develop or "blossom" over a range of time and ultimately may develop into acute respiratory distress syndrome (ARDS).

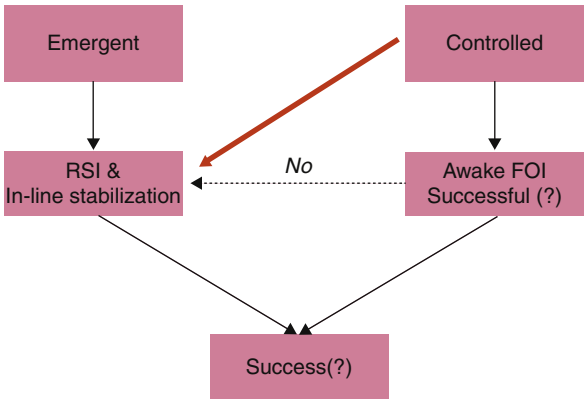

FIGURE **36-2** A logical management algorithm for controlled versus emergent airway management for a patient with a cervical spine injury. *RSI*, Rapid sequence induction; *FOI*, fiberoptic intubation.

ARDS is a common problem in trauma care. It may be a result of injury or the resuscitation of the patient. It has been estimated that between 10% and 40% of patients with traumatic injury will develop ARDS over their hospital course. Pathologically, ARDS is a result of protein-rich fluid leaving the pulmonary capillaries. As the disease progresses, the pulmonary capillary leakage is compounded by embolic events, which further increase intracapillary pressure and intensify interstitial leakage. ARDS culminates in hypoxia and decreased pulmonary compliance. Ventilating these patients is a challenge. Clinicians are often faced with the inability to appropriately oxygenate the patient without using high pressures to ventilate.[46] High pressures and decreased compliance sets the patient up for barotrauma and worsening pulmonary disease.

A variety of pulmonary techniques have been described for managing these patients. They range from high-frequency oscillation ventilation to cardiopulmonary bypass. At this time no one technique appears to be superior. It is widely accepted, however, that these patients should be ventilated using low tidal volumes to reduce peak pressures, and the plateau pressures should be maintained at less than 32 cm H_2O.[47,48] Although attempting to correct an Sa_{O_2} that is less than normal (less than 95%) by increasing the Fi_{O_2} may seem to be a desirable action, it would likely not be the best practice because of the toxic effects of oxygen over time, which can potentially worsen gas exchange.

Circulation

Up to thirty-five percent of trauma fatalities in the United States are due to hemorrhage and hemorrhagic shock.[49] A vast majority of patients that survive their initial injury and reach the hospital are coagulopathic when they die.[49,50] Hemorrhagic shock is the leading cause of early and late mortality after trauma.[51] Hemorrhagic shock is defined as a pathologic event that is triggered by the loss of circulating blood volume and results in a reduction in oxygen delivery to the tissue.

The physiologic response to hemorrhagic shock is a dynamic and complex process. Reductions in blood volume cause an immediate change in vascular tone and global systemic vascular resistance (SVR). Blood is shunted from low metabolic "ischemia-tolerant" vascular beds, such as skin and bone, to highly metabolic tissues (e.g., brain, heart, gut) with the intent of maintaining cellular perfusion and aerobic respiration. Early shunting compensates for relative hypovolemia. If short lived, compensated shock has very few long-term sequelae.

Unfortunately, uncontrolled hemorrhage is a likely event in major trauma. As the degree of blood loss worsens, vascular shunting increases. In this state, patients rapidly progress from a compensated state to decompensated shock. Vascular shunting continues during decompensated shock. Blood is directed away from lower metabolic organs, such as the kidneys and gut, in an attempt to maintain perfusion in higher metabolic structures. During decompensated shock, changes to SVR are less likely to adequately maintain perfusion. The body attempts to further compensate a dwindling stroke volume and cardiac output by increasing heart rate and contractility.

Unfortunately, compensatory mechanisms are imperfect. Prolonged reductions in perfusion will result in cellular injury. During protracted shock events, venous oxygen reserves are extracted and used as arterial oxygen supply declines. Metabolic imbalances between oxygen demand and delivery produce toxic metabolic by-products. As a result of this imbalance, cells are unable to

maintain vital metabolic functions. Energy production falls. Intracellular energy-dependent pumps fail, reducing cell wall integrity.

In an attempt to maintain energy production, cells transition from aerobic to anaerobic respiration. The conversion to anaerobic respiration is made at a significant cost to the cell. In addition to vast reductions in energy production, lactic acid and free radicals are produced. These toxic cellular by-products induce cellular injury, further reducing cellular function.

Despite vigorous resuscitation, hemorrhagic shock may result in patient death. The mortality rate for shock is approximately 50% if treatment is initiated at 30 minutes from the onset; the rate rises to 90% if 1 hour elapses before treatment is initiated.[52,53] This high mortality rate associated with the delayed treatment of hemorrhagic shock is the basis for the initiation of fluid resuscitation and hemostasis in the field. The "Golden Hour" was initially modeled from data collected from young, healthy males in military service during the Vietnam War. The Golden Hour represents a period of time (60 minutes) in which selected patients will likely survive hemorrhagic shock if perfusion is restored. This observation, however, cannot be extrapolated to the general population because, as stated, it was based on young, healthy men. It is likely, however, that when generalizing to the population at large, the Golden Hour is actually a nonspecific time that is age and health status dependent. The Golden Hour is likely an inverse relationship. As patients age, their ability to compensate during hemorrhagic shock decreases.

Hemorrhagic shock progresses through stages over time. Stage I of the three stages of shock is often called *nonprogressive shock* or *compensated shock*. A negative-feedback control mechanism of the circulation tries to return the cardiac output and arterial pressure to normal levels. This phenomenon is mediated through the baroreceptor reflexes, central nervous system (CNS) ischemic responses, contraction of blood vessels, release of vasopressin (antidiuretic hormone), formation of angiotensin, and compensation mechanisms that tend to return the blood volume back toward normal by mobilization of fluids from other spaces of the body.

Stage II of shock is also known as *progressive shock*. A positive-feedback mechanism comes into play with this phase of shock. When shock becomes severe enough, components of the cardiovascular system start to deteriorate. This deterioration is associated with cardiac depression caused by ischemia, vasomotor failure, thrombosis of small vessels, increased capillary permeability, release of endotoxins by ischemic tissues, and generalized cellular degeneration.

Stage III of shock is also called *irreversible shock*. This stage occurs when adenosine triphosphate reserves are depleted and toxic substances are released from apoptotic cells. Death follows as the natural consequence of not successfully halting progressive shock.

A successful resuscitation will often leave patients in a temporary hypermetabolic/hyperdynamic state. This is due to a "metabolic debt" for the period of ischemia. Patients often remain tachycardic despite appropriate resuscitation and sedation. Unfortunately, an apparent "successful" resuscitation does not mean survival. As such, morbidity as a result of hemorrhagic shock can be classified as early and late events. Acute irreversible shock presents as the classic massive hemorrhage and death. In this case, the resuscitation attempt does not match the blood loss. Ongoing hemorrhage and hypoperfusion worsens, leading to acidosis, coagulopathy, and death.

Subacute irreversible shock appears clinically opposite to acute irreversible shock. In this instance, fluid volume is restored, hemorrhage is controlled, but the patient has suffered a significant "dose" of shock and cellular ischemia that cannot be overcome. Ultimately, the "metabolic debit" is too great. Over time these patients succumb to multiorgan failure and related sequelae secondary to cellular hypoperfusion. Table 36-1 details ATLS classification of hemorrhagic shock.

Treatment of Hemorrhagic Shock

Patients admitted for care with a traumatic injury often present with obvious signs of blood loss and have the potential to be in compensated shock with an unknown degree of hypovolemia. Quantifying or estimating potential blood loss is a challenging issue. Routine monitors often are inadequate in detecting losses until the late stages of shock when physiologic compensation begins to fail. Patients may have large blood volume losses and yet appear at first to be relatively normovolemic.

Blood loss can be hidden in several locations in the body (e.g., the thorax, abdomen, pelvis, and lower extremities), thereby masking the blood loss and complicating the treatment plan. In addition, blood losses at the scene of injury are often not quantified. Blood loss to the environment (street) must be considered. The management of hemorrhagic shock from a traumatic injury follows a logical pathway as described in ATLS.[54]

Fluid Resuscitation. The balance between the appropriate amounts of fluid is one of the greatest challenges of successful trauma resuscitation. Resuscitation is commonly seen from one perspective, that of blood pressure. Fluid resuscitation, however, should not be viewed only in terms of blood pressure (i.e., perfusion) but also in terms of the degree and state of repair of the injury. For limited injuries with little or no active bleeding, ATLS resuscitation guidelines advise brisk isotonic crystalloid infusion (up to 2 liters) and component therapy for a larger resuscitation with greater blood loss.[15]

Unfortunately, therapy is not quite as simplistic in the case of ongoing or massive injury. The administration of fluid, in and

TABLE 36-1 Advanced Trauma Life Support Classification of Shock

	Class 1	Class 2	Class 3	Class 4
Blood loss (%)	<15	15-30	30-40	>40
Heart rate (beats/min)	<100	>100	>120	>140
SBP (mmHg)	Normal	Normal	Decreased	Decreased
Pulse pressure	Normal or increased	Decreased	Decreased	Decreased
RR (breaths/min)	14-20	20-30	30-40	>35
Mental state	Slightly anxious	Mildly anxious	Anxious, confused	Confused, lethargic

Modified from American College of Surgeons Trauma Committee. *Advanced Trauma Life Support for Doctors*. 8th ed. Chicago: American College of Surgeons; 2008.
RR, Respiratory rate; *SBP,* systolic blood pressure.

of itself, may actually worsen the patient's clinical state if fluid administration is not timed appropriately. This necessary balance of body fluids is easily visualized when one considers a garden hose (vasculature), a water spigot (blood supply), and a sprinkler (perfusion). Imagine that a hose is connected to a water spigot and sprinkler. Water flows to the end of the hose and into the sprinkler in varying rates as the spigot is opened and closed causing variations of pressure. If the hose ruptures, water will move down the hose and exit at the tear. Depending on the rate of pressure, water may not reach the sprinkler at all. To maintain "normal" sprinkler function, water pressure would have to increase. Although this might seem advantageous, an increase in water pressure would also cause more water to exit at the tear in the hose. The additional loss of water or—in the case of a bleeding blood vessel—the additional loss of blood, would cause blood containing nutrients, coagulation factors, catecholamines, and oxygen-carrying capacity to be lost. This, of course, would be detrimental to the patient.

For these reasons, early resuscitative efforts (before surgical repair) and fluid administration should be done by hypotensive resuscitation. The concept of hypotensive resuscitation was first described in the early twentieth century. Hypotensive resuscitation is a clinical methodology that guides fluid resuscitation in a manner that avoids excessive bleeding by targeting fluid administration toward maintaining a lower than *normal* systolic blood pressure. Even though targets may vary, most clinician's target systolic blood pressure (SBP) at or near 85 to 90 mmHg.[55] This reduction in systolic pressure reduces bleeding and ultimately has been shown to reduce mortality.

This finding was most notably described by Bickell et al.[56] with a research project commonly referred to as the Houston Trial. The Houston Trial enrolled 598 patients with penetrating thoracoabdominal trauma. The subjects were randomized in the field to a fluid administration or no fluid administration group. The research protocol continued through the primary evaluation and ended as patients were transported to the operating room. The Houston Trial found that there was a significant difference in fluids administered between groups and that the resuscitation group had a higher mortality than the nonresuscitation group ($p = 0.04$). When possible, the initial fluid resuscitation should be minimized until hemostasis occurs and then administered only to avoid cardiovascular collapse. After hemorrhage has been controlled, a systolic blood pressure greater than 100 mmHg and heart rate less than 100 bpm can be the goal.

Intravenous Access. Appropriate intravenous access is a priority when managing a patient in hemorrhagic shock. The speed of intravenous fluid administration is directly related to the radial diameter of the catheter as described by *Poiseuille's law.* Larger catheters allow for increased flow by reducing turbulence. Patients should have access that has the least impediment to flow. In addition, catheter length should be minimized. As a rule of thumb, IV access should be "short and fat." Although central access is not necessary for resuscitation, patients suffering from significant hemorrhagic shock are often too vasoconstricted to cannulate large veins. Central venous access should be considered early in the management plan. Large-bore single- or double-lumen catheters should be used for central access.

In addition to size, location of the access is essential. IV access should be redundant, and placed in locations that will not deliver fluid directly to an injured area and that may not reach central circulation. For instance, a femoral catheter should not be used when major abdominal vascular or pelvic injury has occurred. Intravenous access above the diaphragm would provide the most assurance that the fluid would not "dump" into the abdomen or retroperitoneum. In general, there should always be access above the diaphragm.

Intravenous Fluids. Isotonic crystalloid infusions expand plasma volume, increase cardiac output, and ultimately cause an increase in blood pressure. In addition, they may reduce vasoconstriction, hemodilute the blood, and induce immune dysfunction. As discussed earlier, vigorous fluid resuscitation must be tempered with the understanding that fluid increases blood pressure and subsequently causes bleeding. Bleeding causes recurrent hypotension and begins a vicious cycle of fluid—bleeding—hypotension.

At the trauma center, red blood cells (RBCs) are replaced to provide adequate oxygen-carrying capacity. Shed blood is replaced with a 1:1 volume of packed RBCs and a 3:1 volume of crystalloids.

Serial electrolyte levels, hemoglobin and hematocrit levels, and arterial blood gas analysis are obtained approximately every hour in severely injured, unstable patients in surgery until the patient is stable. Additionally, coagulation parameters are observed closely in patients with signs of active bleeding. Colloids usually allow rapid restoration of intravascular volume but can contribute to a later episode of pulmonary edema and increased bleeding if hemostasis has not been achieved. Balanced electrolyte solutions (isotonic solutions) are given to help maintain perfusion.

Dextrose-containing solutions are generally undesirable for use in initial resuscitation fluid administration. Rapid determination of blood glucose levels is critical in patients with diabetes and in children. Traumatized infants and children in shock may rapidly consume their gluconeogenic substrate, allowing significant hypoglycemia to occur.[57] Although patients are more likely to become hyperglycemic than hypoglycemic after traumatic injury, hypoglycemia can occur. Significant hyperglycemia is associated with further neurologic injury.[58]

Traumatically induced hyperglycemia is so common that it is often called *diabetes of injury*.[59] Withholding glucose or giving it in moderate amounts in order to maintain blood glucose levels at less than 150 mg/dL is advisable if brain ischemia occurs, because data have shown that hyperglycemia existing before an ischemic or a hypoxic event increases ischemic damage.[60]

Coagulopathy and Trauma

A vast majority of patients that survive their initial injury and reach the hospital are coagulopathic when they die.[49,50] It is estimated that nearly a quarter of all trauma admissions present in varying degrees of coagulopathy on admission.[50]

Once coagulopathy develops, patient morbidity and mortality drastically increase. Coagulopathy is an independent predictor of mortality. In otherwise healthy patients, an elevated prothrombin time (PT) on admission indicates rapid hemorrhage, massive injury, and a steadily worsening perfusion state.[61] In addition to the loss of life; coagulopathy indirectly levies a burden on society and the healthcare system. As such, management strategies to reduce the morbidity and mortality of trauma-induced coagulopathy have become of particular interest.

Clot Formation. Hemostasis is a complex process involving proteins—cofactors and blood products that converge in a series of reactions intended to produce the fibrin and platelet network (with trapped red blood cells) that is a clot. Clot formation begins with an initial vascular insult. Tissue injury immediately causes the release of tissue factor (TF) from the endothelium. At the same time, vascular spasm causes platelets to migrate from the vascular lumen towards the site of injury. TF binds with activated, circulating factor VII (FVIIa). The interaction of FVIIa with TF begins the conversion of prothrombin (II) to activated thrombin (IIa) resulting in a "thrombin burst" on the surface of the platelet.

Conversion of thrombin completes the coagulation process yielding fibrin (I) connections that stabilize clot formation.[61,62] Under normal conditions, fibrinolytic pathways maintain appropriate clot size and location, limiting clot formation to the site of vascular injury.

Pathology and Causes of Coagulopathy. Massive injury can disrupt the clotting cascade at several points in the process, resulting in life-threatening consequences. Four mechanisms have been identified as primary causes of trauma-induced coagulopathy. These mechanisms are (1) dilution of factors; (2) hypothermia/acidosis; (3) severe traumatic brain injury (TBI); and (4) hemorrhagic shock.[49] Trauma-induced coagulopathy (TIC) has both endogenous and exogenous components. Endogenous acute traumatic coagulopathy is associated with shock and hypoperfusion. Exogenous coagulopathy arises from effects of dilution resulting from fluid resuscitation and consumption through bleeding and loss of coagulation factors. Coagulopathy is present in 10% to 34% of injured patients, depending on injury severity, acidosis, hypothermia, and hypoperfusion.[63]

Dilution. Traumatic injury often requires massive resuscitation to replace blood volume and restore perfusion. ATLS guidelines advocate fluid administration but do not provide clear guidance for the administration of procoagulant products such as plasma, cryoprecipitate (CRYO), and platelets.[15,64,65] Although required for initial resuscitation, crystalloid fluid administration dilutes coagulation factors and platelets and increases hydrostatic pressure. This ultimately leads to an inadequate clot and nonsurgical bleeding. Unfortunately, there does not appear to be any "magic concoction" to optimally resuscitate patients while maintaining the ability to form clots.

Resuscitation is a dynamic process. Treating one deficit, for instance anemia, with red blood cells will dilute coagulation factors and platelets leading to coagulopathy. The addition of crystalloid or nonblood colloids further exacerbates this tenuous situation.[63,66-68] Various authors advocate a balanced administration of RBCs, plasma, and platelets (1:1:1) for massive resuscitation. Balanced administration of blood products functionally represents whole blood. Figure 36-3 compares the balanced administration of blood products. This is supported by military data from Operation Iraqi Freedom.[69] Although it is an improvement, balanced component therapy falls short of the ideal whole blood replacement by virtue of (1) dilution with anticoagulant and nutritive solutions as blood is collected and processed, (2) losses due to centrifuging, separation, and readministration, and (3) losses over time in storage.

Establishing clinical end-points for correcting coagulopathy is challenging and historically has not been standardized. In an attempt to rectify this, a consensus statement of the College of American Pathologists, American Society of Anesthesiology, and European Task Force for Advanced Bleeding Care in Trauma recommends administering procoagulant products to maintain an international normalized ratio (INR) of less than or equal to 1.5 and a platelet count greater than 50,000.[64] Although these end-points are helpful in creating a standard methodology of care, and for replacement of factors in stable patients, it must be acknowledged that acute care based on laboratory data may be unrealistic. Laboratory analysis is time consuming and may not provide information rapidly enough in an actively bleeding patient. The clinician is frequently required to make decisions about transfusion in anticipation of the patient's course, which is why we recommend empiric 1:1:1 therapy until the situation is stable enough to guide therapy by laboratory values.

Hypothermia and Acidosis. Occult hypothermia is an uncommon event.[70-72] Less than 9% of trauma admissions are hypothermic on presentation.[73,74] Despite this, hypothermia remains an issue. Removal of clothing (**E**nvironment in ATLS management), muscle relaxation, cold intravenous fluid administration (resuscitation), and frequent examination (removal of blankets) contributes to heat loss. Hypothermia may result in significant coagulopathy. The vast majority of patient hypothermia can be attributed to radiant heat loss due to the gradient differences of patient and environmental temperature.[72]

Hypothermia induces a variety of physiologic changes. Although the precise mechanism is unclear, there is agreement that hypothermia alters platelet function and reduces fibrin enzyme

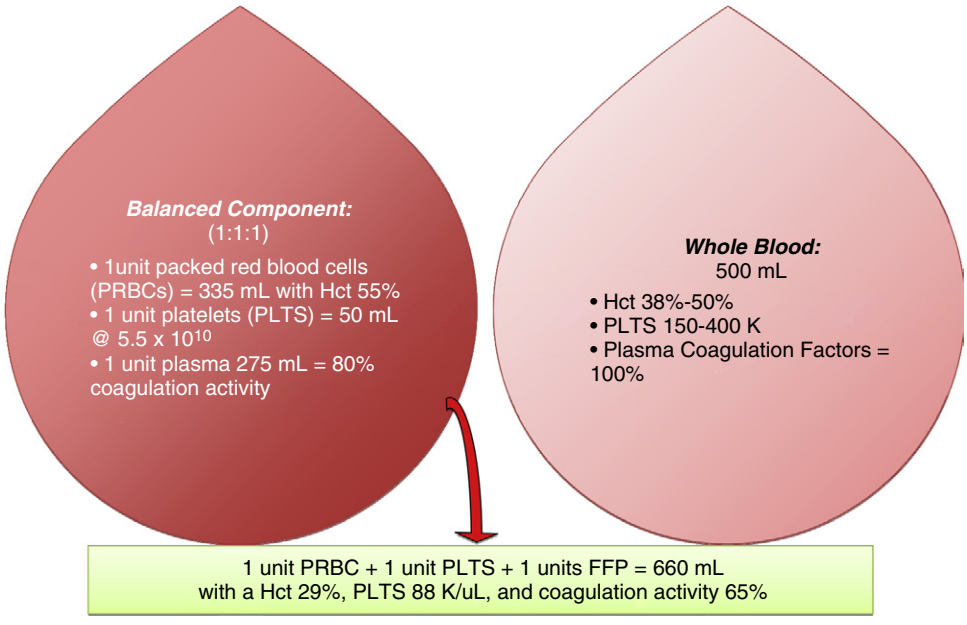

FIGURE **36-3** A comparison between whole blood administration and balanced component therapy. Balanced component therapy closely mimics whole blood. *Hct*, Hematocrit.

kinetics.[71,75] Hypothermia and acidosis compromise thrombin-generation kinetics via different mechanisms. Hypothermia primarily inhibits the initiation phase of thrombin generation. In addition, hypothermia inhibits fibrinogen synthesis, leading to a potential deficit in fibrinogen availability.[76] The clinical effect of hypothermia is a slowly formed and fragile clot that is unable to inhibit bleeding.[75]

Acidosis often accompanies massive injury, hemorrhage, and hypothermia. Acidosis, in and of itself, does not appear to have a significant impact on coagulation.[70,75] In the presence of hypothermia, however, acidosis can contribute to a potentially lethal triad of acidosis, hypothermia, and coagulopathy.[64,69] It is believed that acidosis impairs coagulation proteases and becomes clinically significant at pH less than 7.1.[69] Unfortunately, the administration of sodium bicarbonate to correct acidosis does not appear to be clinically effective to increase clotting function.[75]

The management of hypothermic and acidotic patients is fairly intuitive. The most efficacious management is to re-warm the patient and focus on returning perfusion to correct acidosis. Obviously, warming fluids as they are given and controlling the ambient room temperature of the resuscitation unit/operating room is essential. Hypothermia can be minimized when proper care is taken.

Activated Protein C Pathway. Trauma-induced coagulopathy is often thought of as a result of environmental or therapeutic interventions. Resuscitation necessitates large volumes of intravenous fluid to be administered causing hypothermia and dilution in the face of acidosis, leading to the lethal triad. In many ways, coagulopathy was a "cost of doing business." Recent research has challenged this belief.

The activated protein C (APC) pathway has been identified for decades. Although the role of the APC in fibrolytic pathways has been well established, its pathologic role in trauma-induced coagulopathy is only now emerging.[75] It is believed that the APC pathway is initiated when thrombin binds with thrombomodulin. The thrombin-thrombomodulin (T-T) complex is a normally occurring anticoagulant that develops as a negative feedback during clotting to limit clot to the area of injury.[77] APC is a vitamin K–dependent serine protease that induces anticoagulation by inhibiting factors V and VIII.[78] In a nonpathologic state, APC functions to limit clot propagation, ultimately maintaining blood flow in uninjured vessels. In the presence of damaged and hypoperfused tissue, however, it is believed that the APC pathway may lead to systemic coagulopathy.

Traumatic Brain Injury. Traumatic brain injury (TBI) in isolation is self-limiting, often producing very little blood loss. Despite this, TBI continues to be a significant cause of morbidity and mortality (25%-50%), often requiring neurosurgical intervention.[79-81] Although the mechanism is not fully understood, it is believed that TBI causes a local release of tissue factor (TF) from injured neurons, activating the protein C pathway and triggering the release of anticoagulant mediators.[80,81]

Early management of TBI should include rapid administration of plasma. The end-point of plasma administration should be to normalize the PT and INR. Because the plasma requirement needed to reverse TBI-induced coagulopathy is unpredictable, often requiring large quantities of plasma to reduce bleeding and normalize clot formation, administering plasma is recommended early, even before the initial PT or INR laboratory results return.[82]

Plasma administration may be time consuming and result in delays in surgical intervention. Because of this, several researchers advocate the early administration of recombinant factor VIIa (rFVIIa) for TBI-related coagulopathies. Although controversial, the use of rFVIIa in some studies has demonstrated an 80% reduction in blood product administration, reduced time to neurosurgical intervention, and decreased ICU admission for the treatment of patients with TBI.[82]

Shock. Research by Brohi et al.[83] suggests that hypoperfusion may be the sentinel step in trauma-induced coagulopathy. Like TBI, it is believed that hemorrhagic shock leads to activation of the protein C pathway, resulting in fibrinolytic coagulopathy.[77,82] Although the exact mechanism is unclear, it is believed that occult hemorrhage and hypoperfusion may increase T-T complexes, resulting in APC and clotting factor inactivation. This finding is consistent with observed clinical presentations. As previously noted, nearly half of all trauma fatalities are due to coagulopathic patients in hemorrhage and hemorrhagic shock who have no sign of TBI, hypothermia, or significant prehospital resuscitation.[49,77,83]

Management strategies for these patients should include a vigorous yet controlled resuscitation. In addition to ATLS guidelines, warm fluids, and early blood product administration, the goal of the resuscitation team should be to maintain perfusion while controlling blood pressure: not too low and not too high. Research has demonstrated that increased systolic blood pressures greater than 85 mmHg increases fluid/blood product administration and blood loss while having little impact on morbidity and mortality.[84,85]

Disability (Neurologic)

Neurologic assessment begins the moment the patient enters the hospital. Patient mentation, behavior, and response to stimuli all provide the clinician with a picture of any neurologic injury. A Glasgow Coma Scale (GCS) score is assigned during the primary or secondary survey and reassessed throughout the hospital course. Head injuries are classified grossly as blunt or penetrating, and the severity of the injury is based upon the GCS score.

The GCS evaluates the best eye response, best verbal response, and best motor response with a minimum score of 3 and maximum score of 15. A GCS of 13 or higher correlates with a mild brain injury, 9 to 12 a moderate injury, and 8 or less a severe brain injury.[85] See Table 19-5 for the Glasgow Coma Scale.

Head Injury

Patients with head injury may sustain primary traumatic brain injury (TBI) that cannot be anatomically corrected, only prevented. The goal of care is the prevention of secondary brain damage resulting from intracranial complications that are aggravated by intracranial bleeding, edema, and resultant increased intracranial pressure (ICP). Common extracranial causes of death in head-injured patients are hypoxia and shock. Anesthesia management of head-injured patients includes early control of the airway and maintenance of cardiovascular stability.

Management of neurologic injury follows a similar treatment pathway as that for other trauma patients. GCS of less than 8 necessitates endotracheal intubation. Goals for airway management should be to maintain Spo_2 greater than 90% with normoventilation to help reduce hypercarbia and hypoxemia, both of which contribute to elevated intracranial pressure. Judicious use of induction agents and neuromuscular blocking agents can facilitate a straightforward intubation. Attempts to perform an awake intubation in an obtunded, semicomatose, head-injured patient may promote coughing, bucking, and thrashing about, along with concomitant increases in the ICP that carry the risk of tentorial herniation. Nasal intubation may be problematic in the head-injured patient because of possible basilar skull fractures that can facilitate contamination and ultimate sepsis from nasal microorganisms introduced into the cranial vault. Late sepsis also can

occur from a sinus infection caused by prolonged nasal tracheal intubation. Gastric tubes are placed orally in head-injured patients for the same reasons.

Although hypotension is always a matter of concern, it is even more so for patients with neurologic injury. Cerebral perfusion pressure (CPP) describes the relationship of mean arterial pressure (blood pressure) and intracranial pressure. Systemic blood pressure directly affects cerebral blood flow. Hypoxemia in addition to hypotension is associated with a mortality of 75%.[86,87] As such, cardiopulmonary status must be maintained while controlling ICP.

Patients with a suspected open- or closed-head injury are placed in a head-up position to help promote venous drainage and reduce ICP. Management of ICP is a challenge. There is no exact treatment threshold; however, most experts support treatment for ICP greater than 20 to 25 mmHg. No one technique (total intravenous anesthesia [TIVA] vs. general anesthesia [GA]) has demonstrated superiority to another. Although some anesthetic agents may decrease cerebral metabolic demand, they also may reduce cerebral blood flow, which may not be a desired effect when trying to increase cerebral blood flow. Aggressive management of CPP has been correlated with improved patient outcome.[87] Patients with neurologic injury are more likely to die when their blood pressure falls below 90 mmHg. Clinical targets should be to maintain a mean arterial pressure at a minimum of 70 to 75 mmHg to maintain a CPP of at least 50 mmHg. This gross target should be maintained until ICP monitoring can be initiated.

ICP monitoring is indicated for many instances of moderate and severe brain injury. Current American Association of Neurological Surgeons (AANS) recommendations are for the placement of a ventriculostomy for ICP monitoring. It is the most accurate, cost-effective, and safe method for monitoring ICP.[87] Ventriculostomies allow for close monitoring of ICP as well as treatment of elevated ICP by drainage of cerebrospinal fluid (CSF). Anesthetists should be familiar with this equipment and how to safely calibrate the drainage system/close the system as indicated for the treatment of these patients.

The goal in treating intracranial hypertension is to promote adequate oxygenation and nutrient supply by maintaining CPP, oxygenation, and glucose supply without hyperglycemia.[88,89] Therapeutic maneuvers involve one or more of six treatment options: (1) decrease cerebral blood volume; (2) decrease CSF volume; (3) administer diuretics; (4) perform decompressive craniectomy; (5) resection of injured tissue; and (6) evacuate hematomas. Moderate short-term hyperventilation to a $Paco_2$ of 30 to 35 mmHg helps reduce increased ICP. However, excessive hyperventilation ($Paco_2$ of 25 mmHg) or less is not recommended. Hyperventilation is recommended as a temporizing measure for the reduction of elevated ICP and is avoided during the first 24 hours after injury when cerebral blood flow (CBF) is often critically reduced. If hyperventilation is used, jugular venous oxygen saturation ($SvjO_2$) measurement or brain tissue oxygen monitoring is recommended.[87] Prompt endotracheal intubation, administration of hyperosmotic diuretics, consideration of moderate short-term hyperventilation, and possible CSF drainage are considered for the reduction of cerebral swelling and the prevention of further brain injury.

Patients with significant head injury benefit from the placement of an arterial line in addition to the standard monitoring, which includes capnography and pulse oximetry. The placement of an ICP monitoring device facilitates the observation of changes in ICP dynamics that are influenced by drug administration and other manipulations. Intracranial hypertension exists when the ICP is at a sustained elevation of greater than 15 mmHg. Therapeutic maneuvers are aimed at maintaining CPP with a range of 50 to 70 mmHg and oxygen delivery Spo_2 of 90% or greater.[87]

The safety of isoflurane, desflurane, and sevoflurane has been demonstrated. Avoidance of nitrous oxide is recommended at least until the full extent of injuries is known because it may aggravate potential pneumocephalus and pneumothorax in the traumatized patient. In the head-injured patient, ketamine is generally avoided because it tends to increase the ICP. Temporary reduction of ICP is often achieved using small incremental doses of propofol, moderate levels of hyperventilation (short-term), mannitol and/or furosemide for diuresis, and elevation of the patient's head in relation to the heart for a beneficial gravitational influence. Etomidate has been advocated for use in trauma patients due to its minimal hemodynamic effects, but the resulting adrenal suppression is a disadvantage and it is not used for patients with TBI.[37] Although no significant clinical effects have been reported from single doses of etomidate, long-term use may be associated with increased mortality in multiple-trauma patients.[60,90-92] Approximately 50% of patients with moderate or severe TBI have at least transient adrenal insufficiency (AI). Younger age, greater injury severity, early ischemic insults, and the use of etomidate and metabolic suppressive agents are associated with AI. Lower cortisol levels are associated with lower blood pressure and higher vasopressor use.[93]

Blood pressure is monitored carefully to avoid hypotension (systolic blood pressure) less than 90 mmHg. Hyperosmolar therapy with mannitol 0.25 to 1 g/kg is effective for control of elevated ICP. Steroids have not been shown to improve outcome or reduce ICP.[94]

SPECIAL TOPICS IN TRAUMA ANESTHESIA

Spinal Cord Injury

Approximately 10,000 *spinal cord injuries* (SCIs) occur each year in the United States, and the median age at injury is 25 years. There are more than 250,000 spinal injury patients living in the United States. The leading cause of death in patients with SCI at the scene is respiratory failure from muscle weakness and aspiration. Most injuries occur in young males in the second and third decades of life. The SCI injuries are usually sustained from motor vehicle accidents, falls, assaults, diving injuries, and other sport injuries. Few severe injuries have as devastating physical and psychological effects as those caused by spinal cord trauma. Eventual outcome after an acute SCI depends on three factors: (1) the severity of the acute injury; (2) the prevention of exacerbation of the injury during rescue, transport, and hospitalization; and (3) the avoidance of hypoxia and systemic hypotension, which can further compromise neural function.[95-97] See Table 36-2 for the common mechanisms of spinal injuries.

Most SCIs occur in the cervical spine (55%) with other injuries fairly evenly divided among the thoracic, thoracolumbar, and lumbar regions. The most common resulting injuries are incomplete quadriplegia followed by complete paraplegia, complete quadriplegia, and incomplete paraplegia. SCIs can be categorized as complete or incomplete injuries. Complete injuries represent an absence of motor, sensory, bowel, and bladder function below the level of injury. There is some preservation of neurologic function with incomplete injuries.[98,99] Spinal cord injury should be ruled out in any traumatized individual. The nature of the accident should help guide the diagnosis. The mechanism of injury usually helps in the diagnosis of possible SCI. If an individual has been thrown from an automobile, a 1 in 13 chance exists that a cervical fracture has been sustained. If the victim remains in the car, the chances of such an injury improve to 1 in 436. Cervical SCI should be assumed to be present in any patient who has sustained trauma to the head or face, in any unconscious trauma patient,

TABLE 36-2 Classification of Spinal Injuries

Mechanism of Spinal Injury	Stability
Flexion	
Wedge fraction	Stable
Flexion teardrop fracture	Extremely unstable
Clay shoveler's fracture	Stable
Subluxation	Potentially unstable
Bilateral facet dislocation	Always unstable
Atlanto-occipital dislocation	Unstable
Anterior atlantoaxial dislocation with or without fracture	Unstable
Odontoid fracture with lateral displacement fracture	Unstable
Fracture of transverse process	Stable
Flexion-Rotation	
Unilateral facet dislocation	Stable
Rotary atlantoaxial dislocation	Unstable
Extension	
Posterior neural arch fracture (C1)	Unstable
Hangman's fracture (C2)	Unstable
Extension teardrop fracture	Usually stable in flexion; unstable in extension
Posterior atlantoaxial dislocation with or without fracture	Unstable
Vertical Compression	
Bursting fracture of vertebral body	Stable
Jefferson fracture (C1)	Extremely unstable
Isolated fractures of articular pillar and vertebral body	Stable

From Marx JA, et al. *Rosen's Emergency Medicine*. 7th ed. Philadelphia: Mosby: 2010:341.

BOX 36-1

Six Signs and Symptoms Correlated with Spinal Cord Injuries

Paralysis
Inability to move the arms or legs should always raise suspicion of spinal cord injury.

Pain
Conscious patient may complain of pain localized at the site of the spinal injury.

Position
Patient holding the head upright or the neck with both hands may be indicating a Jefferson-type C1 fracture; the "hold-up" position (arms and hands held over the head as in a robbery) can indicate a C4, C5 fracture; the "prayer position" (arms folded across chest) indicates a possible C5, C6 fracture.

Paresthesias
Complaints of numbness, a "pins-and-needles" sensation, a burning sensation (dysesthesia), or a feeling of electric shock passing down the vertebral column or of water flowing down the back may indicate the presence of a spinal cord injury.

Ptosis
Drooping eyelid and myotic pupil, which are signs of Horner syndrome, may indicate a cervical spinal cord injury.

Priapism
Penile erection occurs in about 3% to 5% of spinal cord injuries. Its presence indicates that the sympathetic nervous system is involved.

and in any patient who complains of pain before or after careful palpation of the cervical spine. The clinician should be aware of the six conditions that are highly correlated with SCIs: paralysis, pain, position, paresthesias, ptosis, and priapism (Box 36-1). A comparison of cervical spine injuries and their acuity is noted in Table 36-2.

If SCI is suspected, care should be taken to prevent further extension of the injury. A properly fitted cervical collar should be carefully placed before the patient is moved or extricated.

Precautions should be taken for the prevention of further extension of actual or potential neurologic deficits. Spinal immobilization should be completed before the patient is moved. The head should be stabilized in neutral alignment with no extension, flexion, or rotation. Stabilization can be accomplished by placing a cervical collar on the patient, splinting, and/or sandbagging the head in neutral alignment. The patient should be placed on a long spinal back board before he or she is moved.[98]

All patients with suspected SCI must be assessed for adequacy of a patent airway. Care should be used to avoid extension, flexion, or rotation of the neck in the attempts to open the airway. A gentle "chin lift" maneuver may be adequate for securing a patent airway without disturbing the neutral neck position. Oxygen should be administered by mask immediately in the patient whose airway is secured at the scene. Hypoxia and hypercarbia can further accentuate the damage sustained with SCIs. These injuries at the C1 or C2 level result in complete respiratory paralysis. Death follows within a few minutes if artificial ventilation is not commenced rapidly. In such patients, a laryngeal mask airway (LMA) or a Combitube airway may be placed in the patient at the scene by paramedics. Although these devices initially may be adequate for allowing transport to a medical facility, they are replaced with an endotracheal tube as quickly as possible after the patient is admitted to a treatment facility.

If the patient with an SCI is breathing spontaneously on arrival at the treatment facility, the adequacy of ventilation should be immediately assessed. If the patient is not able to protect his or her airway (because he or she is unconscious or semiconscious; has an absent or diminished gag reflex or cough; or has intraoral or facial injuries with significant edema, or bleeding, or both), rapid intubation is needed. If ventilation appears to be reasonable, chest and cervical spine radiographic evaluation and neurologic examinations can be started while an arterial blood gas determination is completed. A lateral view of the cervical spine can be obtained quickly, and it reveals most unstable fractures. For a complete evaluation of the cervical spine, multiple films or CT scanning or MRI may be required. An adequate evaluation must include all seven cervical vertebrae; C7 is the most common site of injury.[99]

In children and uncooperative adults or in patients in whom awake intubation fails, a carefully selected dose of propofol and a neuromuscular blocking agent is used for inducing general anesthesia for the intubation.[100] Orotracheal intubation can be safely performed with neck immobilization and inline stabilization. Although there is debate in the literature, it is preferable to intubate these SCI patients orally. SCI patients have the best chance of recovery if hypoxia, hypercarbia, and hypotension are avoided or rapidly corrected if encountered. Arterial blood gas values

indicating that ventilation is suboptimal are corrected by intubation and mechanical ventilation. If there is a delay in establishing the airway, the patient is given ventilation by mask while cricoid pressure is maintained until the airway is secured. Severely traumatized patients who are hypoxic on arrival undergo ventilation by mask with application of cricoid pressure until the intubation is completed. This method prevents further hypoxic insults that can occur during the apneic period between the administration of a muscle relaxant and the completed intubation. Often, time does not allow the luxury of adequate preoxygenation in an already compromised hypoxic patient with respiratory inadequacy. To prevent further hypoxic insult and the resultant potential life-threatening dysrhythmias, these patients are continuously ventilated while cricoid pressure is applied. This measure helps maintain or improve oxygenation until laryngoscopy and intubation are completed.

Use of Muscle Relaxants in Patients with Spinal Cord Injury

As previously discussed, succinylcholine may precipitate cardiac arrest in patients with massive muscle injury or denervation, such as that seen in patients with SCIs, crush injuries of muscles, or burns. The basis for this problem involves supersensitivity and upregulation of the neuromuscular junction to the depolarizing effect of succinylcholine.[101] This phenomenon results in the release of large quantities of potassium during muscle contraction. Normal depolarization results in a small potassium flux across the muscle cell membrane. If a muscle is crushed, burned, or denervated, acetylcholine receptors proliferate around the injured cell, so that when the muscle is depolarized, the flux of potassium is increased significantly.[102] The problem is thought to develop in response to succinylcholine several days after the injury. Succinylcholine is not recommended for intubation of the patient with acute SCI because muscle fasciculation may exacerbate the SCI.[66] It is also contraindicated for routine use in children.[101,102] A conservative approach to caring for patients with SCI would be to avoid the use of succinylcholine by using a nondepolarizing muscle relaxant such as rocuronium or non-relaxant-assisted airway control techniques.[100]

Spinal Shock

A triad of *hypotension*, *bradycardia*, and *hypothermia* frequently results from a relative sympathectomy in SCI patients. The *spinal shock* is progressively intensified the more cephalad the SCI. Patients with SCIs at the T6 level or higher have severely impaired CNS function. Sympathetically mediated cardioaccelerator responses no longer oppose vagal innervation, allowing the heart rate to slow dramatically. Loss of sympathetic tone allows vasodilation, pooling of the peripheral circulation, and decreased venous return to the heart. This situation results in a decreased cardiac output and hypotension. The SCI also interrupts sympathetic pathways from the hypothalamus (temperature control center) to peripheral blood vessels. The patient in spinal shock is unable to constrict vessels or shiver in order to produce heat or to dilate vessels to dissipate heat. The patient's body temperature has a tendency to migrate toward the environmental level.

Treatment

Patients in spinal shock are hypotensive and bradycardic with warm, pink extremities. In contrast, patients in hemorrhagic shock tend to be hypotensive and tachycardic with cold, clammy skin. Use of invasive monitoring is critical for fluid resuscitation and appropriate intervention with vasoactive drugs—often norepinephrine infusion. An indwelling arterial catheter is mandatory in the acute phase of spinal shock. Moment-to-moment control of arterial blood pressure is essential for the replacement of fluids and for the use of vasoactive drug therapy. In addition, arterial blood gas assessments are facilitated by an indwelling arterial catheter.

The SCI patient is frequently unable to maintain adequate cardiac filling pressures. However, over-aggressive fluid therapy can precipitate pulmonary edema. For the maintenance of adequate arterial blood pressure and cord perfusion, pressor therapy may be initiated.

Other Considerations

Patients with SCI are extubated as quickly as possible after spinal stabilization surgery. If the patient requires intubation because of associated pulmonary injuries or dysfunction, then a weaning program is started when it can be tolerated by the patient. With frequent assessment of respiratory status, this weaning is usually begun within the first few days. Useful guidelines for assessing the adequacy of ventilation include measurement of the tidal volume (greater than 5 mL/kg), negative inspiratory force (−20 to 25 cm H_2O pressure—needed for adequate cough), and vital capacity (greater than 15 mg/kg). Patients with a high SCI often lose innervation of the intercostal and abdominal musculature.

For these reasons, continued assessment of adequate diaphragmatic innervation, a characteristic needed for the generation of adequate ventilation, is mandatory. Some patients require tracheostomies. Chest physiotherapy is initiated for all patients as soon as possible in order to reduce the risk of pulmonary congestion and infection. Oral or nasogastric tubes are placed for decompressing the stomach. This measure eases diaphragmatic excursion for improved ventilation and reduces the risk of aspiration. Peptic ulceration with loss of sympathetic innervation in the patient with a high SCI is a well-described complication, especially in patients receiving steroids.

Surgical Intervention and Anesthesia Approach

Although external immobilization devices, including a Halo vest, are sometimes used, many neurosurgeons believe that prolonged use of external fixation devices is contraindicated in patients with unsatisfactorily reduced spines. Frequently, spinal stabilization and/or decompression procedures are performed after initial resuscitation and diagnostic workup.

The neurosurgeon and anesthesia team document the current neurologic status and note any deficits before the start of anesthesia and intubation. In an awake intubation, the patient is assessed before and after endotracheal tube placement and after the patient is positioned for surgery.

Whether an anterior or a posterior surgical approach is used in cervical SCI depends on the nature of the injury. Internal fixation devices are commonly placed in the acute phase for stabilization of lower SCIs. At times, these procedures can be associated with significant surgical blood loss. Careful monitoring and replacement of blood loss are essential. Use of an autotransfusion device often saves considerable banked blood use in these procedures.

In patients deferred for elective spinal stabilization procedures, awake fiber optic intubations are performed. In controlled conditions, this measure allows the use of local, topical, and transtracheal anesthesia without the risk of pulmonary aspiration that is present in emergency procedures. Glycopyrrolate is commonly given before administering local anesthesia to the airway as an antisialagogue. Once moderate sedation is accomplished, superior laryngeal nerve block, topical oral pharyngeal, and transtracheal sprays are applied as necessary. At this point there are no data that suggest that nasal intubation is superior to oral intubation. It is preferable that endotracheal intubation be done orally if it can be accomplished safely. Anesthetic techniques that avoid

hypotension and provide good cardiovascular stability are recommended. Baseline analgesia is provided with opioids (generally fentanyl, sufentanil, or remifentanil). Muscle relaxation is provided with a nondepolarizing neuromuscular blocking agent to promote cardiovascular stability. Succinylcholine is avoided during the patient's remaining lifetime after a spinal cord injury with permanent neuromuscular deficits.

Nitrous oxide is avoided because many SCI patients may have a head injury or possible pneumothorax. Following head injury, nitrous oxide can cause a pneumocephalus to develop, with a subsequent rise in the intracranial pressure. Following injury to the chest wall, use of nitrous oxide with positive pressure can cause rapid expansion of a subclinical pneumothorax into a rapidly increasing and life-threatening pneumothorax with mediastinal shift.

Ketamine can be useful as an induction agent in unstable patients. Ketamine produces a transient increase in ICP; however, many clinicians consider this action secondary to maintaining stable vital signs, and consequently, it is often used in these situations.[103,104] Dexmedetomidine is also a useful adjunct.

Autonomic Hyperreflexia (Mass Reflex)

Trauma centers are chosen quite often to treat acute trauma patients during the initial hospitalization and also for future related surgery. In this setting, the anesthesia plan addresses the implications of *autonomic hyperreflexia,* which is a sudden massive sympathetic discharge resulting from stimulation below the level of spinal cord transection. Hyperreflexia is seen in 85% of SCI patients with lesions above T5 to T8. Signs of this condition include paroxysmal hypertension, bradycardia, and cardiac dysrhythmias in response to stimuli below the level of transection (such as bladder catheterization). Hyperreflexia is not observed until the spinal shock phase has passed. It is therefore usually seen when patients return to surgery for such procedures as cystoscopies, performed later in their recovery phase.

Autonomic hyperreflexia is caused by stimulation below the level of the lesion—typically caused by distention of the bladder or rectum that is caused by defecation, childbirth, and even cutaneous stimulation. It can occur intraoperatively with local, spinal, and nitrous oxide–opioid general anesthesia.

If autonomic hyperreflexia occurs, it is treated by removal of the stimulus, deepening anesthesia, and administration of direct-acting vasodilators. Untreated, the hypertension crisis may progress to seizures, intracranial hemorrhage, or myocardial infarction. No episodes have been reported with the use of potent inhalation anesthetics. Bradycardia is treated with atropine or glycopyrrolate.

Orthopedic Injury and Trauma Anesthesia

Although most *orthopedic injuries* are not usually immediately life threatening and are considered in the secondary evaluation of the trauma patient, they can be associated with significant hemorrhage and other extensive systemic physiologic derangements, such as shock, fat emboli, and thromboembolic hypoxic respiratory failure. Major hemorrhage associated with fractures requires massive intraoperative fluid resuscitation, although rapid exsanguination from major fractures is unlikely. Modern intramedullary rodding devices often allow patients to ambulate within 24 hours of surgery, drastically reducing the incidence of thrombophlebitis and its subsequent morbidity.[105]

Because the ideal time to repair open fractures operatively is within the first few hours after injury, all patients brought to the operating room for emergency surgical repairs are considered to have full stomachs and are anesthetized with techniques that are aimed at reducing the risk of aspiration. Certain secondary vascular injuries commonly occur with specific fracture sites because the sharp edges of fractured bones are forced into blood vessels and nerves in proximity to the fracture site.[106]

Massive hemorrhage can be associated with pelvic fractures. The displaced pelvic fragments can sever the arteries, veins, and nerves that exit the pelvis to the perineum and the lower extremities. This can result in major blood loss into the retroperitoneal space, with continued hemorrhage from movement of unstable fragments that shear away hemostatic elements that have formed in these ruptured blood vessels. Although blood loss from pelvic fractures involving the iliac artery is notorious, significant blood loss also can occur from fractures associated with disruption of the axillary, brachial, femoral, and popliteal arteries.

Severe shock can result from major bleeding into fracture sites, particularly in pelvic and long-bone fractures. Close monitoring and replacement of initial and ongoing blood loss are needed during the anesthetic management of these cases.

Hypoxic respiratory failure is a common sequela of long-bone fractures. The hypoxia results from continuous seeding of marrow fat into the venous circulation. All patients with major fractures, especially fractures of the lower extremities and pelvis, receive frequent assessment of arterial blood gases. Endotracheal intubation and mechanical ventilation are recommended for the treatment of fracture-induced hypoxia and the prevention of further lung damage. If patients are extubated immediately after fracture fixation, despite evidence of poor oxygenation and a large pulmonary venous admixture, they may develop acute respiratory distress syndrome and fat emboli syndrome. These patients benefit from continued mechanical ventilation and positive end-expiratory pressure (PEEP) that is titrated for the reduction of intrapulmonary shunting.[107]

Continuum of Care

Recovery from serious, traumatic injury is often a prolonged process. The practice of damage control surgery is to provide rapid, life-saving procedures and delay definitive repair until after the patient has been stabilized. Based on a variety of factors, patients may experience complications such as multiorgan failure, ARDS, prolonged mechanical ventilation, and infection as they convalesce. During this time, patients may require a variety of surgeries ranging from simple washouts of wounds to open reduction of the pelvis or to thoracic or abdominal surgeries. Patients may be transported to the operating room while intubated, or may be on vasoactive pressers, insulin, or total parenteral nutrition. Whether ICU therapy will be continued in the operating room is unclear; often this determination is provider/institution dependent.

Unfortunately there are currently very little anesthetic-ICU data that can quantify the positive or negative impact of anesthetic care on patient outcome. Many reasons could account for this gap. The particular injury and its degree of severity, coexisting disease, lack of ICU-anesthesia experience, and the amount of surgical time are likely just a few of the variables that cloud obvious anesthetic-related outcomes. It is important to recognize that actual anesthetic time is typically a fraction of the hospital course of critically injured patients. As such, the magnitude of the effect of anesthesia is largely unknown—or ignored.

Despite this general gap in clinical knowledge, it is logical to recognize the need to coordinate care throughout the surgical course of the trauma patient. The benefits of coordinated care have been demonstrated in some surgical–critical care literature; these include reducing hospital length of stay and reducing ventilator-associated sequela.[108,109] Recognition of the importance of maintaining the continuum of care from the ICU to the operating room

is paramount, and the anesthetic should always be tailored to the patient rather than tailoring the patient to a specific anesthetic.

SUMMARY

Traumatic injury is a leading cause of morbidity and mortality in the United States and around the world. Despite development, innovation, and changes to public policy, traumatic injury continues to pervade modern society. Consequently, a comprehensive understanding of trauma care is important for modern anesthesia practice. Trauma management has moved away from the community-based level and developed into a systems-based approach, coordinating prehospital care with larger centers, public policy, and a rational approach through use of ATLS. The organization of trauma care in the United States has substantially improved survival and quality of outcomes for severely injured patients.

Ideally, the anesthetist's involvement should begin as soon as the patient reaches the trauma facility. Care should follow the general algorithm developed in ATLS. Anesthesia providers and the trauma team should focus on ensuring an adequate airway and breathing while diagnosing and controlling injuries almost simultaneously. The principles of successful management of the trauma patient are based on organization and preparation, assessment of the patient's injuries, proper priority for therapeutic interventions, achievement and maintenance of a patent airway, fluid resuscitation, application of appropriate continuous invasive and noninvasive monitoring, correction of acid-base and electrolyte disturbances, and careful titration of anesthetic and adjunctive agents.

The degree of functional outcome of trauma patients is largely dependent on the early involvement of sound principles of anesthesia care in the resuscitation and overall anesthetic management during the perioperative period. In a well-managed team approach, assessment and treatment are carried out in rapid succession or even simultaneously.

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CHAPTER 37

Outpatient Anesthesia

◆ *Rex A. Marley and Troy Calabrese*

The concept of outpatient anesthesia is not unique to the past three decades. It was introduced in dentists' offices with the administration of nitrous oxide. Physicians' offices were next to offer this type of service for superficial procedures that required at most the administration of local anesthesia. In 1909, Nicoll[1] first reported on 8988 outpatient surgical procedures performed at the Glasgow Royal Hospital for Sick Children. In 1916 in Sioux City, Iowa, Waters[2] opened the first freestanding unit designed for outpatient surgery.

The evolution of and demand for outpatient care have not slowed since first described by these pioneers. Surgical innovation, new anesthetic drugs and techniques, and changes in insurance carrier demands have increased the type and number of procedures performed at ambulatory care centers or traditional hospital operating rooms. Within the United States, outpatient procedures at freestanding centers increased nearly 300% between 1996 and 2006. An estimated 35 million outpatient surgical procedures were performed in 2006. The most common ambulatory procedures included myringotomy and tonsillectomy for patients under 15 years of age, large intestine endoscopy and therapeutic injection for patients aged 15 to 44 years, and intraocular lens extraction for patients 75 years or older. Currently, more than 62% of all elective procedures are performed on an outpatient basis.[3] In addition, difficult procedures performed even on patients with complex medical conditions are more routinely being performed on an outpatient basis. It is the responsibility of the attending anesthesia provider to ensure that these complex medical conditions are managed optimally before, during, and after the procedure.

It is expected that the patient will enter the outpatient surgical care facility, undergo the procedure, and then be released without needing an overnight stay. Outpatient surgery, in addition to office-based and free-standing ambulatory surgery centers, includes the "23-hour observation" patient, who may be admitted to the inpatient or overnight facility yet is discharged before staying in the hospital 24 hours. Surgical procedures requiring the expertise of an anesthesia provider in the office setting are becoming increasingly popular. Office-based surgery can be performed more efficiently and at lower cost than surgery performed in the hospital.[4] Presently, 12 million operations annually, representing about 10% of all outpatient procedures, are performed in an office-based setting.[5] Optimal anesthesia and surgical techniques for office-based surgery are similar to ambulatory procedures performed at traditional ambulatory surgical centers. Although office-based surgery can be performed safely, it is not without risk. Current issues of discussion include patient and procedure selection, recovery, complication management, perioperative management, and facility requirements.[6] Office-based anesthesia practice standards and guidelines have been developed by the American Association of Nurse Anesthetists (AANA),[7] the American Society of Anesthesiologists (ASA),[8] and the Joint Commission.[9]

FEATURES OF OUTPATIENT SURGERY

Advantages

Financial

An advantage of ambulatory surgical settings has been the economic benefit for consumers, third-party payers, and medical facilities. Patients may benefit not only from reduced medical cost but also from minimized costs of outside child care and from resumption of normal living activities at an earlier time. Third-party payers concerned about cost containment are increasingly identifying procedures that may be performed *only* in the outpatient setting. Cost savings exceeding 50% have been reported for selected surgeries (e.g., laparoscopic cholecystectomy) performed on an outpatient basis.[10] Ambulatory centers, secondary to their design, facility layout, and patient selection, tend to operate more efficiently than hospital-based operating theaters in regard to surgical volume.

Medical

One medical advantage of ambulatory surgery is the increased availability of hospital beds for patients requiring hospital admission. For patients who are susceptible to infection (e.g., children, immunosuppressed patients, cancer patients, and transplant recipients), minimizing time and contact in the inpatient hospital setting may decrease the risk of nosocomial infections.[11]

Patient Satisfaction

Patients report greater satisfaction with outpatient procedures because of shorter waiting times and lower costs.[12,13] Delays secondary to lack of available beds, as seen with inpatient facilities, are less likely to occur.

Social

Children benefit from outpatient surgery because it minimizes separation from parents and causes less disruption in a child's feeding schedule. The continued presence of and care offered by the parents are especially beneficial for children with mental or physical impairments.[14] Geriatric patients show better cognitive and physical capacity when separation from familiar surroundings and family is minimized. The elderly are better able to maintain their normal living routines (e.g., diet, medication, and sleep pattern). Postoperative confusion is decreased in geriatric patients undergoing outpatient procedures because they receive less medication and are returned to a familiar environment sooner than their inpatient counterparts.[15]

Staffing

The ambulatory surgery setting is more convenient than the inpatient surgery setting for the staff because it offers more efficient use of time, uniform work schedules, and more predictable surgical outcomes.

Disadvantages

The outpatient setting may have several disadvantages:

- The degree of patient privacy is less than that in the inpatient setting.
- The patient must make multiple trips to the physician's office or the ambulatory setting for evaluation and screening.
- Adequate home care must be ensured once the patient is discharged from the facility after surgery.
- Compliance and efficacy related to preoperative and postoperative instructions may not be as good as when the patient is admitted to the hospital before surgery.
- Because of the emphasis on efficiency, children have less time to adapt to the surgical setting than they would as inpatients.
- Observation time and monitoring for the occurrence of adverse events are decreased in the outpatient setting.
- Management of complications can be problematic at a freestanding or office-based facility secondary to a lack of resources.

Demographic Considerations

Patient Age

Patients of any age can receive outpatient anesthesia; age should not be a limiting factor when determining appropriateness for ambulatory procedures. Approximately 6% of outpatients are younger than 15 years, and more than 14% are at least 75 years of age.[3] More than 60% of all anesthesia administered for pediatric surgery is performed on an outpatient basis.[14]

Surgical Time

Earlier guidelines recommended limiting the amount of time of an outpatient surgery to less than 1.5 to 2 hours.[16] The reasoning was that the longer surgery lasts, the more likely patients will experience severe pain or vomiting.[17,18] Surgical time exceeding 2 hours was also thought to be a strong predictor for delayed discharge and unplanned hospital admission postoperatively.[19] However, other factors such as the skill of the surgeon, the type of surgery performed, the patient's condition, and the anesthetic technique used must be considered. Arbitrarily limiting the length of surgery to less than 2 hours is no longer considered necessary; procedures exceeding 4 hours are routinely performed without complications in ambulatory centers.

Suitable Procedures

The list of procedures suitable for the ambulatory setting is constantly evolving. Endoscopy of the large and small intestine is the most common type of outpatient procedure, and ophthalmologic surgery is the second most common.[3] The outpatient surgical procedure should not involve extensive blood loss or physiologic shifts of considerable fluid volumes because these processes necessitate protracted patient observation and hydration. In the past, the potential for blood transfusion implied the need for the procedure to be conducted at an inpatient facility. Now the increasing popularity of autologous blood donation for possible future transfusion has facilitated the application of transfusion during or after the outpatient surgery when needed.[20]

The list of surgical procedures deemed acceptable for outpatient surgery is ever expanding; routinely included are surgeries such as laparoscopic cholecystectomy,[21] lumbar laminectomy,[22] cervical laminectomy and fusion,[23] thyroidectomy,[24] hysterectomy,[25] and tonsillectomy.[26] The norm regarding suitable outpatient procedures continues to be challenged, with the addition of more potentially higher-risk procedures, that is, craniotomy for tumor,[27-29] adrenalectomy,[30] and gastric bypass surgery.[31] Facilities with a 23-hour observation area designed for extended patient assessment is often the desired location for procedures such as outpatient tonsillectomy and higher-risk procedures.

Procedures requiring prolonged immobilization are best conducted on an inpatient basis. For procedures associated with postoperative discomfort, arrangements for parenteral opioid therapy in the home may be made, provided that adequate pain relief can be achieved with safe doses of opioids.

PATIENT SELECTION

Proper patient selection minimizes the number of hospital admissions that follow outpatient surgery. Primary predictors of unanticipated hospital admission are related to the type of surgical procedure and subsequent complications, that is, nausea and vomiting, pain, or significant operative fluid shifts or blood loss. Evaluation of patients to determine who is appropriate for outpatient surgery and anesthesia requires consensus and cooperation between the surgical and anesthesia staff. Factors to consider in determining the suitability of a patient for outpatient surgery include the following:

- *The anticipated surgical procedure for the patient.* The proposed surgery should have an insignificant incidence of intraoperative and postoperative problems and should not require intense postoperative patient management.
- *The physical and psychosocial health of the patient.* The patient is ideally in his or her usual good health, or if ill, the condition should be well controlled. A reduction in postoperative complications has been shown if the patient's medical condition is stable for at least 3 months before surgery.[32] The patient and family should be receptive to the outpatient philosophy and the perioperative adaptations that will be required of them.
- *The surgeon's skills and cooperation.* Early referral to the anesthesia department for patients of questionable appropriateness helps streamline the outpatient process and minimize delays on the day of surgery.

Selection Criteria

Acute Substance Abuse

The patient with a history of substance abuse should be evaluated before the day of surgery. Counseling for such patients includes the warning that preoperative substance abuse will lead to cancellation of the surgery. A distinction between long-term and acute substance abuse must be made. A urinary drug screen should be performed in patients suspected of substance abuse. The patient with signs of acute substance intoxication is an inappropriate ambulatory surgery candidate because of the increased likelihood of impaired autonomic and cardiovascular responses. The surgery should be rescheduled after the patient is detoxified and treated. Patient management strategies should emphasize methods of minimizing postoperative pain, because substance abusers are typically intolerant to pain. Regional or local anesthetic techniques, if their use is suitable to the surgeon and appropriate for the type of operation being performed, may be used if the patient wishes to abstain from sedatives and opioids. Postoperatively, pain may be minimized by the use of local wound infiltration, regional techniques, and the prophylactic use of nonsteroidal analgesics. Placing a catheter in the wound and instilling local anesthesia, either continuously or intermittently, has been shown to prolong pain relief and improve patient satisfaction and should be considered for this patient population.[33]

Age

Patient age by itself should not be the deciding factor for outpatient suitability. Meridy[34] retrospectively examined the charts of

patients ranging in age from 9 months to 92 years and noted that most perioperative complications occurred in the 20- to 49-year age group. Patients older than 85 years, who required multiple hospitalizations within 6 months of the surgery, have been shown to have an increased risk of unanticipated hospitalization and death after outpatient surgery.[35] Although multiple medications and preexisting comorbidities are more likely in the elderly, there is a paucity of data supporting increased adverse outcome in these high-risk elderly patients.[36]

Premature Infant. The premature infant (gestational age of 37 weeks or less at birth) is an inappropriate candidate for outpatient surgery because of potential physiologic aberrations. The premature infant may:

- Exhibit anemia
- Not have fully developed gag reflexes (and thus be more prone to aspiration of liquid or solid food)
- Have immature temperature control and be susceptible to the effects of hypothermia, which could contribute to postoperative apnea
- Demonstrate immature brainstem functioning, which predisposes the infant to pathologic respiratory conditions

The infant with a hemoglobin value less than the predicted normal value for that age will require additional evaluation before surgery. Hemoglobin values in the premature infant may drop to between 7 and 8 g/100 mL, 1 to 3 months after birth.[37] The presence of anemia (hematocrit less than 30%) may increase the incidence of apnea in the newborn.[38] Some investigators have recommended delaying elective surgery until the hematocrit is increased to greater than 30% through supplementation of iron intake.[39]

In the perioperative period, the preterm infant is at greater risk for developing respiratory complications, including apnea, than is the full-term infant.[38] The preterm infant is susceptible to short apnea (6 to 15 seconds), prolonged apnea (greater than 15 seconds), or periodic breathing (three or more periods of apnea of 3 to 15 seconds separated by less than 20 seconds of normal respiration). Short or prolonged apnea and periodic breathing predispose the infant to hypoxemia and bradycardia. An obstructive component that leads to quicker oxyhemoglobin desaturation appears to be part of postoperative apnea in these infants.[40] These infants have developed prolonged apnea as late as 12 hours after surgery.[38]

The older the infant, the less likely that respiratory complications such as apnea will occur. In evaluating the suitability of a former preterm infant for outpatient surgery, conservative measures are best; inpatient status should be assigned if significant concerns exist. These patients benefit from the intensive monitoring available in the inpatient setting. Much discussion has been held as to the postgestational age (gestational age plus postnatal age) at which the former preterm infant may safely undergo outpatient anesthesia. Healthy former premature infants whose postgestational age is less than 50 to 60 weeks[41,42] should be admitted to the hospital for extended monitoring. Postoperative apnea has been described even in the full-term infant.[44] The ability to exactly predict the susceptibility of an infant to postoperative apnea is lacking.[45] Patients should be evaluated individually for appropriateness for outpatient surgery, and consideration should be given to growth and development, feeding problems, upper respiratory tract infections (URTIs), apneic history, and disorders of metabolic, endocrine, neurologic, or cardiac systems. All infants with a history of prematurity should be closely observed for signs of apnea and bradycardia. If any of these signs are evidenced in the postanesthesia care unit, patients should be admitted and observed. An infant with a history of apnea or bradycardia must be apnea free and without monitoring for at least 6 months to be considered for outpatient surgery.[43] Efforts should be made to schedule surgery for these patients as early in the day as possible to allow for extended observation time.

Beyond simply delaying surgery, attempts to minimize the likelihood of postoperative apnea in susceptible infants have been examined. Spinal anesthesia without sedation resulted in less prolonged apnea, oxyhemoglobin desaturation, and bradycardia than did general anesthesia or spinal anesthesia with ketamine sedation.[39] However, apnea and delayed respiratory failure have been reported in children who have had spinal or caudal anesthesia.[45] Infants treated with endotracheal intubation or mechanical ventilation (or both) for respiratory distress syndrome at birth have been shown to have abnormal arterial blood gas values and abnormal pulmonary function results as late as 1 year after treatment.[46] Infants exhibiting signs of bronchopulmonary dysplasia should not be considered for outpatient surgery.[47] Patients with a history of bronchopulmonary dysplasia are at risk for sudden infant death.[48]

Infants with a history of apneic events or who have siblings who developed sudden infant death syndrome (SIDS) are at risk for SIDS. The greatest at-risk age for the development of SIDS is between 1 month and 1 year of age.[49] In infants who have lost a sibling to SIDS, the risk of dying from the same syndrome is four to five times that of the general population.[50] Patients at risk for the development of SIDS should not be considered for outpatient surgical procedures until they are at least 6 months to 1 year old.[51]

Full-Term Infant. Healthy, full-term infants (older than 37 weeks' gestational age at birth) can be considered for minor outpatient surgery. Full-term infants with histories of apneic episodes, failure to thrive, and feeding difficulties are not suitable candidates for outpatient surgery. Infants with a history of respiratory difficulties at birth are not suitable outpatient candidates unless they are free of respiratory symptoms at the time of surgery and at the time of hospital discharge.[51] There are no formal practice guidelines from major anesthesia or pediatric organizations regarding outpatient surgery in infants. However, individual hospitals frequently establish a cutoff age of 50 to 56 weeks of postconceptual age in infants born before 37 weeks, and also consider factors such as anemia, prior apnea, and coexisting disease. Postoperative monitoring recommendations range from 12- to 24-hour admission for cardiorespiratory monitoring. Some facilities also restrict day surgery procedures for term infants to only those infants older than 44 to 46 weeks of postconceptual age, or the facilities require a longer observation period (e.g., 4 hours) in phase II recovery.[52] Some evidence-based suggested guidelines are listed in Box 37-1.

Geriatric Patient. The decision of whether to perform ambulatory surgery on a geriatric patient (age 65 years or older) should be individualized and based on physiologic age rather than on chronologic age. Existing medical problems are a concern when considering the geriatric patient for outpatient surgery. There are more concomitant age-related diseases that should be optimally treated preoperatively in this group of patients. Patient age exceeding 85 years is a predictor of hospital admissions after outpatient surgery.[35,53] Thoughtful preoperative planning for the elderly patient's post-discharge care is paramount to ensure a safe and successful outpatient experience. The elderly population presenting for outpatient surgery has increased dramatically and will continue to increase as the population ages.[54] Appropriate home care and transportation to and from the outpatient center with a responsible caregiver must be ensured.

Special Considerations

Convulsive Disorders. Surgery for patients with seizure disorders should be scheduled early in the day so patients can be observed

BOX **37-1**

Suggested Guidelines for Outpatient Surgery in Infants

- Appropriate short-acting anesthetic agents may facilitate emergence and discharge.
- Where possible, regional anesthetic techniques and nonopioid analgesics should be used instead of opioids.
- A loading dose of caffeine citrate 20 mg/kg may decrease postoperative apnea in former premature infants.
- If the surgical procedure is suitable, consider spinal anesthesia without sedation in former premature infants; however, postoperative monitoring is still recommended in the at-risk age range.
- Former premature infants should be admitted for observation unless they are over 54 to 56 weeks of postconceptual age (depending on degree of prematurity) and are without anemia, ongoing apnea, or other significant medical problems. Infants meeting these criteria also need to have had an uneventful anesthetic and recovery room course before consideration of discharge.
- Term infants are acceptable for outpatient procedures providing they are otherwise healthy, the procedure is not likely to result in significant physiologic changes or postoperative pain requiring opioid medications, and the anesthetic proceeds uneventfully. It may be prudent to monitor these patients in the recovery area for several hours postoperatively.
- All infants should be cared for in a facility with adequate and appropriately sized equipment, and medical and nursing staff with appropriate expertise and adequate ongoing experience in caring for this age group.

From Everett LL. How young is the youngest infant for output surgery. In: Fleischer LA, ed. *Evidence-Based Practice of Anesthesiology*. 2nd ed. Philadelphia: Saunders; 2009:469-474.

for 4 to 8 hours after the operation before they are discharged. It is important to establish the patients' ability to maintain their schedule for anticonvulsant medications. Patients with uncontrolled seizure activity are not deemed appropriate for outpatient surgery by most institutions.

Cystic Fibrosis. The extent of pulmonary involvement is the primary determinant of appropriateness for ambulatory surgery in patients with cystic fibrosis. Such patients should be evaluated several days before the proposed surgery; patients with symptomatic respiratory distress are better treated in an inpatient setting, where appropriate respiratory-care management and hydration can be administered.[55] Protective airway measures should be instituted in the cystic fibrosis patient secondary to an increased risk of gastroesophageal reflux disease and pulmonary aspiration.[56]

Malignant Hyperthermia Susceptibility. Malignant hyperthermia susceptibility is impossible to predict because it occurs in phenotypically normal individuals.[57] A malignant hyperthermia (MH)–susceptible patient is defined as having one or more of the following[58-63]:

1. A previous episode of MH
2. Masseter muscle rigidity with previous anesthesia
3. A first-degree relative with history of an MH episode or positive muscle biopsy
4. Diseases with known mutations on chromosome 19; may include, but are not limited to, central core myopathy, King-Denborough syndrome, Native American myopathy, and hypokalemic periodic paralysis
5. Patients with heat-induced rhabdomyolysis

Diseases not associated with MH susceptibility include mitochondrial myopathies, Noonan syndrome, osteogenesis imperfect, and neuroleptic malignant syndrome.[57]

The MH-susceptible patient who has received a trigger-free uneventful anesthetic does not require overnight hospitalization based exclusively on being MH susceptible. The ambulatory facility should have the requisite monitoring and resuscitation capabilities, including a minimum of 36 vials of dantrolene, for managing the MH patient.[64] A point-of-care monitor (capable of measuring blood gases and electrolytes) and urinalysis with a dipstick (to detect myoglobinuria) are useful monitoring devices used in the free-standing ambulatory center.[65] The patient should be scheduled as early in the day as possible to allow for extended patient observation for at least 1 hour in the postanesthesia care unit (PACU) plus an additional hour in phase 2 recovery, and the lack of symptoms of MH should be ensured before discharge is considered.[66] A patient who exhibits marked rigidity of the jaw muscles should not be discharged. Overnight observation is required for temperature rise, myoglobinuria, elevated creatine kinase (CK) levels, or progression to an MH episode. Patients who experience milder increases in jaw tension should be observed for signs and symptoms of MH for at least 12 hours. If there is evidence of myoglobinuria (i.e., dark, cola-colored urine), elevated temperature and pulse rate, or abnormality of acid-base balance, the patient should be emergently transferred and admitted to the nearest full service facility and observed overnight.[66,67] Written discharge instructions should include: (1) how to monitor the patient's temperature at home, (2) how to recognize the signs and symptoms of MH, and (3) contact information if emergency medical advice is required.[68]

Morbid Obesity. The uncomplicated morbidly obese patient is an appropriate candidate for select outpatient surgery.[69] The morbidly obese patient with significant preexisting cardiac, hepatic, pulmonary, or renal disease has to be evaluated on an individual basis and may best be managed as an inpatient. Late problems are more likely to occur when the body mass index (BMI) reaches 35 to 40 kg/m^2; this was once considered to be the cutoff point for ambulatory surgery. With the introduction of select bariatric procedures into the outpatient setting, this exclusionary criterion has been reevaluated. A higher incidence of postoperative hypoxemia has been observed in patients with a BMI of 35 kg/m^2 or higher.[70] However, unanticipated hospital admission after ambulatory surgery was not increased in obese patients with an average BMI of 44 kg/m^2.[71] The laparoscopic adjustable gastric banding procedure has opened the door for bariatric surgery to be performed on an outpatient basis, because this procedure does not open the digestive tract.[72-74] Initial reports of outpatient laparoscopic Roux-en-Y procedures are being investigated for safety and appropriateness.[75] The ability to sufficiently manage postoperative pain and address postoperative ambulation should be discussed preoperatively by the surgeon and anesthesia provider. The morbidly obese patient is at risk for persistent hypoxemia in the PACU, which may necessitate overnight supplemental oxygen therapy.

Morbid obesity is associated with an increased risk of obstructive sleep apnea (OSA).[76] Preoperative airway evaluation (e.g., Mallampati classification, nuchal girth, redundant pharyngeal tissue) is important. A high Mallampati airway classification, reduced thyromental distance, and restricted mandibular mobility were predictive of difficult endotracheal intubation, yet an increasing BMI was not associated with difficulty.[77] An assessment of intubating conditions in the patient with OSA found a 22% incidence of difficult endotracheal intubation.[78] The likelihood of

a difficult airway has to be assessed preoperatively, and the ability to manage the difficult airway has to be ensured.

If continuous positive airway pressure (CPAP) is part of the patient's management of OSA, the patient, undergoing general anesthesia, should be instructed to bring his or her CPAP machine into the surgery center for use in the immediate postoperative recovery phase. Intraoperative benzodiazepine[79] and opioid usage, out of concern for worsening airway obstruction, should be minimized or avoided in these patients, and pain should be controlled with alternative techniques (e.g., nonopioid analgesics, regional anesthesia techniques, local wound infiltration with local anesthesia) when possible.[80] Moderate to severe OSA patients requiring postoperative opioids should not undergo ambulatory surgery.[81]

No increase in unanticipated hospitalizations has been shown in OSA patients who are deemed eligible to undergo ambulatory surgery.[82,83] The decision concerning whether to provide for the patient with OSA in the ambulatory setting should be contingent on certain criteria being met. The Society for Ambulatory Anesthesia has recently released a consensus statement on preoperative selection of adult patients with OSA scheduled for ambulatory surgery. Patients with a known diagnosis of OSA and optimized comorbid medical conditions can be considered for ambulatory surgery if they are able to use a continuous positive airway pressure device in the postoperative period. Patients with a presumed diagnosis of OSA, based on screening tools such as the STOP-Bang questionnaire, with optimized comorbid conditions can be considered for ambulatory surgery if postoperative pain can be managed predominantly with nonopioid analgesic techniques. On the other hand, OSA patients with nonoptimized comorbid medical conditions may not be good candidates for ambulatory surgery. All obese patients should be assessed with the STOP-Bang questionnaire as part of the preoperative evaluation (see Box 43-2). A score greater than 3 indicates a high suspicion for OSA. As noted above, unless the patient's comorbid conditions are optimized and they are able to use CPAP after discharge and achieve postoperative pain relief without opiates, they are not candidates for outpatient surgery (Box 37-2).[84] Strict adherence to preoperative eligibility requirements and home care protocols is essential.[85] Consideration should be given to scheduling these patients early in the day to allow for prolonged observation of an additional 3 hours prior to discharge.[86] Patients with obstructive sleep apnea may be considered for discharge home if they are without (1) signs of moderate to severe OSA, (2) recurring PACU respiratory issues, that is, apnea, bradypnea, oxyhemoglobin desaturation, and (3) potent postoperative opioids for analgesia.[87]

Reactive Airway Disease. Before surgery is performed, the severity of reactive airway disease must be assessed, and optimal disease management should be achieved. A chest radiograph is indicated only if the patient is suspected of having an acute infiltrative process or if deterioration in the patient's physical condition has occurred. Likewise, arterial blood gases are indicated when signs and symptoms of chronic respiratory insufficiency are suspected. The patient may be best managed as an inpatient if indications for a chest radiograph or arterial blood gases are met. Consultation with the patient's internist may help in formulating therapeutic modalities and establishing baseline conditions for this patient. Patients receiving long-term medication therapy should continue to take their medications until the time of surgery. All parties involved must anticipate the possibility of admitting the patient to the hospital if the symptoms of the disease become exacerbated.

Sickle Cell Disease. The possibility of sickle cell hemoglobinopathy should be considered in every African American when obtaining the preoperative medical history. If individual or family history is suggestive of the disease, a Sickledex may be obtained in children 6 months of age and older to determine the presence of sickle-shaped red blood cells.[88] The patient with sickle cell disease is at risk for crisis development if acidosis, dehydration, or hypoxia occur. These patients often present for cholecystectomy because cholelithiasis is a well-recognized complication of chronic hemolysis.[89]

The select patient diagnosed with sickle cell disease is an acceptable outpatient candidate, but this patient is not without risk.[90] Sickling of the red blood cells may occur when the patient with sickle cell trait is subjected to hypoxia.[91] If the patient with sickle cell anemia is to be cared for in the ambulatory setting, certain criteria must be satisfied:

1. The patient should have no major organ disease as a result of the sickle cell disease.
2. The patient should not have had a sickle cell crisis for at least 1 year.
3. The patient should be compliant with the prescribed medical care.
4. On discharge, the patient should be within 15 minutes' travel time to a facility prepared to care for the patient.
5. The patient should receive close follow-up postoperative care.

The procedure should not be a prolonged surgery that is associated with blood loss. The patient should arrive earlier than normal so adequate intravenous hydration can be established. The patient's surgery should be scheduled early in the day to allow for extended postoperative monitoring before the patient is discharged from the ambulatory center.

BOX **37-2**

The Society for Ambulatory Anesthesia Consensus Statement on Preoperative Selection of Adult Patients with Obstructive Sleep Apnea Scheduled for Ambulatory Surgery

- Patients with known OSA whose comorbid conditions are optimized and are who are able to use CPAP after discharge are candidates for ambulatory surgery.
- Patients with known OSA whose comorbid conditions are not optimized are not candidates for ambulatory surgery and may benefit from further treatment.
- Patients with a presumptive diagnosis of OSA, optimized comorbid conditions, and postoperative pain that can be managed with nonopioid analgesics are candidates for ambulatory surgery.
- Patients with a presumptive diagnosis of OSA and nonoptimized comorbid conditions are not candidates for ambulatory surgery and may benefit from further treatment.

All obese patients should be assessed via the STOP-Bang method for presumptive OSA (see Box 43-2).

Comorbid conditions include hypertension, arrhythmias, heart failure, cerebrovascular disease, and metabolic syndrome.

Adapted from Joshi GP, et al. Society for Ambulatory Anesthesia consensus statement on preoperative selection of adult patients with obstructive sleep apnea scheduled for ambulatory surgery. *Anesth Analg*. 2012: Aug 10. [Epub ahead of print].
OSA, Obstructive sleep apnea; *CPAP*, continuous positive airway pressure.

Social Considerations

Factors other than physical condition must be weighed in considering a patient for outpatient surgery (Box 37-3). The lack

BOX 37-3

Social Considerations in Ambulatory Surgery

- Patient compliance
- Presence of responsible caregiver
- Discharge accommodations
- Access to assistance
- Financial and insurance considerations

of appropriate home conditions and care makes the outpatient option less desirable.

Unacceptable Patient Conditions for Ambulatory Surgery

Certain situations make ambulatory surgery impractical. Each patient must be considered individually for acceptability as an outpatient surgical candidate. Patients believed to be at increased risk for outpatient surgery and to be unacceptable candidates for such surgery are those with any of the following[32]:

- Unstable ASA physical status classification III or IV (e.g., cardiac, renal, endocrine, pulmonary, hepatic, or cancer diagnoses)
- Active substance/alcohol abuse
- Psychosocial difficulties, that is, responsible caregiver not available to observe the patient the evening of surgery (see Box 37-3)
- Poorly controlled seizures
- Morbid obesity with significant comorbid conditions, that is, angina, asthma, OSA
- Previously unevaluated and poorly managed moderate to severe OSA
- Ex-premature infants younger than 60 weeks postconceptual age requiring general anesthesia with endotracheal intubation
- Uncontrolled diabetes
- Current sepsis or infectious disease necessitating separate isolation facilities
- Anticipated postoperative pain not expected to be controlled with oral analgesics or local anesthesia techniques

PATIENT EVALUATION AND PREPARATION

To recognize anesthetic risks and determine the patient's suitability for the planned procedure, preoperative evaluation is mandatory for all patients preparing to undergo outpatient anesthesia and surgery. Challenges for the outpatient team will be organizing and accomplishing all the necessary tests and evaluations while causing the least inconvenience to the patient and maintaining an expedient surgical process. The preoperative interview elicits pertinent patient information and clarifies risk factors that may affect surgery and outcome. Additionally, by obtaining a thorough current and past medical history—including a personal and family anesthetic history—the staff may determine what further patient workup is required before surgery. A formalized preanesthesia assessment clinic is the most comprehensive and cost-effective process for preoperative evaluation and preparation.[92] Preoperative screening also allows the staff to communicate what will be expected of the patient in the perioperative phases.

Consultations, laboratory tests, and diagnostic procedures should be performed based on clinical findings rather than on a preestablished regimen of "standard" tests. Without any discoveries from the medical history and physical examination, the probability of observing a significant abnormality is negligible in diagnostic procedures, including electrocardiogram, chest radiograph, and laboratory tests. Abnormal test results obtained from routine testing potentially alter patient care only 0.22% to 0.56% of the time.[93] Routine preoperative laboratory screening is neither cost-effective nor predictive of postoperative complications.[94-96]

Patient Interview

Patient screening should take place sufficiently in advance of the scheduled surgery to allow time for necessary risk assessment, preoperative testing, specialty consultations, and adjustments in patient care. Proper timing of the patient assessment, particularly for the patient with complex medical conditions, minimizes surgical delays and cancellations. The high-risk patient should be evaluated at least 1 week before the scheduled procedure. With respect to client convenience, the otherwise healthy individual who does not have the opportunity to visit the clinic can be evaluated on the day of surgery. In this circumstance, there is a higher potential for surgical postponement or cancellation with last-minute discovery (e.g., inappropriate fasting, suspected difficult airway).

Patient Orientation

The preoperative interview allows the staff to convey what is expected of the patient and what the patient can expect perioperatively. Providing instructions to the patient, verbally and in writing, results in improved patient compliance. An information packet given to the patient at the interview is beneficial. It should detail specific instructions and concerns related to the procedure (Box 37-4).

Patients and family members should have the opportunity to become acquainted with the ambulatory surgery facilities and the anticipated sequence of events. This includes orientation to the laboratory and procedure areas, changing areas, waiting room, play areas, and the short-stay area, where the patient remains after surgery until discharge. This orientation is designed to reduce patient and family fear by providing relevant perioperative information (e.g., directions, anticipated schedule, instructions for physiologic preparation of the child, expected postoperative course, and discharge instructions), offering reassurance, and enhancing coping skills through familiarity. A variety of techniques may be incorporated to prepare the child for the operative procedure. Children can be oriented to equipment that is commonly used in the perioperative setting (e.g., anesthetic mask, intravenous therapy equipment, the anesthesia machine and circuit, blood pressure cuff, thermometer, and postoperative oxygen therapy devices). Children can be told when and where they will be reunited with their parents after surgery.

History and Physical

Results of a thorough medical history and physical examination performed by a member of the medical staff should be available in the patient's chart before the surgery is performed. A separate anesthesia history should be incorporated into a questionnaire specifically designed for preanesthetic evaluation; the anesthesia provider should review this history with the patient.

Such a review may be accomplished in a written format and would include a general review of the major systems, history of allergies, current medications, past and present medical problems, laboratory and diagnostic test results, and patient and family response to previous anesthetics. Prior anesthesia records should be examined for complications, response to anesthesia, and postoperative course. Patient evaluation should be conducted within 30 days of the scheduled surgery for medically stable patients and within 72 hours of the scheduled surgery for high-risk patients. The clinician should determine whether any changes might have occurred since the original history and physical examination were

BOX **37-4**

Preoperative Patient Instructions

Preoperative Instructions
- Tell the patient when and where laboratory tests, consultations, and diagnostic procedures will be completed.
- Clarify the appropriate time for the patient to be without food and drink.

Registration on the Day of Surgery
- Tell the patient the time to report for surgery, and mention that a wait can normally be expected.
- Describe the location of the parking areas.
- Tell the patient where to report for surgery.

Ambulatory Center Policies
- Inform the patient and family about expected conduct.
- Explain the ambulatory facility policies to the patient and family.
- Describe the family waiting area and services (e.g., dining areas).
- Review advance-directive information as required by law in some states.
- Review the patient's right-to-privacy policies.
- Outline the facility's cancellation policies: late arrival, nonadherence to fasting guidelines, inappropriate transportation home, lack of responsible person to help patient postoperatively, interim changes in patient's health status (e.g., upper respiratory tract infection [URTI]).

Personal Considerations
- Tell patient to wear comfortable, loose-fitting clothing that may be easily stored.
- Instruct patient to wear no jewelry or makeup (remove nail polish from at least one nail).
- Instruct patient to bring personal toilet items (e.g., comb, brush, toothbrush) as required.
- Caution patient to leave valuables at home.
- Tell caregiver to bring child's favorite toy, comforter, or pacifier, or light reading material for the older patient.

Postoperative Considerations
- Inform patient and family of the discharge time, including the time spent in the postanesthesia care unit and the customary length of stay until discharge.
- Instruct patient in the manner of discharge, the appropriate transportation arrangements, and the necessity for the presence of a responsible caregiver.
- Give the patient postoperative instructions: no driving, alcohol, or major decisions postoperatively for at least 24 to 48 hours after anesthesia (see Box 37-13 for additional information)
- Inform the patient where, how, and to whom complications should be reported. Supply telephone numbers.
- Indicate the possibility of hospital admission.

Considerations if the Patient's Physical Condition Changes
- Tell the patient to contact the surgeon.
- Tell the patient to contact the anesthetist.
- Tell the patient to call regarding cancellations or physical condition changes (e.g., URTI).

performed, and an update note should be made on the day of the procedure. A review of current vital signs, laboratory test results, diagnostic reports, and fasting status should be made.

Laboratory Evaluation

Each ambulatory center should have a consensus regarding the minimum testing requirement for surgery. These testing criteria depend on the proposed surgical procedure, the patient's medication history, and the patient's physical condition. Some states and regions have established minimum testing requirements. However, conducting a battery of preoperative laboratory tests without specific indications that they are needed has not been shown to reduce patient morbidity,[94] is not cost effective, and may even place the patient at increased risk.[95] Discriminating laboratory testing, based on findings from the history and physical examination and primarily designed to evaluate a patient's comorbidities and surgical risk, seems to be indicated. Normal laboratory test and diagnostic procedure results are deemed current if the tests are performed within 6 months of surgery if the patient's physical condition remains stable.[96,97] Exceptions include serum potassium level determinations, which should be obtained within 7 days of surgery for patients receiving diuretics or digitalis, and blood glucose level determinations, which should be obtained on the same day of surgery for patients with diabetes controlled by medication. Physical conditions and systemic illnesses in which preoperative laboratory testing is appropriate are listed in Box 37-5.

Pregnancy Testing

The medical facility should have established guidelines delineating when testing for pregnancy is appropriate and informed consent must be obtained. Anesthetic concerns include the effect of surgery and anesthesia on the developing fetus and the potential to trigger preterm labor. If the medical history and physical examination indicate that the patient may be pregnant, or if pregnancy might complicate the surgery, then pregnancy testing should be performed. It is important that the patient be educated as to the potential risks of exposing a fetus to an anesthetic. Whenever possible, especially in the adolescent population, a female staff member should question the patient in the absence of family members.[98] Suggested pregnancy testing guidelines are given in Table 37-1.

Diagnostic Procedures

Chest Radiography. Performing routine preoperative chest radiography is not recommended without specific indications for the necessity of the test from the history and physical examination. Clinical findings obtained from the history and physical are as efficient as a chest radiograph. A chest radiograph should be considered preoperatively if the patient (1) presents with new pulmonary signs or symptoms, (2) has end-stage renal disease, or (3) has decompensated heart failure, and only if the test might change patient management or outcome. Patients with these symptoms might not be suitable candidates for ambulatory surgery, except for brief, minor procedures, for example, ophthalmologic surgery.[96]

Electrocardiography. Few data support the routine performance of 12-lead electrocardiographic screening before elective surgery, because it has not been shown to be cost effective, is a poor predictor of perioperative complications, and is of limited value in detecting ischemia in asymptomatic individuals. It has been proposed that routinely acquiring a preoperative electrocardiogram is not indicated in the patient undergoing ambulatory surgery.[97]

BOX **37-5**

Indications for Laboratory Testing

Complete Blood Count
- Hematologic disorder
- Vascular procedure
- Chemotherapy
- Unknown sickle cell syndrome status

Hemoglobin/Hematocrit
- Age less than 6 months (less than 1 year if born premature)
- Hematologic malignancy
- Recent radiation or chemotherapy
- Renal disease
- Anticoagulant therapy
- Procedure with moderate-to-high blood loss potential
- Coexisting systemic disorders (e.g., cystic fibrosis, prematurity, severe malnutrition, renal failure, liver disease, congenital heart disease)

White Blood Cell Count
- Leukemia and lymphomas
- Recent radiation or chemotherapy
- Suspected infection that would lead to cancellation of surgery
- Aplastic anemia
- Hypersplenism
- Autoimmune collagen vascular disease

Blood Glucose Level
- Diabetes mellitus
- Current corticosteroid use
- History of hypoglycemia
- Adrenal disease
- Cystic fibrosis

Serum Chemistry
- Renal disease
- Adrenal or thyroid disease
- Chemotherapy
- Pituitary or hypothalamic disease
- Body fluid loss or shifts (e.g., dehydration, bowel prep)
- Central nervous system disease

Potassium
- Digoxin therapy
- Diuretic therapy

Creatinine and Blood Urea Nitrogen
- Cardiovascular disease (e.g., hypertension)
- Renal disease
- Adrenal disease
- Diabetes mellitus
- Diuretic therapy
- Digoxin therapy
- Body fluid loss or shifts (e.g., dehydration, bowel prep)
- Procedure requiring radiocontrast

Liver Function Tests
- Hepatic disease
- Exposure to hepatitis
- Therapy with hepatotoxic agents

Coagulation Studies
Prothrombin Time and Activated Partial Thromboplastin Time
- Leukemia
- Hepatic disease
- Bleeding disorder
- Anticoagulant therapy
- Severe malnutrition or malabsorption

Platelet Count and Bleeding Time
- Bleeding disorder
- Abnormal hemorrhage, purpura, easy bruisability

Urinalysis
- Not indicated as a routine screening test

Pregnancy
- Possibility of pregnancy

Serum Medication Levels
- Monitor for medications (e.g., theophylline, phenytoin, digoxin, carbamazepine) if patient exhibits signs of ineffective therapy, potential drug side effects, poor drug compliance, or has recently changed medication therapy without documentation of drug level

TABLE **37-1** Recommendations for Preoperative Pregnancy Testing

Population Type	Recommendations
Menstruating females under 13 years of age	No pregnancy test unless history is either indicative of sexual activity or is inconclusive.
Patients of childbearing age (over 13 years of age until 1 year after last reported menses)	Preoperative pregnancy test should be offered to all patients regardless of history, except in patients with a history of hysterectomy or bilateral salpingo-oophorectomy.
Testing on the day of surgery	Urine pregnancy test is sufficient.
Testing within 1 week of surgery	Serum pregnancy test is preferable.
All patients	Well-documented informed consent must be obtained from patients or their guardians.
All patients	A thorough and detailed history should be obtained from all patients.

From Steffey TS, Twersky RS. Is routine preoperative pregnancy testing necessary. In: Fleischer LA, ed. *Evidence-Based Practice of Anesthesiology*. 2nd ed. Philadelphia: Saunders; 2009:28-32.

Fasting Status and Aspiration Risk

Part of the preoperative evaluation process identifies patients at risk for aspirating gastric contents into the lungs and developing aspiration pneumonitis. Factors associated with an increased risk of pulmonary aspiration of gastric contents are listed in Box 37-6.[15,98,99] Recent ingestion of food and liquid before surgery contributes to an increased risk of aspiration. Solid foods must be digested to a bolus diameter of less than 2 mm before the food can pass through the pylorus. This process normally takes several hours for solids, whereas liquids pass through the pylorus in 1 to 2 hours. Historically, patients have been required to fast for extended periods in an attempt to ensure an empty stomach. However, sustained fasting does not ensure that the stomach will be empty at the time of surgery. The traditional policy of fasting after midnight fails to address several variables that influence gastric emptying for surgery:

- The time of the scheduled surgery
- The time at which the patient retired for the night
- The variability of gastric emptying for solids and fluids across individuals

Several problems have been associated with prolonged fasting:

- Dehydration
- Hypoglycemia
- Hypovolemia
- Increased irritability
- Enhanced preoperative anxiety
- Reduced compliance with preoperative fasting orders
- Thirst and related discomfort (e.g., hunger, headache, unhappiness)

Data suggest that liquids (e.g., clear apple juice, clear broth, coffee, gelatin, Popsicles, pulp-free orange juice, water, and weak tea) may be given to healthy, unpremedicated patients up to 2 hours before surgery without placing them at increased risk for aspiration. There is no increase in gastric volume, nor is there a decrease in gastric pH, at the time of elective surgery. The studies that allowed patients to consume clear liquids until 2 to 3 hours before surgery demonstrated that although the patients appeared to be at no greater risk of aspirating gastric contents, the pH of the stomach contents remained less than 2.5. In light of these findings, recommended fasting guidelines for the otherwise healthy individual have been liberalized (Table 37-2).[100]

BOX 37-6

Risk Factors for Pulmonary Aspiration

- Age extremes (younger than 1 year or older than 70 years)
- Anxiety
- Ascites
- Collagen vascular disease (e.g., scleroderma)
- Depression
- Esophageal surgery
- Exogenous medications (opioids or premedications [e.g., barbiturates] and anticholinergics)
- Failed intubation or difficult airway history
- Gastroesophageal junction dysfunction (e.g., hiatal hernia)
- Mechanical obstruction (e.g., pyloric stenosis, duodenal ulcer)
- Metabolic disorders (e.g., hypothyroidism, chronic diabetes, hepatic failure, hyperglycemia, obesity, renal failure, and uremia)
- Neurologic sequelae (e.g., developmental delays, head injury, hypotonia, seizures)
- Pain
- Pregnancy
- Prematurity with respiratory problems
- Smoking
- Type and composition of gastric contents (e.g., solid foods, milk products)

Special Considerations

Daily Medications

Patients should continue to take their prescribed cardiopulmonary medications on the morning of the surgery. The medications may be taken with a minimum of water (up to 150 mL in adults and up to 75 mL in children) up to 1 hour before anesthesia.

Warfarin Sodium. An early decision regarding whether the administration of warfarin sodium should be (1) continued, (2) discontinued, or (3) interrupted and bridging anticoagulation be accomplished with subcutaneous low-molecular-weight heparin or intravenous unfractionated heparin be initiated must be made in consultation with the surgeon and the patient's internist. The question of whether the disadvantages of stopping the administration of this medication before surgery outweigh any advantage must be addressed. If the decision to withhold warfarin is made, the drug should be discontinued approximately 5 days before the scheduled surgery, and an international normalized ratio (INR) should be determined on the day of surgery. With adequate hemostasis, warfarin should be resumed 12 hours to 24 hours after surgery.[101] A complete discussion on the perioperative management of anticoagulants can be found in Chapter 34.

Diabetes

Recommended care for the diabetic patient who is undergoing ambulatory surgery is a subject of debate and lacks clear guidelines. The patient with diabetes is at increased risk for cardiovascular, pulmonary, and neurologic events and should receive an early and thorough preoperative evaluation, including electrocardiography, history

TABLE 37-2 Preoperative Fasting Recommendations

Ingested Materials	Minimum Fasting Period* (hr)
Clear liquids†	2
Breast milk	4
Infant formula	6
Non-human milk‡	6
Light meal§	6
Heavy meal; fried or fatty food	8

From American Society of Anesthesiologists Committee. Practice guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration: application to healthy patients undergoing elective procedures: an updated report by the American Society of Anesthesiologists Committee on Standards and Practice Parameters. *Anesthesiology*. 2011;114(3):495-511. These recommendations apply to healthy patients who are undergoing elective procedures. They are not intended for women in labor. Following the guidelines does not guarantee complete gastric emptying.

*The fasting periods noted above apply to all ages.

†Examples of clear liquids include water, fruit juices without pulp, carbonated beverages, clear tea, and black coffee.

‡Because non-human milk is similar to solids in gastric emptying time, the amount ingested must be considered when determining an appropriate fasting period.

§A light meal typically consists of toast and clear liquids. Meals that include fried or fatty foods or meat may prolong gastric emptying time. Both the amount and type of foods ingested must be considered when determining an appropriate fasting period.

and physical examination, and indicated laboratory analysis. The patient with insulin-dependent diabetes whose diabetes is not well controlled and whose serum glucose levels are prone to wide fluctuations may be best treated in the inpatient setting depending upon the type of surgery. Considerations for care of the patient with diabetes who is undergoing ambulatory surgery include the following [102]:

- Schedule the patient's surgery for early in the day.
- Obtain baseline information regarding the patient's glycemic control.
  - Previous 3- to 4-month trend for blood glucose and glycosylated hemoglobin A1c (HbA1c), if available for review, to assess glycemic control
  - Type (e.g., oral antidiabetics and insulin), dose, and schedule of antidiabetic therapy
  - Hypoglycemic events: occurrence, frequency, manifestations, and blood glucose level when symptoms occur
  - Hospitalization history related to glycemic control issues
- Instruct the patient to have nothing to eat or drink after midnight the night before surgery if the procedure is scheduled for early in the day.
- Monitor the patient's blood or serum glucose levels on arrival to the ambulatory center by use of a capillary test strip or laboratory analysis.
- Prevent hypoglycemia while maintaining blood glucose levels at less than 180 mg/dL.
- Manage preoperative oral antidiabetic and noninsulin injectable therapy.
  - Continue usual routine prior to day of surgery
  - Withhold therapy on the day of surgery
- Manage preoperative insulin therapy (Table 37-3).
- Return the patient to preoperative activities of daily living (e.g., baseline activity status, nutrition habits) as soon as possible.
- Make the patient aware that admission to the hospital is likely if persistent nausea and vomiting prevent resumption of normal dietary intake.

Heart Murmur

The surgical patient with a heart murmur requires further workup if the condition was previously undetected. Heart murmurs are categorized as innocent or pathologic. Pathologic murmurs may be due to complex congenital malformations or heart disease and have accompanying physical dysfunction, whereas with innocent murmurs, the patient may be completely asymptomatic. Whether the murmur is benign, functional, or caused by organic heart disease, cardiologic assessment should be obtained before the induction of anesthesia.[103]

Rhinorrhea

From 20% to 30% of all children display symptoms of rhinorrhea a good portion of the year. Children younger than 2 years of age are prone to 5 to 10 viral respiratory infections annually.[104] For the child undergoing ambulatory surgery, individual patient evaluation is required for a runny nose. The history and physical examination are beneficial in determining the cause. The differential diagnosis of rhinorrhea should include the following:

- Allergic (seasonal) rhinitis
- Bacterial infection (early stages)
- Flu syndrome
- URTI
- Vasomotor rhinitis
- Nothing found

The clinician obtaining the patient history should try to ascertain the allergic or acute nature of the runny nose and determine whether it is normal for the child or an illness has recently developed and worsened. Recently acquired (within 12 to 24 hours of surgery) rhinorrhea or chronic rhinorrhea in the otherwise fit child is not a contraindication to surgery. The differentiation between a noninfectious and an infectious runny nose might influence the decision of whether the procedure should be delayed (Box 37-7). Surgery might be delayed for only 2 weeks in the child with localized infectious rhinorrhea.[105,106]

Considerations for Postponing Surgery

Lack of Drug Compliance

The patient with uncontrolled hypertension or diabetes who has wide swings in blood pressure or blood glucose levels may not be suitable for outpatient surgery; such conditions should be optimally managed before outpatient surgery and anesthesia are performed.

TABLE 37-3 Patient Instructions for Preoperative Insulin and Noninsulin Administration

Insulin Regimen	Day Before Surgery	Day of Surgery	Comments
Insulin pump	No change	No change	Use "sick day" or "sleep" basal rates
Long-acting, peakless insulins	No change	75%-100% of morning dose	Reduce nighttime dose if history of nocturnal or morning hypoglycemia; on the day of surgery, the morning dose of basal insulin may be administered on arrival to the ambulatory surgery facility
Intermediate-acting insulins	No change in the daytime dose; 75% of dose if taken in the evening	50%-75% of morning	See comments for long-acting insulins
Fixed combination insulins	No change	50%-75% of morning dose of intermediate-acting component	Lispro-protamine only available in combination; therefore use NPH instead, on day of surgery
Short- and rapid-acting insulin	No change	Hold the dose	
Noninsulin injectables	No change	Hold the dose	

Adapted from Joshi GP, et al. Society for Ambulatory Anesthesia consensus statement on perioperative blood glucose management in diabetic patients undergoing ambulatory surgery. *Anesth Analg.* 2010;111:1378-1387; Kadoi Y. Anesthetic considerations in diabetic patients. Part 1: preoperative considerations of patients with diabetes mellitus. *J Anesth.* 2010;24(5):739-747; Akhtar S, et al. Scientific principles and clinical implications of perioperative glucose regulation and control. *Anesth Analg.* 2010;110(2):478-497.

Fasting Status

For safety reasons, the patient not adhering to the fasting guidelines should not undergo surgery, and the rationale of not eating before surgery should be reinforced.

Suspicion of Pregnancy

If the patient responds that she may be pregnant or if clinical signs are indicative of pregnancy, surgery should be delayed until determination of whether the patient is pregnant can be made. Decisions about whether surgery should be performed and what type of anesthesia should be used can be based on pregnancy test results.

Upper Respiratory Tract Infection

Acute respiratory infections are one of the leading medical causes for surgery cancellation in children. In patients with an acute infection, differentiating between a bacterial infection as causative of the upper respiratory tract infection (URI) or lower respiratory tract infection (LRI) and other causes—such as uncomplicated viral infection (afebrile, clear secretions) or allergic conditions—is important. Differentiating between a noninfectious process and an infectious process is paramount in the decision regarding whether the procedure should be performed. This differentiation may be difficult to make early in the course of the disease. Symptoms of URI include the following:

- Elevated white blood cell count (greater than 12,000 with a left shift)
- Mucopurulent nasal secretions
- Inflamed and reddened mucosa (nasopharyngeal and oropharyngeal) (with allergic rhinitis, e.g., nasal mucosa is ashen and boggy)
- Positive chest findings (e.g., congestion, rales)
- Temperature of 37.5° C to 37° C (greater than 37° C usually associated with lower respiratory tract involvement)
- Tonsillitis
- Viral ulcers in the oropharynx

Other accompanying symptoms may include conjunctivitis, coughing (nonproductive), fatigue, itching, laryngitis, malaise, myalgia, sneezing, and sore throat. Laboratory and diagnostic testing in children with suspected URI includes nasal or throat cultures if signs of an infectious process are observed. A chest radiograph is not warranted, especially if chest sounds are clear. Similarly, the value of obtaining a white blood cell count has been challenged because the results may be normal and typically do not influence whether to proceed with the surgery.[107]

BOX 37-7

Differential Diagnosis of Rhinorrhea

Noninfectious Runny Nose

- Allergic rhinitis
  - Seasonal
  - Perennial
- Vasomotor rhinitis
  - Emotional (crying)
  - Temperature

Infectious Runny Nose

- Viral infections
  - Nasopharyngitis (common cold)
  - Contagious disease (e.g., chickenpox, measles)
- Acute bacterial infections
  - Streptococcal tonsillitis
  - Meningitis

Anesthetizing the patient who has a URI or LRI has been shown to increase the incidence of respiratory-associated complications two- to seven-fold. Bronchial reactivity may persist for 6 to 8 weeks after a viral LRI .The anesthetized patient with a respiratory tract infection is more prone to experience breath holding, bronchospasm, coughing, hypoxemia, increased secretions, laryngospasm, pneumonia, atelectasis, croup, and stridor. Risk factors for the development of perioperative adverse respiratory events include endotracheal intubation (less than 5 years of age), history of prematurity, history of reactive airway disease, exposure to secondhand smoke, surgery involving the airway, the presence of copious secretions, and nasal congestion.

A minimum of 4 hours of postoperative observation is appropriate before the patient is considered for discharge from the ambulatory setting. Each case should be reviewed individually. The decision to operate frequently depends on the urgency of the surgery, the duration and complexity of the surgery, and the need for instrumentation of the airway. Children with uncomplicated respiratory infection may undergo elective procedures without significantly increasing anesthesia complications.[106-108] Further discussion on the management of children with respiratory infection is in Chapter 48. Guidelines for deciding whether surgery should be performed in children with respiratory infections are given in Box 48-1.

Each case has to be reviewed individually and consideration given to the urgency of the surgery, the duration and complexity of the surgery, the number of times the procedure has been canceled, and the wishes of the family and patient.

PREMEDICATION

Premedicating the ambulatory surgery patient with sedative agents is done on an individual basis and with minimally effective doses. The concern about giving anxiolytic and sedative medications is related to their potential to prolong the patient's stay. Prophylactic drugs for postoperative nausea and vomiting (PONV) are commonly used in patients at risk. Nonsteroidal antiinflammatory drugs (NSAIDs) given orally, when indicated for analgesia, should be considered preoperatively.[17] Preemptive analgesia may reduce postoperative pain by preventing surgically induced peripheral and central sensitization.[109] Lower postoperative pain scores and less opioid use have been seen when NSAIDs were given prior to surgery.[110] However, the use of premedication should not become routine; rather, the decision to administer these agents should be based on individual need and desired benefit.[111] Common indications for preoperative medication are as follows:

- To decrease patient anxiety and fear
- To facilitate smooth induction and emergence from anesthesia
- To supplement anesthesia and reduce the need for general anesthetic agents
- To reduce the volume and acidity of gastric contents
- Prophylaxis for postoperative nausea and vomiting
- To provide a more pleasant stay in the PACU

Pulmonary Aspiration Prophylaxis

Patients at higher risk for aspirating gastric contents should be given medications before surgery to raise gastric pH and lower gastric volume, with the hope of minimizing their risk for pulmonary aspiration. Pulmonary aspiration prophylaxis in the patient not at risk is not recommended.[100]

Antacids

The value of oral antacids lies in their ability to rapidly reduce gastric acidity; they are effective in raising pH in 15 to 20 minutes.[112]

This characteristic is useful in emergency situations, but it is of limited application in the ambulatory setting. Although oral antacids raise gastric pH, they have the disadvantage of increasing gastric volume. Clear, nonparticulate oral antacids (e.g., two tablets of Alka-Seltzer Gold in 30 mL of water; 30 mL [0.4 mL/kg pediatric dose] of 0.3 M sodium citrate [Bicitra]) are preferred over particulate antacids, such as Maalox or Mylanta, because particulate antacids may produce pulmonary injury if aspirated.[113]

Gastrokinetics

Reducing the volume of gastric fluid with the gastrokinetic agent metoclopramide (Reglan) helps minimize the risk of aspiration. Metoclopramide has been demonstrated to decrease gastric fluid volume by reducing gastric emptying time without increasing pH in adults and in children. Metoclopramide may also reduce the risk of pulmonary aspiration by increasing lower esophageal sphincter tone. It appears to exert a central antiemetic effect via dopamine receptor blockade of the chemoreceptor trigger zone.[114] The combination of metoclopramide with a histamine$_2$ (H_2)-receptor antagonist has been shown to be effective in raising gastric volume pH and decreasing gastric volume content.[115]

The intramuscular dose is 10 mg for adults (0.1 mg/kg for children) given at least 45 minutes before surgery. The intravenous dose is 10 to 20 mg (0.15 to 0.2 mg/kg) given over the course of 3 to 5 minutes at least 30 minutes to 45 minutes before surgery. These regimens allow sufficient time for the desired results to be achieved. The oral dose, 10 mg for adults (0.1 mg/kg for children), achieves peak plasma concentrations 40 to 120 minutes after administration.[32]

H_2-Receptor Antagonists

Selective and competitive H_2-receptor antagonists, such as cimetidine (Tagamet), famotidine (Pepcid), ranitidine (Zantac), and nizatidine (Axid), block hydrogen ion release by gastric parietal cells. These drugs do not alter the pH of gastric fluid already present in the stomach. All are available over the counter. These medications may be administered the night before surgery, on the day of surgery, or both, to reduce gastric acidity. Famotidine and ranitidine have longer durations of action, are more potent, and exhibit a lower potential for side effects than cimetidine.[116]

Cimetidine. In one study, an intravenous adult cimetidine dose of 300 mg helped reduce the risk of pulmonary aspiration. The oral dose is 300 mg (3 to 4 mg/kg) for adults and 7.5 mg/kg for children, given from 1.5 to 3 hours before surgery. This is effective in reducing the risk of chemical pneumonitis if pulmonary aspiration occurs.[116]

Famotidine. The intravenous dose of famotidine is 20 mg for adults, given 15 to 30 minutes before surgery; this is effective in increasing gastric pH. When given electively, oral famotidine (40 mg) is given the night before surgery and on arising the morning of surgery. When compared with ranitidine, famotidine was slower in raising the gastric pH to safe levels.[117]

Ranitidine. The intravenous dose of ranitidine is 50 to 100 mg or 1 to 2.5 mg/kg. This drug decreases the risk associated with pulmonary aspiration. The oral dose of 150 to 300 mg for adults (2.5 mg/kg for children), given 1 to 3 hours before surgery, increases gastric pH, whereas gastric fluid volume may not be less than 25 mL. Comparable results were noted when ranitidine (150 mg) was given at bedtime and again on arising on the morning of surgery or when it was given orally 1 to 2 hours before surgery.[116]

Gastric Proton-Pump Inhibitors

Omeprazole. Omeprazole (Prilosec) causes dose-dependent intracellular inhibition of gastric acid secretion in humans without affecting gastric volume. Omeprazole has a longer duration of action than the H_2-receptor antagonist agents in suppressing gastric acid secretion and appears to cause no significant side effects.

The intravenous dose of omeprazole is 40 mg, administered after the induction of anesthesia. This is as effective as ranitidine in raising gastric pH above 2.5.

The oral dose is 80 mg, given the evening before surgery. This has increased mean gastric pH to 4.56, compared with the pH of 2.05 that was achieved with the administration of a placebo. Orally administered omeprazole 40 mg was not found to be as effective as either famotidine 40 mg or ranitidine 300 mg in protecting against pulmonary aspiration in parturients.[116]

Lansoprazole, Rabeprazole, and Esomeprazole. Orally administered lansoprazole (Prevacid), 30 mg, rabeprazole (Aciphex) 20 mg, or esomeprazole (Nexium) given the day prior to surgery and on the morning of surgery were not as effective in raising pH and lowering gastric volume as a single morning-of-surgery dose of ranitidine 150 mg. Intravenous preparations of esomeprazole 20 and 40 mg and lansoprazole 30 mg are available.[118]

Pantoprazole. Pantoprazole (Protonix) is marketed as an intravenous solution, and also as tablets, which may prove useful for perioperative use. Intravenously administered pantoprazole 40 mg was comparable with ranitidine 50 mg in increasing pH and reducing gastric fluid volume.[119]

ANESTHETIC CONSIDERATIONS

Anesthetic techniques suitable for outpatient surgery include general anesthesia, regional anesthesia, and monitored anesthesia care. The goals for outpatient anesthesia, regardless of the type administered, are listed in Box 37-8, and factors influencing the choice of anesthesia are shown in Box 37-9. The ideal anesthetic agent for ambulatory anesthesia—whether it is administered inhalationally, intravenously, locally, or regionally—is one with the appropriate pharmacokinetic traits (i.e., rapid onset and offset, short duration, inert metabolites, and insignificant side effects).

BOX 37-8

Goals of Outpatient Anesthesia

- Minimize the physiologic changes associated with anesthesia.
- Provide a fast, smooth onset of anesthetic action.
- Promote intraoperative amnesia and analgesia.
- Afford suitable operating circumstances.
- Minimize perioperative anesthetic side effects.
- Allow rapid offset of anesthetic influence while maintaining patient comfort.

BOX 37-9

Considerations for Choice of Anesthetic

- Surgical requirements
- Skill of anesthesia provider
- Patient choice
- Patient age
- American Society of Anesthesiologists physical status classification
- Level of care available once patient is discharged from outpatient facility
- Risk of postoperative nausea and vomiting
- Postoperative analgesia requirements

General Anesthesia

General anesthesia is the most widely used anesthetic technique for ambulatory surgery. General anesthesia should be achieved with the less-soluble inhalation agents or with short-acting intravenous agents that have the capability of reversal if required. A combination of potent rapid-onset and rapid-offset inhalation agents (e.g., desflurane, sevoflurane), along with intravenous agents (e.g., propofol, intravenous opioids, short-acting muscle relaxants, NSAIDs, and dexmedetomidine), comprise general anesthesia in contemporary practice. The popularity of general anesthesia in the ambulatory setting is related to its acceptance by the patient, the anesthesia provider, and the surgeon, and to the consistent pace that can be maintained with regard to achieving a satisfactory state of anesthesia.

Depth-of-Anesthesia Monitoring

Recent advances in depth-of-anesthesia monitoring technology have made their mark in ambulatory anesthesia. The data indicating that the routine use of bispectral index monitoring (BIS) during outpatient anesthesia improves outcomes is mixed. Some of the purported advantages of BIS monitoring in the outpatient setting include reducing the amount of anesthetic agent required, faster emergence from anesthesia, and a reduction in phase II vomiting.[120-125]

Airway Management

Issues regarding the use of general anesthesia with a facemask, a laryngeal mask airway (LMA), or an endotracheal tube in patients undergoing outpatient surgery are the same as those in patients undergoing inpatient surgery. The indications for intubating the trachea depend on the constraints of the surgery and the individual patient concerns (e.g., risk of regurgitation and aspiration, hypoventilation, access to the airway, use of muscle relaxants, and airway obstruction).

Drawbacks to endotracheal intubation specific to the outpatient setting must be considered. Irritation and trauma to the upper airway and trachea are a concern, especially in children. The development of postextubation croup is rare (0.1%), but the potential for its occurrence must be considered in the plan for discharging the patient.[126] Careful attention paid to minimizing intubating trauma, ensuring that an air leak is present at less than 40 cm H_2O, and avoiding large-diameter endotracheal tubes helps reduce the incidence of postextubation croup in children.[127]

The LMA has proven to be a popular and cost-effective airway management tool in the ambulatory setting. Patients tolerate LMAs at a lower dose of anesthetic than that needed for an endotracheal tube. Neuromuscular blocking agents are rarely necessary for airway management, and the incidence of airway morbidity such as coughing and sore throat is lower with LMAs than with endotracheal tubes. These advantages may facilitate faster recovery and earlier discharge of patients. Limitations include incomplete protection against aspiration of gastric contents and inadequate delivery of positive pressure ventilation.[128,129]

Intravenous Fluid Therapy

Debate exists over whether all patients undergoing brief (less than 15 minutes) anesthesia require intravenous cannulation for uncomplicated surgery in which rapid recovery is expected. If an intravenous catheter is not inserted in children undergoing general anesthesia, the equipment and personnel trained in intravenous line placement should be immediately available in case they are needed.

The optimum amount of perioperative fluid therapy remains unclear. The three common total fluid regimens include restrictive, liberal, and hemodynamic goal directed. Each technique has its proponents.[130-133] Benefits of liberal fluid therapy include less thirst postoperatively, a lower incidence of sore throat; and a lower incidence of dizziness, drowsiness, and faintness on standing compared with patients for whom fluids were withheld perioperatively. Less postoperative nausea and vomiting also has been reported.[134] Fluid restriction has been used as part of fast-track surgery to reduce the length of stay compared to application of liberal fluids.[133] Authors of a recent large-scale meta-analysis noted that outcomes favored a goal-directed therapy rather than liberal fluid therapy without hemodynamic goals. Whether goal-directed therapy is superior to a restrictive fluid strategy remains uncertain.[130]

Intravenous cannulation should be used, and perioperative fluid should be administered in the following situations:

1. *Procedures lasting longer than 30 minutes*. Longer surgical times increase the risk of hypothermia, increase the amount of anesthetics delivered to the patient, and result in a delay of resumption of normal diet.
2. *Procedures with an increased incidence of postoperative nausea and vomiting*. Intravenous access permits the administration of antiemetic medications and allows hydration.
3. *Procedures associated with postoperative discomfort*. If anticipated postoperative pain is unlikely to be controlled by nonintravenous means, an avenue should be established for the administration of intravenous analgesics.
4. *Prolonged fasting before surgery*. If the child has been fasting for more than 15 hours, intravenous hydration is desirable for the maintenance of fluid and glucose homeostasis.
5. *Procedures associated with intraoperative and postoperative bleeding*.
6. *Procedures associated with the use of perioperative antibiotics or patients who require the perioperative administration of antibiotics*.

Regional Anesthesia

The use of regional anesthesia in the ambulatory setting is well established. Regional anesthesia improves pain scores, decreases opiate use, and lowers the incidence of postoperative nausea and vomiting. Thus more patients can be discharged home in less time with high satisfaction.[135]

Local wound infiltration, peripheral nerve block, intravenous regional anesthesia, ophthalmic blocks (e.g., retrobulbar or periorbital), brachial plexus anesthesia, spinal anesthesia, and epidural anesthesia are all successfully used for outpatient surgery. The proper application of outpatient regional anesthesia requires knowledge of the anticipated surgical procedure, anesthesia requirements, length of procedure, and appropriate patient selection. The shortest-acting agent capable of providing satisfactory central neuraxial blockade should be used in the ambulatory setting if unreasonable delays in discharge are to be avoided. Peripheral nerve blockade with longer-acting local anesthetics can provide up to 24 hours of analgesia postoperatively. Although there are several advantages to regional techniques, there are potential disadvantages including whether the performance of these blocks requires more time than general anesthesia and the possibility they may reduce the overall efficiency of an outpatient unit. Regional techniques are not as reliable as general anesthesia and may further delay surgery. There is also the issue of postoperative complications including postspinal headache, transient neurologic symptoms (TNS) after spinal anesthesia, and urinary retention.[136] The advantages and disadvantages of the use of outpatient regional anesthesia are listed in Box 37-10.

Recommendations for the safe and effective use of regional anesthesia in outpatient surgery are noted in Box 37-11. Specific regional techniques are discussed in detail in Chapters 44 and 45.

POSTOPERATIVE CONSIDERATIONS

After the surgical procedure, care is provided in either the PACU (phase I) or the short-stay unit (phase II) until the patient is ready for discharge from the ambulatory setting. The location and the level of nursing care required vary according to the patient undergoing the procedure, the type of anesthesia used, and the surgical procedure. Properly addressing potential or realized complications in the most efficient manner possible expedites patient management and promotes a timely discharge process. Complications that might delay the patient's departure from the ambulatory facility include nausea, vomiting, and pain. Each outpatient facility has specific criteria for discharge that should be met before the patient is released from the facility.[137] A thorough discussion of the current practices in postanesthesia recovery is provided in Chapter 50.

BOX 37-10
Advantages and Disadvantages of Outpatient Regional Anesthesia

Advantages
- Recovery times are shorter than those of general anesthesia.
- Unanticipated admission to the hospital is reduced.
- Phase I recovery bypass (fast-track) eligibility is high.
- Provides excellent immediate postoperative pain relief.
- Results in better postoperative pain scores than general anesthesia.
- Common side effects associated with general anesthesia (e.g., airway trauma, dizziness, "hangover," myalgia, nausea and vomiting, pharyngitis) are minimized.
- The patient who fears general anesthesia or "loss of control" has a satisfactory alternative.

Disadvantages
- Cooperation of the patient and the surgeon is required.
- Regional anesthesia may require more time to provide than general anesthesia. In an ambulatory setting, where surgeries and patient stays tend to be of short duration, regional anesthesia may not be as well received. If a team approach is used, patient stays may be minimized by early placement of the proposed regional anesthetic if appropriate.
- Inherent problems associated with regional anesthesia, regardless of inpatient or outpatient status, include the sympathetic block associated with spinal and epidural anesthesia, which may complicate the discharge course if residual block results in orthostatic hypotension.

Postoperative Complications and Management

With today's standard of anesthesia care, major morbidity and mortality after ambulatory surgery are extremely rare; however, a variety of adverse postoperative events may lead to unplanned hospital admission (Box 37-12).[138] Postoperative nausea and vomiting and pain are the most common reasons for hospitalization after ambulatory surgery. Certain procedures (e.g., laparoscopic sterilization; laparoscopic inguinal herniorrhaphy; head and neck; ear, nose, and throat; urologic; orthopedic) are also associated with a higher incidence of unplanned hospital admissions. The hospital admission rate after ambulatory surgery is less than 2%.[139]

Nausea and Vomiting

Persistent nausea and vomiting are responsible for delays in discharge and for increases in patient cost and are a common factor in unanticipated hospital admission after outpatient surgery. The reported incidence of PONV is approximately 30% on average and as high as 80% in high-risk patients. Postdischarge nausea and vomiting (PDNV) has been reported to occur in up to 50% of patients. Up to 35% of these patients did not experience PONV.[140,141] Many anesthetic and nonanesthetic-related factors affect the susceptibility of patients to postoperative nausea and emesis.[142] Nonanesthetic-related factors contributing to increased episodes of emesis include the following[143-151]:

- *Age*. There is a higher incidence of postoperative vomiting in children, particularly in those between 3 and 12 years of age. A gradual decrease in the incidence of postoperative nausea and vomiting has been shown after 50 years of age.

BOX 37-11
Recommendations for the Use of Regional Anesthesia in Outpatient Surgery

- Local anesthesia is ideal and should be used whenever possible as the sole anesthetic regimen, or be included for postoperative analgesia after any technique.
- Peripheral nerve blockade is highly effective in providing postoperative analgesia and rapid discharge when used for upper or lower extremity surgical procedures. It is also effective for truncal operations such as hernia repair. The use of continuous catheter techniques provides maximum benefit.
- Performance of a block in a separate induction room may reduce the additional time otherwise required for regional anesthesia.
- If neuraxial blockade is chosen, spinal anesthesia has the advantages of rapid onset and high reliability. Unfortunately, there appears to be a persistent risk of transient neurologic symptoms (TNS) with the current agents. Low-dose bupivacaine (less than 6 mg) provides a low risk of TNS with the potential of a short discharge time, but with a high degree of variability and a limitation of adequate surgical anesthesia to the lower extremity and rectal area.
- Performance of an epidural anesthetic provides a more rapid discharge than with most of the current spinal techniques, and it provides the added advantage of flexibility in duration and extent of blockade if a catheter is placed.
- Excessive sedation must be avoided if the advantage of a high degree of alertness and rapid discharge is to be maintained.
- Discharge times after spinal anesthesia also require careful selection of drug and dose. The addition of epinephrine to subarachnoid local anesthetics increases the potential for urinary retention and for prolonged discharge times. The use of fentanyl may be a better choice for intensifying local anesthetic effect without prolonging discharge due to urinary retention.
- Urinary retention after a short-acting spinal anesthetic in low-risk patients is not any more frequent than with general anesthesia, and these patients can be discharged without mandatory voiding.

Adapted from Mulroy MF, Strodtbeck W. Is regional anesthesia appropriate for outpatient surgery. In: Fleischer LA, ed. *Evidence-Based Practice of Anesthesiology*. 2nd ed. Philadelphia: Saunders; 2009:359-363.

- *Apprehension*. Preoperative anxiety may increase the likelihood of vomiting. Proposed mechanisms by which apprehension contributes to vomiting include swallowed air, with resultant abdominal distention, increased gastric volume, and increased catecholamine levels.
- *Gastroparesis*. Several pathologic conditions are associated with gastroparesis, such as ileus, bowel obstruction, diabetes mellitus, muscular dystrophies, collagen vascular disorders, uremia, raised intracranial pressure, and pregnancy. The accompanying delayed gastric emptying means a greater gastric content and thus a greater chance of vomiting.
- *Gender*. Emesis occurs in adult females more than in males. After 70 years of age, gender is no longer a distinction for developing postoperative nausea and vomiting.
- *Individual predisposition*. Patients relating a previous history of nausea and vomiting after anesthesia or a history of motion sickness are at increased risk for nausea and vomiting after subsequent anesthetics.
- *Food ingestion*. Recent ingestion of food before undergoing anesthesia increases the probability of vomiting, as does vomiting during the induction of anesthesia.
- *Nonsmoking status*. Cigarette smokers seem to experience less postoperative nausea and vomiting than nonsmokers.
- *Type of surgery*. Prolonged surgical times correspond to an increased risk of vomiting. Certain surgical procedures—for example, arthroscopy, laparoscopy, lithotripsy, intestinal operations, ovum retrieval, orchiopexy, otoplasty, retinal detachment, tonsillectomy with or without adenoidectomy, and strabismus—are associated with an increased incidence of postoperative vomiting.

Anesthetic-related factors contributing to emesis include the following:

- *Premedications*. Preoperatively administered opioid analgesics, primarily the longer-lasting agents, increase postoperative vomiting due to opiate-induced stimulation of the central chemoreceptor trigger zone.

BOX 37-12

Risk Factors for Unanticipated Hospital Admission

Surgical
- Pain
- Bleeding
- Extensive surgery
- Surgical complications
- Abdominal surgery
- ENT and urology surgery

Anesthesia
- Nausea and vomiting
- Somnolence
- Aspiration

Social
- Discharge without escort

Medical
- Medical complications related to DM, IHD, and sleep apnea
- Medication error

From Shnaider I, Chung F. Outcomes in day surgery. *Curr Opin Anaesthesiol*. 2006;19:622-629.
DM, Diabetes mellitus; *ENT*, otorhinolaryngology; *IHD*, ischemic heart disease.

- *Induction of anesthesia*. Inhalation induction may result in gastric distention from positive pressure ventilation via the anesthesia facemask and is known to increase postoperative vomiting. For intravenous induction of anesthesia, propofol is mildly antiemetic and etomidate and ketamine are emetic.
- *Maintenance of anesthesia*. Several variables are known to increase the incidence of postoperative vomiting:
  - Longer anesthesia times
  - General anesthesia when compared with regional or local anesthetic techniques
  - Volatile inhalation anesthetics when compared with intravenous hypnotic agents
  - Intraoperative opioid administration
  - Nitrous oxide

Postanesthetic-related factors contributing to emesis include the following:

- *Ambulation*. More commonly seen in phase II recovery when the patient is mobilized in preparation for discharge, especially in patients receiving opioid analgesics.
- *Postural hypotension*. Dizziness, syncope, and nausea may be a problem if there is a significant reduction in blood pressure on standing.
- *Uncontrolled pain*. Etiologic factors may include increased catecholamine concentrations, increased level of consciousness, or peripheral sensitization after direct tissue injury with the resultant release of endogenous nociceptor activators.
- *Postoperatively administered opioid analgesics*.
- *Oral intake*. Fluids given routinely to patients before discharge from phase II recovery results in a greater incidence of vomiting or prolonged phase II stay than do fluids given to patients only if they are requested.[152]
- *Lower inspired oxygen concentrations*. Higher concentrations (50% to 80%) of intraoperative and postoperative supplemental oxygen therapy have been suggested to reduce the incidence of PONV, although the results from studies have been mixed.[153-157]
- *Reversal agents*. Opioid and benzodiazepine receptor antagonists and neuromuscular reversal agents may increase nausea and vomiting. In regard to neuromuscular reversal, it appears that only higher doses of neostigmine (greater than 2.5 mg) may demonstrate emetic tendencies.[158]

Suggested management of nausea and vomiting involves preoperatively administered pharmacologic interventions.[159-162] However, evaluating the efficacy of these agents is difficult because the cause of nausea and vomiting is multifactorial. Oral fluids should be withheld, and intravenous fluid hydration can be maintained with normal saline or lactated Ringer's solution until the emesis is controlled. Patients at high risk for postoperative nausea and vomiting will benefit from prophylactic antiemetic therapy. Antiemetic drugs should be administered singularly or in combination, based on the number of identified risk factors. Patients at high risk will benefit from multimodal drug therapy. Combination therapy permits targeting multiple receptors, as well as administering agents with prolonged effects to complement medications with rapid-onset properties. When postoperative nausea and vomiting does occur in the postoperative phase, pharmacologic treatment should consist of medications from a pharmacologic class different than from the prophylaxis antiemetic administered. Antiemetic management strategies based on patient risk are noted in Figure 37-1.

Acupressure/Acupuncture. P6 acupoint stimulation can be effective in preventing or minimizing postoperative nausea and vomiting. The mechanism of action is uncertain, but endorphin release or serotonin changes have been suggested as possible causes.[147]

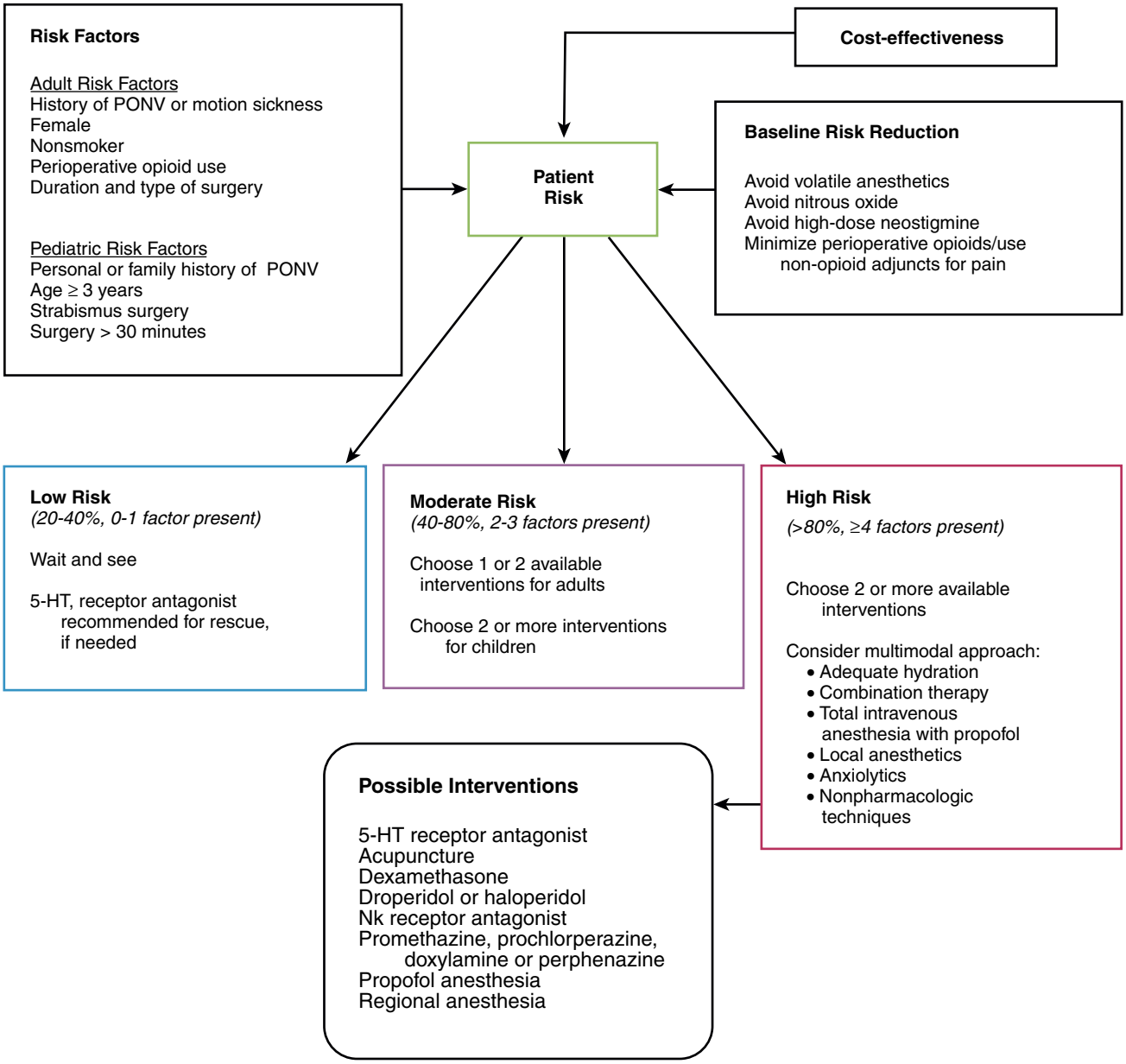

FIGURE **37-1** Antiemetic management strategies based on patient risk. (From Le TP, Gan TJ. Update on the management of postoperative nausea and vomiting and postdischarge nausea and vomiting in ambulatory surgery. *Anesthesiol Clin*. 2010;28[2]:225-249.) *PONV,* postoperative nausea and vomiting; *5-HT,* serotonin; *Nk,* neurokinin.

Aprepitant. Aprepitant (Emend) is a neurokinin-1 receptor antagonist. Oral administration of 40 to 80 mg within 3 hours of induction of anesthesia is recommended for high-risk, nonpregnant patients. Aprepitant has been shown to be more effective than ondansetron for preventing PONV and PDNV, especially in the first 48 hours.[163]

Dexamethasone. Studies have found dexamethasone to be effective in reducing the incidence of postoperative nausea and vomiting. For adults, dexamethasone 5 to 10 mg, given alone or in combination with other antiemetic agents, was effective in reducing postoperative vomiting.[164-165] In children, 0.0625 mg/kg was as effective as 1 mg/kg intravenously in preventing vomiting after tonsillectomy. Administering dexamethasone immediately after induction of anesthesia avoids the perineal pruritus seen when the drug is administered to an awake patient. Dexamethasone may be beneficial in the treatment of postoperative nausea and vomiting when used in combination therapy with other agents. The time until discharge from the phase II recovery area has been shortened after ambulatory surgery in patients receiving dexamethasone.[166,167] The incidence of vomiting in phase III is reduced if dexamethasone is administered during surgery.

This beneficial effect could be secondary to its long duration of action, with effects lasting as long as 24 hours. Adverse effects from a single dose of dexamethasone have not been reported.[168] The exact antiemetic mechanism is unknown; however, improvements in mood and sense of well-being, central inhibition of prostaglandin synthesis, inhibition of endogenous opioid release, and changes in the permeability of the blood-brain barrier to serum proteins have been suggested.[169] Blood glucose levels transiently increase after dexamethasone administration.[170]

Dolasetron. Dolasetron (a selective serotonin type 3 receptor antagonist), 12.5 mg given intravenously, is effective in preventing and treating postoperative vomiting. Dolasetron should be administered within 15 minutes before the end of anesthesia. A single oral dose of 100 mg of dolasetron given 1 to 2 hours before surgery is effective for the prevention of postoperative vomiting. One comparative study found 50 mg of dolasetron given intravenously to be as effective as 4 mg of ondansetron for the prevention of postoperative nausea and vomiting.[171]

Droperidol. Droperidol (Inapsine, a butyrophenone/dopamine receptor antagonist), 10 to 20 mcg/kg given intravenously, has been effective in reducing vomiting. Prophylactically administered droperidol, 20 mcg/kg given intravenously immediately after induction, was superior to metoclopramide, 5 or 10 mg orally, in reducing postoperative vomiting.[116] This dose appears to offer a compromise between reducing vomiting and extending the patient's stay owing to prolonged sedation.[172]

Caution should be exercised with the use of larger doses of droperidol (50 to 75 mcg/kg), because the occurrence of side effects (e.g., anxiety, dizziness, drowsiness, extrapyramidal symptoms, hypotension) and the potential to delay discharge may be increased. In 2001 the Food and Drug Administration (FDA) placed a "black box" advisory on the packaging label regarding the use of droperidol and risk of fatal dysrhythmias. The FDA recommends 12-lead electrocardiographic monitoring of patients for 2 to 3 hours after drug administration, which creates concerns over time efficiency in the ambulatory setting.[173] The FDA has recently agreed to reassess this issue, given that the overwhelming consensus among anesthesiologists and nurse anesthetists is that droperidol is safe when used in small doses as an antiemetic. Since the FDA-mandated advisory, the use of droperidol in anesthesia has decreased significantly.[174] A further discussion of the clinical use of droperidol can be found in Chapter 9.

Ephedrine. Ephedrine (an indirect-acting sympathomimetic agent), 0.5 mg/kg given intramuscularly at the end of surgery, was found to be as effective as droperidol, 40 mcg/kg given intramuscularly, in minimizing nausea and vomiting while producing less sedation. Similarly, ephedrine, 0.5 mg/kg given at the end of abdominal surgery, reduced the incidence of nausea and vomiting during the first 3 hours postoperatively. Ephedrine, 10 to 25 mg given intravenously, has been recommended for the treatment of nausea and vomiting associated with the postural hypotension of ambulation before the patient is discharged from the facility.[175]

Metoclopramide. Metoclopramide (a benzamide) exerts beneficial gastric effects by increasing lower esophageal sphincter tone, promoting gastric emptying by increasing gastric and small-bowel motility, presumably through cholinergic, antidopaminergic, and antiserotonin (at higher doses) receptor effecs.[176] Conflicting reports have been published about the efficacy of metoclopramide as an antiemetic. A review of placebo-controlled studies involving metoclopramide failed to find any clinically significant antinausea effect at low dosages.[177] Metoclopramide is ineffective as an antiemetic at lower dosages (e.g., 10 mg) in the adult population[178] unless used in combination with other antiemetics (e.g., dexamethasone).[179] Larger doses of metoclopramide (0.4 to 0.5 mg/kg or generic 50 mg IV) in the adult patient may offer some antinausea benefit individually and when used in conjunction with ondansetron or dexamethasone.[180,181] By itself, even at moderate doses of 0.5 mg/kg, metoclopramide is not as effective as ondansetron.[182] An advantage of metoclopramide is its lack of sedative traits; this quality reduces the potential for delaying patient discharge. The intravenous administration of 0.15 mg/kg of metoclopramide has been recommended for the treatment of nausea and vomiting in patients in the PACU who appear sedated.[183] Metoclopramide is not without side effects; extrapyramidal symptoms have been associated with its use.[184]

Ondansetron. Ondansetron (a selective serotonin type 3 receptor antagonist), 0.15 mg/kg given intravenously, is widely used as an antiemetic and rescue drug for PONV. In the adult patient, 4 mg of ondansetron appears to be as effective as 8 mg when it is administered intravenously in the PACU as a treatment for nausea and vomiting.[169]

Palonosetron. Palonosetron (Aloxi) is a second-generation serotonin type 3 receptor antagonist with a long duration of action. Intravenous doses of 0.025 to 0.075 mg are effective in preventing both PONV and PDNV.[185]

Scopolamine. Transdermal scopolamine has a 2- to 4-hour onset of action and should be applied before surgery (preferably the night prior). Timing of the patch placement may be challenging in the ambulatory setting. Side effects, including dry mouth, drowsiness, contact dermatitis, and visual disturbances, are generally mild. Toxic psychosis has been reported in pediatric and elderly populations.[186]

Postoperative Pain

Appropriate postoperative pain management helps minimize the stress of surgery, thereby fostering a quicker convalescence. Uncontrolled postoperative pain causes triggering of the stress response, patient uneasiness, and neurohumoral responses, and increases nausea and vomiting, psychologic distress, discharge delays, and unanticipated hospital admission. Pain management should begin with the use of wound infiltration with local anesthesia such as bupivacaine or bupivicaine liposomes (Exparel), the use of peripheral or regional nerve block, perineural, incisional, or intraarticular local anesthesia catheters, and the administration of opioid and nonopioid (i.e., NSAIDs) analgesics preoperatively or intraoperatively, particularly in procedures associated with discomfort after emergence from anesthesia. These practices decrease analgesic requirements in the immediate recovery period, resulting in reduced pain scores and decreased postoperative nausea and vomiting.[187]

The severity and onset of postoperative discomfort are influenced by previously administered analgesics. Immediate control of pain in the PACU can be achieved by incremental titration of small intravenous doses of a short-acting opioid analgesic such as fentanyl (12.5 to 75 mcg) or alfentanil (50 to 300 mcg) every 2 to 3 minutes until nociceptive pain relief has been achieved. Nonopioid analgesics should be considered to treat inflammatory pain or neuropathic pain. They have the advantage of improving overall analgesia, promoting early mobilization, and minimizing opioid-related side effects. Once patient discomfort has been controlled and the patient is tolerating oral fluids, early management of pain with oral analgesics (similar to those the patient will be taking after discharge) should be considered. This allows for evaluation of the analgesic's effect on pain alleviation, the patient's mental condition, and the patient's respiratory drive. The outpatient's analgesic medication should be safe and easily managed by the patient or caregiver once the patient is discharged from the facility.

Discharge Criteria

Before the patient is discharged from the ambulatory facility, he or she must meet certain criteria of recovery from the effects of surgery and anesthesia. A consistent method of evaluating the patient for discharge readiness offers the advantages of reproducibility, standardization, and objectivity; however, no single universally accepted standard exists for determining discharge readiness.

BOX **37-13**

Key Education Points for Discharge Instructions

Medications
- Detail the name, purpose, and dosage schedule for each medication. Emphasize the importance of following the directions on the label.
- The patient should resume medications taken before surgery per the physician's order.
- If pain medication is not prescribed, nonprescription, nonaspirin analgesics (e.g., acetaminophen, ibuprofen) may be effective to treat mild aches and pains.
- Additional pain medication may be ordered by the physician after surgery. The patient should take these medications as directed, preferably with food to prevent gastrointestinal upset.

Activity Restriction
- Caution the patient to take it easy for the remainder of the day following surgery. Postoperative dizziness or drowsiness is not unusual after surgery and anesthesia and may last several days.
- For the next 24 hours, the patient should not drive a vehicle, operate machinery or power tools, consume alcohol (including beer), make important personal or business decisions, or sign important documents.
- Describe the permissible activity level in specific behavioral terms (e.g., do not lift objects greater than 20 lb); describe any limitation of activities.

Diet
- Explain any dietary restrictions or instructions.
- If no dietary restriction, instruct the patient to progress as tolerated to a regular diet.

Surgical and Anesthesia Side Effects
- Anticipated sequelae of surgery, such as bleeding and pain, should be delineated.
- Common side effects associated with anesthesia include dizziness, drowsiness, myalgia, nausea and vomiting, and sore throat.

Possible Complications and Symptoms
- Instruct the patient and responsible caregiver in pertinent signs and symptoms that could be indicative of postoperative complications.
- The patient should call his or her physician if any of the following develop:
  - Fever greater than 38.3° C (greater than 101° F) orally
  - Persistent, atypical pain
  - Pain not relieved by pain medication
  - Bleeding that does not stop or prolonged, unexpected drainage from the wound
  - Extreme redness/swelling around the incision, drainage of pus
  - Urinary retention after 8 hours or as otherwise instructed
  - Unremitting nausea or vomiting

Treatment and Tests
- Procedures the patient or responsible caregiver are expected to perform, such as dressing changes or the application of warm, moist compresses, should be described in detail.
- A complete list of necessary supplies should be included.
- If any postoperative tests are to be conducted, instructions as to the date, time, test location, and any pre-visit preparation should be listed.

Access to Postdischarge Care
- Provide the telephone number of the responsible and available physician.
- Provide the telephone number of the ambulatory center and the hours of operation.
- Provide the name, address, and telephone number of the appropriate emergency care facility.

Follow-up Care
- Identify the date, time, and location of the patient's scheduled return visit to the clinic or surgeon.

Modified from Marley RA, Moline BM. Patient discharge from the ambulatory setting. *J Post Anesth Nurs*. 1996;11:41

For discharge to occur, the patient must be clinically stable and able to continue the recovery process at a remote recovery location. The decision to discharge is best made on objective criteria outlined in the policies of each ambulatory surgical facility. Distinct objective discharge criteria must be addressed when assessing home readiness of the patient. (*Note:* Before discharge from phase I, the patient's vital signs will be stable, there will be no respiratory impairment, protective reflexes of swallow and cough will be present, and the patient will be oriented to his or her preoperative level. It is assumed that the status of these parameters will not deteriorate during the patient's stay in phase I.) Individually, the following clinical markers should be evaluated in an organized, concise manner:

1. Vital signs should be stable and age appropriate.
2. The patient should be oriented to person, place, and time or at a level appropriate for the patient's developmental and preoperative status.
3. Ambulation can be affected by the surgical procedure and the patient's developmental level. If assistance to ambulate is required, the home caregiver must be capable of meeting this need.
4. There should be no respiratory distress.
5. Swallowing and coughing protective airway reflexes must be present.
6. Bleeding should be minimal or appropriate for the surgical procedure.
7. Pain should be minimal or controlled with an appropriate analgesic regimen.
8. Nausea and vomiting should be minimal.
9. Oral intake prior to discharge is not necessary unless crucial to the patient's continued convalescence at home (e.g., diabetic patient, patient requiring oral analgesics).[51]
10. Voiding is not mandatory before discharge, except for patients at high risk for postoperative urinary retention (e.g., history of postoperative urinary retention, pelvic or urologic surgery, perioperative catheterization).[51]
11. A responsible caregiver should be available.

A complete discussion of postanesthesia discharge criteria can be found in Chapter 50.

Discharge Considerations

During the preparatory phase, the availability of a responsible person who will oversee the patient's care once the patient is discharged should be ascertained before surgery. In some cases,

inpatient admission may be necessary if a responsible individual cannot be located. Postoperative care may be required for up to 48 hours in such cases, especially in elderly patients. The patient and responsible person should be provided with written instructions that are verbally reinforced before the patient is discharged. This information should include the physician's telephone numbers and steps to be taken if questions or complications arise. Once the patient has satisfied the criteria for discharge from the outpatient facility, certain discharge instructions should be reviewed to expedite and streamline the discharge process (Box 37-13).

The period of patient recovery after discharge from the ambulatory facility until resumption of normal activities is termed *phase III*. This is an important and often forgotten aspect of postoperative ambulatory care. Patient-care issues requiring attention continue to be important. It is important to convey to patients that it will take several days before they begin to feel as they did before surgery.

SUMMARY

The numbers and types of surgeries performed on an ambulatory basis will continue to increase, as will the ability of facilities to appropriately treat these patients. As anesthetic techniques and agents are refined, thereby increasing the safety and efficiency of patient care and discharge, new groups of patients will be evaluated for their appropriateness for outpatient surgery. These new groups will continue to challenge our resources for providing ambulatory anesthesia.

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38 CHAPTER Anesthesia for Ear, Nose, Throat, and Maxillofacial Surgery

◆ *Gary D. Clark and Julie A. Stone*

The practice of anesthesia for the ear, nose, and throat (ENT) patient is both challenging and rewarding. The anesthesia practitioner is often required to make decisions regarding difficult airway management and must have the knowledge and skills to navigate abnormal and difficult anatomy. As a specialty, ENT presents specific concerns to the anesthetist in regard to the preparation and management of surgical procedures (Box 38-1). There are several essential goals when providing anesthesia for ENT and maxillofacial (i.e., plastics and dental) surgical procedures:

1. Possessing a thorough knowledge of the airway anatomy and function
2. Selecting and preparing for appropriate technique(s) and approach for airway management
3. Preventing and managing potential airway complications
4. Producing profound selective muscle relaxation during periods of extreme stimulation, yet maintaining the potential for rapid recovery (e.g., suspension laryngoscopy)
5. Maintaining cardiovascular stability during periods of intense surgical stimulation
6. Omitting neuromuscular relaxation for surgical procedures that require isolation of nerves
7. Preventing or containing airway fires
8. Minimizing intraoperative and postoperative blood loss
9. Preventing adverse respiratory and cardiac responses resulting from manipulation of the carotid sinus and body
10. Taking the appropriate postoperative measures to prevent and treat postsurgical airway obstruction
11. Avoiding or limiting the use of nitrous oxide during tympanoplasty or other closed-space grafting

Surgical intervention for ENT procedures uses a variety of specialty equipment, including lasers, endoscopes, and specialized endotracheal tubes (e.g., laser and microlaryngeal tube). The basis of many ENT and maxillofacial surgical procedures includes endoscopic examination of the sinuses; tissue tumors of the head, neck, and oral cavity; abscesses; surgery to the middle ear; papillomas of the airway; hypertrophic tonsils and adenoids; acute epiglottitis; thyroid disorders; and traumatic or congenital facial deformities. The majority of these procedures involve the nose, facial and frontal sinuses, larynx, oropharynx, nasopharynx, tongue, trachea, mandible, and maxilla, as well as other supporting structures of the head and neck. These procedures necessitate sharing the airway with the surgeon and may lead to a tenuous airway and significant challenges perioperatively. Airway compromise in ENT patients may be subtle and can take several forms. Therefore, good communication is essential in the preoperative period to ensure the safest approach to anesthesia.

This chapter describes the pertinent anatomy and physiology of the head and neck for the anesthetist, reviews specialized anesthetic considerations, reviews surgical and anesthesia equipment used during ENT procedures, analyzes some of the common pharmacologic agents used for ENT procedures, and discusses principles of anesthesia for ENT.

FUNCTIONAL ANATOMY OF THE HEAD AND NECK

A fundamental knowledge of the anatomic and physiologic function of the structures of the head and neck is essential for dealing with the myriad decisions arising perioperatively during these procedures. Commonly, the ENT surgical procedure is being performed because the anatomic structures are abnormal, distorted, or deviated. Having a working knowledge of the structures and their relationships before subjecting the patient to respiratory changes produced by anesthesia is imperative.

The anatomic structures of the head and neck and their relationships are complex (Figure 38-1). The sensory and motor supply of the upper airway originates from cranial nerves and includes the trigeminal, glossopharyngeal, facial, and vagus nerves. Understanding the sensory supply is required to provide sufficient local and regional anesthesia. Likewise, motor function evaluated during and after surgical procedures may indicate trauma or damage to muscles. A thorough knowledge of which nerves control muscle function is essential to preventing such trauma.

The relationships of the oropharynx, nasopharynx, nasal chambers, sinuses, esophagus, and lower airway structures such as the larynx, cricoid, thyroid, and vocal cords provide a basis for directing and providing care for the patient receiving ENT surgery. The nose is a major anatomic structure that is responsible for warming, filtering, and providing humidity to the air taken in during inspiration. The structures of the nose include the external nose, the nasal cavity, and frontal, maxillary, and ethmoid sinuses. The nares or nostrils are separated by the septum. The lateral margins of the nares are cartilaginous structures and extend posteriorly over the hard palate, leading to a confluence at the soft palate, oropharynx, and base of the tongue. The oropharynx rests superior to the epiglottis, vocal cords, larynx, and trachea.

The external nose is composed largely of cartilage supported primarily by soft connective tissue and delicate mucous membranes, as is the nasal septum. The nasal cavities are hollow structures formed by a floor, roof, lateral wall, and the septum. The lateral aspects of the nasal cavities contain concha, or turbinates. The turbinates are highly vascular and are divided into three separate compartments: the superior, middle, and inferior. The turbinates greatly increase the surface area of the nasal cavities, aiding in filtration and humidification of inspired gases.

The extensive vascular supply of the turbinates may lead to severe bleeding if the nasal airway or nasoendotracheal tube is not inserted along the superior margin of the hard palate. Congestion of the mucosal veins in the turbinates of the nose causes swelling of these tissues, reducing the size of the nasal cavity (most notably, the paranasal sinuses) and thus creating the feeling of "congestion" during respiration. Inadvertent palatine submucosal insertion of the nasoendotracheal tube can lead to severe bleeding

BOX 38-1

Special Considerations for ENT Procedures

- Use of specialized ventilation techniques
  - Insufflation
  - Intermittent apnea
  - Apneic oxygenation
- Prevention of endotracheal tube fire
- Shared airway
- Surgical field avoidance
- Restricted use of nitrous oxide
- Restricted use of muscle relaxants
- Use of specialized equipment
  - Laser
  - High-frequency jet ventilation (HFJV)
- High percentage of pediatric patients
- Minimizing blood loss

ENT, Ear, nose, and throat.

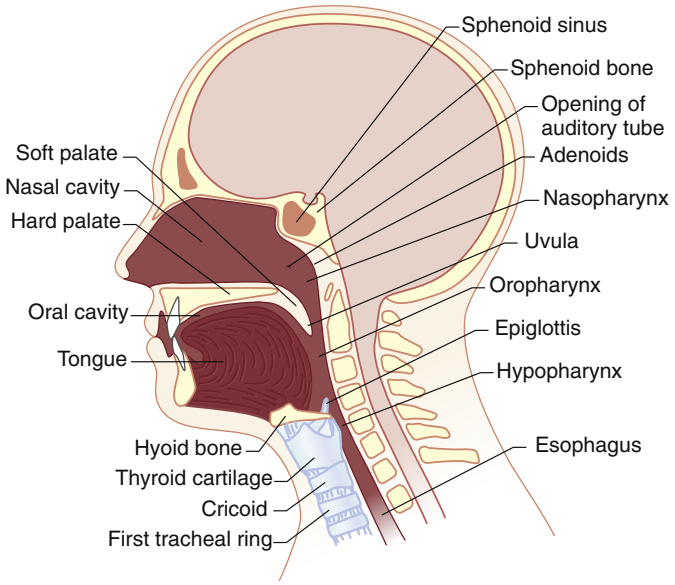

FIGURE **38-1** Anatomy of nasal cavity, oral cavity, nasopharynx, oropharynx, and hypopharynx. (From RD Miller, et al. *Miller's Anesthesia*. 7th ed. Philadelphia: Churchill Livingstone; 2010:2358.)

or infection in the perioperative period if entry of the tube is forced or tissues are engorged. These paired sinuses include the sphenoid, ethmoid, frontal, and maxillary sinuses. They not only serve as resonators for the voice but also filter, humidify, and warm the air during inspiration. These hollow structures are formed of low-density bone and are lined with a thin layer of mucous membranes, reducing the weight of the skull but making these bones more susceptible to fractures and cerebral spinal fluid leak secondary to facial trauma.[1-3]

The pharynx is composed of the terminal end of the nasopharynx, the oropharynx, and laryngopharynx or hypopharynx extending to the sixth cervical vertebra. The medulla inhibits respiration with swallowing; the pharynx then serves as a muscular tube that constricts, allowing the passage of food. The pharynx allows the smooth passage of air and functions as a modulator for the voice. The nasopharynx is continuous with the internal nasal cavities and extends to the soft palate. The nasopharynx communicates with the oropharynx and forms the posterior aspect of the throat. Major structures of the oropharynx include the base of the tongue, soft palate, uvula, and lymphatic structures (tonsils). The tonsils are the most sensitive areas of the oropharynx. Beginning with the anterior margin and progressing bilaterally and posteriorly, the oropharynx is defined by the soft palate, base of the tongue, uvula, palatine tonsils, and adenoids, forming Waldeyer's ring.[1-3]

Hypertrophy of the palatine and adenoid tonsils (exaggerated many times by chronic infection) and of the soft palate and uvula can pose serious airway compromise, particularly in young children. The generous blood supply to the tonsils from branches of the external carotid, maxillary, and facial arteries and their close proximity to the facial and internal arteries are matters of concern regarding potential bleeding during "routine and simple" tonsillectomy. The laryngopharynx includes the epiglottis, which provides protection for the vocal cords, and is the region shared by the esophageal orifice and larynx.

The complexity of the neuromuscular system, which controls the epiglottis, allows the isolation of the trachea from the esophagus during swallowing. Any interruption of this coordinated neuromuscular function of the epiglottis or of any other protective reflexes can provide a dangerous opportunity for the entrance of food or liquid into the larynx and lower airway. As food is squeezed posteriorly, an automatic swallowing reflex is initiated. The larynx is pulled superiorly, allowing the epiglottis to cover and protect the opening of the larynx.[1] The epiglottis does not operate as a movable lidlike structure that falls to close the larynx during swallowing, as is often claimed. Passage of food into the trachea can occur if the muscles and protective elevation of the larynx become rigid or are changed due to nerve interruption. A series of reflex and involuntary processes mediated by the superior laryngeal, recurrent laryngeal, and glossopharyngeal nerves coordinates and regulates glottic closure during swallowing.[1-3]

The larynx is a rigid organ composed of three paired and three unpaired cartilages (arytenoid, corniculate, and cuneiform and thyroid, cricoid, and epiglottis, respectively) and is supported by the hyoid bone. This hollow structure forms a reservoir distal to Waldeyer's ring and provides the connection of the oropharynx to the trachea (Figure 38-2). The primary functions of the larynx are vocalization and articulation; secondarily, it provides protection of the airway and allows respiration.[1] In the adult, the area of the vocal cords, or rima glottis, is the narrowest portion of the larynx. In children, the cricoid ring is the narrowest portion of the airway until approximately 10 years of age. Cuffed tubes are then generally recommended for those older than 8 to 10 years of age to allow for a better seal of the airway, prevent subglottic edema, and reduce the incidence of postoperative airway compromise.[4]

Specific nervous structures of the head and neck are worthy of note because of their superficial location or proximity to operative sites. Surgeons may use audible or visual nerve-locating devices to find these nerves and their appropriate branches. To accurately locate these nerves, neuromuscular blocking agents may be avoided during the maintenance of certain general anesthetics.

The facial nerve (VII) has six major branches: four anterior (temporal, zygomatic, buccal, and mandibular), one inferior (cervical), and one posterior (posterior auricular) branch. The facial nerve located at the tragus of the ear is the motor and sensory supply to the muscles for facial expressions. The zygomatic branch leaves the skull via the stylomastoid foramen and advances anteriorly over the maxilla. The corda tympani branch of the facial nerve conveys taste from the anterior two thirds of the tongue, and the more superficial tri-branched facial nerve controls facial expression. The trigeminal nerve begins at the gasserian ganglion and divides into three branches; they are the ophthalmic (the first division, V_1), maxillary

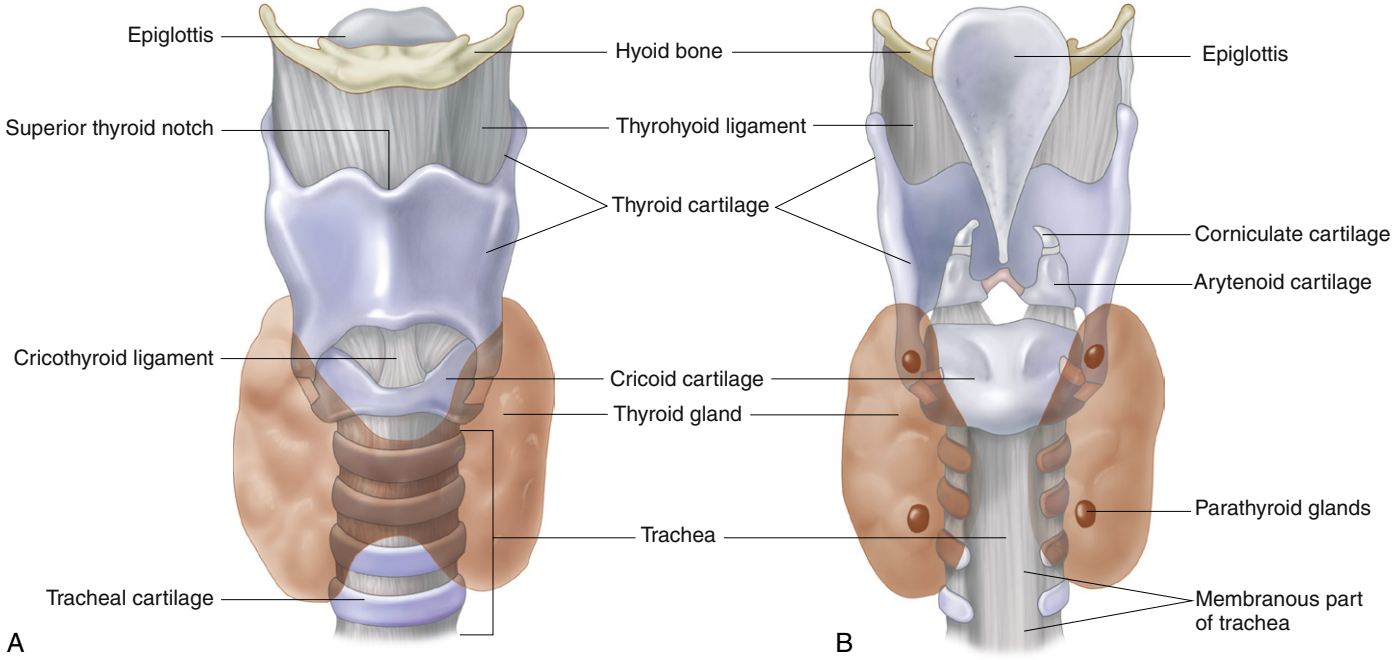

FIGURE **38-2** Laryngeal cartilages. Some softer tissues of the larynx and surrounding structures have been removed to make it possible to see the cartilages of the larynx. Note the position of the nearby thyroid gland. **A,** Anterior view. **B,** Posterior view. (From Patton KT, Thibodeau GA. *Anatomy & Physiology.* 8th ed. St. Louis: Mosby; 2013:804.)

(the second division, V_2), and mandibular (the third division, V_3). All three divisions provide sensory and motor innervation to the nose, sinuses, palate, and tongue. They aid in the motor control of the face and in mastication.[1-3]

The glossopharyngeal nerve provides motor and sensory innervation for the base of the tongue and nasopharynx and oropharynx. The glossopharyngeal nerve is responsible for eliciting the gag reflex during instrumentation of the posterior pharynx and vallecula.

The superior laryngeal and recurrent laryngeal nerves are both branches of the vagus (X). The superior laryngeal nerve descends to the hyoid bone and then branches into the internal laryngeal nerve, which passes through the thyrohyoid membrane, and the exterior laryngeal nerve, which descends over the lateral thyroid cartilage to the distal trachea. The recurrent laryngeal nerve ascends from the vagus up the distal trachea, passing through the cricothyroid ligament into the proximal trachea and vocal cords. The recurrent laryngeal nerve lies between the trachea and esophagus and supplies sensory innervation to the trachea and vocal cords. This branch of the vagus nerve also affects vocal cord closure and sensory function up to the inferior aspect of the epiglottis. Stimulation of the epiglottis with the tip of a straight laryngoscope, blades, suction catheters, and placement of an endotracheal tube in the trachea can produce a vagal response.[3] The paired and unpaired cartilages of the larynx are listed in Table 38-1. Nerve supply to the larynx is given in Table 38-2. The intrinsic muscles of the larynx, their nerve supply, and function are listed in Table 38-3. The extrinsic muscles of the larynx, their nerve supply, and function are listed in Table 38-4.[1-5]

TABLE 38-1 Paired and Unpaired Cartilages of the Larynx

Paired	Unpaired
Arytenoid	Thyroid
Corniculate	Cricoid
Cuneiform	Epiglottis

TABLE 38-2 Nerve Supply of the Larynx

Nerve	Innervation
Sensory Nerves	
Internal laryngeal (vagus)	Laryngeal mucosa above vocal cords (inferior epiglottis)
Recurrent laryngeal	Laryngeal mucosa below vocal cords
Glossopharyngeal	Superior aspect of epiglottis and base of tongue
Motor Nerves	
Recurrent laryngeal	All intrinsic muscles except cricothyroid
External laryngeal	Cricothyroid muscles

PREPARATION AND CONSIDERATIONS FOR EAR, NOSE, AND THROAT PROCEDURES

The Shared Airway and Considerations for Positioning

Operative procedures involving the airway, mouth, or bony structures of the face involve a true sharing of the airway between the surgeon and the anesthetist. Therefore, proper preparation requires planning and communication between the surgeon, surgical personnel, and the anesthetist prior to the surgical procedure. Sharing the airway with the surgeon also requires preparing and planning the use of the appropriate equipment. For example, during laryngoscopy the endotracheal tube may have to be smaller in diameter and moved to one side of the oropharynx to allow the surgeon to work around the tube and to facilitate the surgery. Many times the head of the table is rotated 90 to 180 degrees away from the anesthetist, resulting in a vulnerable airway to which the anesthetist may have little or no access. Of particular concern are

TABLE 38-3 Intrinsic Muscles of the Larynx

Muscle	Innervation	Function
Cricothyroid	Superior laryngeal nerve	Tension and elongates vocal cords
Thyroarytenoid	Recurrent laryngeal nerve	Relaxes vocal cords
Vocalis	Recurrent laryngeal nerve	Relaxes vocal cords
Posterior cricoarytenoid	Recurrent laryngeal nerve	Abducts vocal cords
Lateral cricoarytenoid	Recurrent laryngeal nerve	Adducts vocal cords
Transverse arytenoid	Recurrent laryngeal nerve	Adducts vocal cords
Aryepiglottic	Recurrent laryngeal nerve	Closes glottis
Oblique arytenoid	Recurrent laryngeal nerve	Closes glottis; approximates folds

TABLE 38-4 Extrinsic Muscles of the Larynx

Muscle	Innervation	Function
Sternohyoid	Cervical plexus; C1, C2, C3	Draws hyoid bone inferiorly
Sternothyroid	Cervical plexus; C1, C2, C3	Draws thyroid cartilage caudad
Thyrohyoid	Cervical plexus; hypoglossal nerve; C1 and C2	Pulls hyoid bone inferiorly
Thyroepiglottic	Recurrent laryngeal nerve	Inversion of aryepiglottic fold
Stylopharyngeus	Glossopharyngeal	Folds thyroid cartilage
Inferior pharyngeal constrictor	Pharyngeal plexus; vagus	Aids swallowing

the maintenance of adequate ventilation and patency of the anesthesia circuit and endotracheal tube. Extubation, disconnects, and leaks must be prevented. Adequacy of ventilation is constantly assessed by observing chest movement, auscultation, pulse oximetry, end-tidal CO_2, and blood gas analysis. A sudden loss of breath sounds, rising inspiratory pressures, or a reduction in end-tidal CO_2, particularly in the presence of a sharp reduction in inspiratory effort, may be due to a deflation of the endotracheal tube cuff, obstruction of the endotracheal tube, dislodgment of the endotracheal tube, a disconnection of the anesthesia circuit, or severing of the endotracheal tube during surgical dissection.[5] When coupled with vigilance, the precordial or esophageal stethoscopes are simple devices that should not be overlooked; these devices, in addition to more sophisticated mechanical devices, help the anesthetist maintain assessment of the airway.

Assessment of the airway prior to induction is critical in most ENT patients. Although the induction of anesthesia and securing of the airway are performed in the usual manner (with the anesthetist at the head of the table), the management of the airway can become questionable and difficult while at a distance. Obtaining a thorough history and performing an extensive evaluation of the airway for the ENT patient is crucial. A good examination of the airway will (1) allow for a careful and deliberate approach to airway management, (2) aid in evaluating the need for additional equipment and assistance, and (3) include alternative approaches for the difficult airway if the initial plan proves not to be successful. Once the induction is complete and the airway established, the anesthetist must be prepared to provide adequate ventilation, deliver necessary anesthetic and adjunct agents, place invasive lines, and safely monitor the patient while remaining at a distance and isolated from the airway.

Orchestrating how the patient is turned so that the patient's head is away from the anesthetist demands clear planning. The endotracheal tube should be secured with tape or suture to prevent removal. The invasive line tubing, intravenous access lines, monitoring devices, and breathing circuit require added length to extend to the patient without creating tension at the site before induction. The patient's entire head is frequently draped and prepped into the surgical field, limiting access to the endotracheal tube and breathing circuit connections (Figure 38-3).

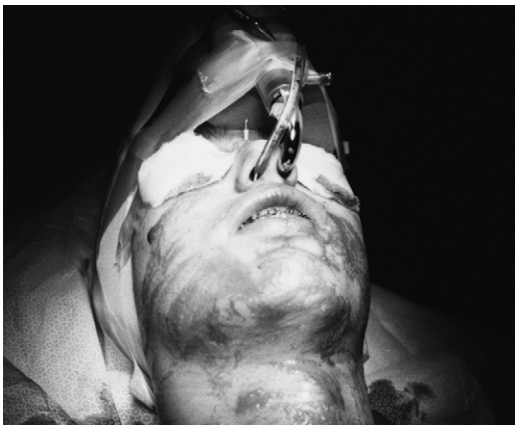

FIGURE 38-3 Illustration of secured airway for a patient undergoing face, neck, or maxillofacial surgical procedures. Note that the tube is positioned to prevent pressure on the lip, nose, or forehead and secured with tape to prevent movement during surgery. The connection is covered by sterile surgical drapes and allows only limited access during the surgical procedure.

When repositioning of the head is necessary, communication between the surgeon and anesthetist is important to reduce the possibility of extubation, position change, or occlusion of the endotracheal tube. Signs of air leaks around the endotracheal tube (e.g., bubbling, the sound of air escaping, or the smell of anesthetic agent from the patient's mouth) may well be more sensitive indicators than mechanical airway monitors. Occlusion of the endotracheal tube is best prevented but can be determined by good auscultation, watching chest wall motion, and monitoring inspiratory pressures and morphology of CO_2 waveforms. The surgeon must communicate any changes in the surgical field, such as changing the position of a suspended or fixed laryngoscope, dark

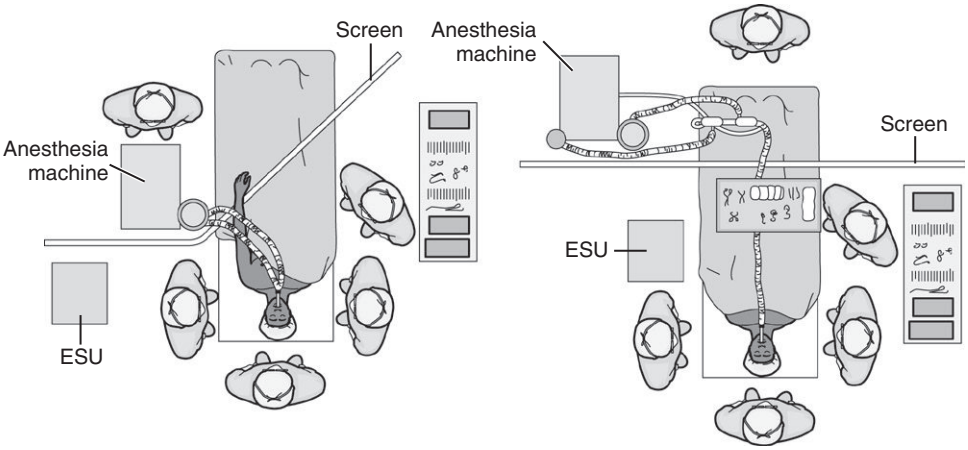

FIGURE **38-4** Position of the anesthetist for surgery of the head and neck. *Left*, The anesthetist is positioned at the side of the table and using a standard circle circuit. *Right*, The anesthetist is positioned at the foot of the bed and using a coaxial (Bain) circuit. *ESU,* Electrosurgical unit. (From Phillips N. *Berry & Kohn's Operating Room Technique*. 12th ed. St Louis: Mosby; 2013:873.)

blood, manipulation of carotid bodies, or the need for a change in the patient's head position.[6] Increased inspiratory pressures or a rapid loss of inspiratory pressure, decreased oxygen saturation, changes in end-tidal CO_2 measurements, or diminished breath sounds should, in turn, be communicated to the surgeon so that inspection of the airway and anesthesia circuit may be undertaken. If unable to arrive at a cause, undraping the patient may become necessary for a thorough examination of tube placement and connections or to find a leak in the anesthesia circuit that could compromise patient ventilation.

Procedures of the head and neck typically require access to all planes of the head by several members of the surgical team.[7] Because a number of problems can be encountered with the intubated patient during the surgical procedure, the surgeon may elect to perform a tracheostomy, then place and suture a flexible endotracheal tube in a fixed position during the procedure. A heightened state of vigilance must be maintained for occlusions from mucous plugs or blood, disconnects, endotracheal tube fires, and other problems that may arise during the anesthetic. During some ENT procedures, the surgical team also may need access to the chest and abdomen for securing grafts for the esophagus or oral cavity. Often this requires the anesthetist to take residence at either the side of the patient or at the foot of the operating table (Figure 38-4). Providing a smooth transition with protection of the established airway and prevention of hypoxia are the primary concerns during movement of an operating table with an anesthetized patient.

The anesthesia circuit and other monitors should be temporarily and briefly disconnected before the bed is turned. This will prevent undue tension on the circuit and other lines that could lead to traumatic extubation or loss of access. Ventilation of the patient with 100% oxygen and adequate tidal volumes for 3 to 5 minutes before disconnection will denitrogenate the functional residual volume and provide an extra reservoir of oxygen during the turn, preventing even a short period of hypoxia. However, if a volatile agent is the primary source of anesthesia, the addition of intravenous anesthesia during this preoxygenation is necessary to maintain an adequate level of anesthesia and/or amnesia during this period. A saturation of 100% is a reasonable goal before the disconnection and table movement.

The degree of table movement should be discussed with the surgeon before any interruption in the anesthesia or the breathing circuit takes place. Turning of the operating table should be a well-organized procedure, understood by all members of the surgical team, and one that takes the minimum amount of time. After relocking the bed, reconnection of the anesthesia circuit must be immediate to reestablish oxygenation and/or anesthesia. Reevaluation and assessment of the tube placement, breath sounds, chest expansion, oxygen saturation, anesthetic level, line and intravenous access, and end-tidal CO_2 should be performed *before* prepping and draping is begun and throughout the case. Once adequate ventilation is established, the use of an "artificial nose" or airway humidifier will help in preserving heat and moisture during long periods of anesthesia.

Attention to simple practical points may prevent airway mishaps. At least one large-bore intravenous line, as well as arterial and central venous pressure lines, should be started on the nonoperative side, if possible on the side of the patient that will be nearest to the anesthetist during the procedure. This will prevent obstruction of flow due to the surgical procedure, afford easier access for drug administration and blood sampling, facilitate the manipulation or maintenance of lines during surgery, and allow the surgeon easy access to the operative field. If such lines must be placed on extremities opposite the anesthetist, adequate extensions should be placed before a change in position of the table to reduce the chance of lines being removed, infiltrated, or disconnected during movement. The calf of the leg may be used for noninvasive blood pressure measurements to prevent dampening of intravenous fluid flows in the upper extremities. Care must be taken to ensure that the measurement of the blood pressure takes into account variations in table changes from the horizontal position to prevent hypotension to vital organs. Monitoring of neuromuscular relaxation may be performed at locations other than the adductor pollicis. Stimulation of the tibial nerve produces flexion of the big toe and is similar to that of the adductor pollicis.[8] Because ENT procedures may take more than 2 hours and can require significant fluid administration, monitoring urinary output with a Foley catheter may be included in the plan.

SPECIALIZED EQUIPMENT FOR EAR, NOSE, AND THROAT PROCEDURES

Endotracheal Tubes Designed for ENT Surgery

A number of endotracheal tubes are available for securing an airway. Standard endotracheal tubes equipped with flexible or

straight connectors are acceptable for many ENT procedures. The diameter and length of the endotracheal tube (ETT) will affect ventilation and seal of the airway. Using a small-diameter ETT in a large adult airway will not only lead to less ventilation through increased resistance but also will allow only a small portion of the cuff to contact the trachea. Using specialized tubes with small diameters allows more even distribution of the cuff over the trachea during inflation. Several of these specially designed ETTs have found wide acceptance in ENT anesthesia. A variety of designs are used to limit encroachment of the ETT into the surgical field, prevent kinking of the ETT when severe angles are necessary, prevent fires in the airway during laser therapy, and provide maximal patient ventilation and safety.[9]

A number of ETTs have been introduced for use in ENT anesthesia. The purpose for the evolution of these various types of ETT cuffs was to reduce cuff pressure on the tracheal wall and allow for improved tracheal perfusion, reduced tracheal injury, and more convenient airway access. Preformed right-angled ETTs, in cuffed and noncuffed types, are available for either oral or nasal intubation of adults or children. Oral Ring, Adair, and RAE tubes (named after inventors Ring, Adair, and Elwyn) are an excellent choice for cleft palate repair, tonsillectomy, uvulopalatopharyngoplasty, and procedures of the eye or upper face. Nasal RAE tubes are particularly well suited to maxillofacial surgery that does not allow for oral intubation. The nasal RAE can be used for cosmetic procedures of the face, surgical procedures of the oral cavity and mandible, or to correct malocclusion. However, although the preformed bend in the RAE tube prevents the ETT from kinking in many instances, it may be too distal or proximal for an individual patient's airways. This then allows the tip of the ETT to rest well below or above the carina. A careful check of the breath sounds and inspiratory pressures is imperative after intubation with the RAE to ensure proper positioning. Nasal intubation and placement of a nasogastric tube in the unconscious patient with facial trauma is best avoided to prevent possible penetration of the brain.[10,11]

Anode, armored, reinforced, and Kant Kink tubes all have an embedded coiled wire or plastic coil strand to produce a tube with greater flexibility and memory. Armored tubes for oral or nasal intubation resist kinking and retain their original integrity. They are useful when acute neck flexion or severe angles of the ETT are required, as in procedures involving the base of the skull or posterior aspect of the neck. However, several reports suggest that even the edentulous patient can on occasion occlude a reinforced ETT.[12] Several varieties of metal-impregnated tubes are available for use with laser surgery; these are designed to reduce the occurrence of an airway fire (Figures 38-5 and 38-6). The cuff of the laser tube is usually filled with saline to dampen or prevent the ignition. In addition, it is recommended that the cuff be filled with dyed saline so that a cuff perforation is readily apparent. Wrapping a standard ETT with reflective tape is not an adequate alternative to these commercially prepared tubes because the wrapped standard ETT will dry and lead to greater flammablility.[13]

Although not classified as an endotracheal tube, the laryngeal mask airway (LMA) and intubating laryngeal mask airway may be used to facilitate intubations as well as control the airway. The LMA does not produce tracheal stimulation, which can be a considerable advantage in ENT procedures. The incidence of coughing on emergence is lower with the LMA than with the endotracheal tube. Another advantage of the LMA is the ability to insert the device without the use of neuromuscular blocking agents or for airway rescue situations. Although LMA is contraindicated in some patients with laryngeal pathology, it is often the airway of choice when dealing with patients with pharyngeal

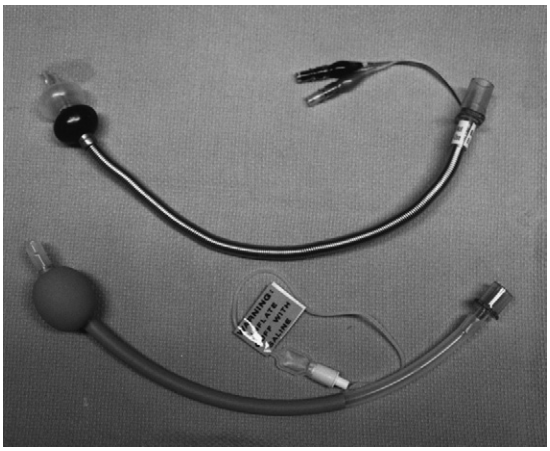

FIGURE **38-5** Endotracheal tubes for laser surgery of the airway.

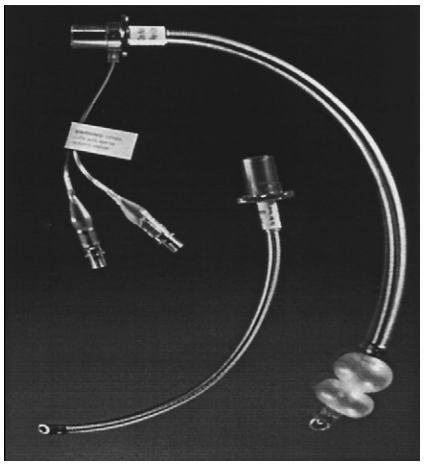

FIGURE **38-6** The Laser Flex endotracheal tube comes with a double cuff or no cuff. The double cuff is typically filled with normal saline. (Courtesy of Mallinckrodt Inc.)

pathology. Indications for LMA use in ENT surgery include a conduit for surgical access to the glottis and trachea, an aid to neurologic monitoring to avoid relaxant use, and as a means to isolate the glottis from bleeding from pharyngeal sources.[14]

SPECIAL CONSIDERATIONS FOR EAR, NOSE, AND THROAT PROCEDURES

Pharmacologic Considerations

The use of local anesthetics is particularly prevalent during nasal and sinus surgery. The most commonly used local anesthetics for ENT surgery include the amide-based drugs. Many procedures are performed using topical and local anesthesia as the sole agent, in combination or supplemented with monitored anesthesia care, intravenous sedation, or general anesthesia. Table 38-5 gives some topical local anesthetics commonly used in ENT surgery. Determination of doses of local anesthetics administered by injection and topically must be carefully calculated because more than one agent in various combinations are commonly used.

Additional information regarding local anesthetics for injection and topical use can be found in Tables 10-7, 10-8, and 10-9.

Vasoactive Drugs

The duration of action of a local anesthetic is proportional to the time the drug is in contact with nerve fibers. For this reason,

TABLE 38-5 Topical Anesthetic Drugs

Drug	Concentration	Dose	Notable Features
Cocaine	4%	3 mg/kg	Only local anesthetic with vasoconstrictive ability Blocks reuptake of norepinephrine and epinephrine at adrenergic nerve endings
Lidocaine	2% and 4% solution 2% viscous solution 10% aerosol 2.5% and 5% ointment 10%, 15%, 20%	4 mg/kg plain 7 mg/kg epinephrine 250-300 mg	Rapid onset Suitable for all areas of the tracheobronchial tree
Benzocaine	*Cetacaine contains:* 14% benzocaine, 2% butamben, and 2% tetracaine		Short duration of action (10 min) Can produce methemoglobinemia
Bupivacaine	0.25%, 0.5%, 0.75%	2.5 mg/kg plain	Slow hepatic clearance Long duration of action
Mepivacaine	1%, 2%	4 mg/kg	Intermediate potency with rapid onset
Dyclonine	0.5%, 1%	300 mg maximum	Topical spray or gargle Frequent use for laryngoscopy Absorbed through skin and mucous membranes

epinephrine in varying concentrations (1:200,000 or 5 mcg/mL; 1:100,000 or 10 mcg/mL; and 1:50,000 or 20 mcg/mL) may be added to local anesthetic solutions to produce vasoconstriction. Vasoconstriction limits systemic absorption and maintains a higher drug concentration in the vicinity of the nerve fibers to be anesthetized, thus extending the effects of the local anesthetic. Addition of epinephrine to a local anesthetic prolongs the duration of blockade and decreases systemic absorption and plasma concentrations, thus decreasing toxicity.[15]

It is estimated that in the United States, topical cocaine (4% to 10% solution) anesthesia is used in more than 50% of ENT procedures performed annually—specifically rhinolaryngology procedures.[16] Cocaine is a naturally occurring ester of benzoic acid that is hydrolyzed by plasma cholinesterase. Applied topically, it is an excellent local anesthetic and vasoconstrictor. The duration of action is approximately 45 minutes.[15] Cocaine produces vasoconstriction by blocking catecholamine reuptake into the adrenergic nerve ending, resulting in vasoconstriction and shrinking of the mucosa. Epinephrine is also injected for ENT procedures and is usually injected shortly after the application of cocaine. This combination of cocaine and epinephrine sets the stage for a significant interaction. Because cocaine that is absorbed into the plasma can block the uptake of epinephrine systemically, a toxic effect of epinephrine can result from the injection. This interaction can result in severe headaches, hypertension, tachycardia, and dysrhythmias.[17]

Anticholinergics

Anticholinergics were used liberally in the early days of anesthesia, predominantly because of the excessive secretions caused by older volatile inhalation agents. With the advent of newer anesthetic agents, excessive secretions are not an issue and the need for anticholinergics has diminished. The antisialagogue effects, however, may still be useful in certain intraoral procedures that require a drier operative field. Glycopyrrolate may be a better choice than atropine because it produces less tachycardia in comparison to atropine. Glycopyrrolate does not readily cross the blood-brain barrier and thus lacks sedative effects.

Corticosteroids

Glucocorticoids may be administered preoperatively and intraoperatively to decrease laryngeal edema formation, reduce nausea and vomiting, and prolong the analgesic effects of local anesthetics. They should be administered as early as possible in the perioperative period so as to reach their peak effect prior to initiating surgery. The use of steroids may reduce the nausea and vomiting experienced after surgery. Dexamethasone was also reported to prolong the analgesic effects of local anesthetics.[18] It has been postulated that prostaglandins, histamine, and other mediators increase the permeability of local vessels, changing nociception at the site of trauma and leading to the sensation of pain. Steroids inhibit the production of prostaglandins and therefore reduce pain. Although the use of steroids may be beneficial, they can also create sufficient immunosuppression to mask inflammation or infection.

Postoperative Nausea and Vomiting

All patients are at risk for postoperative nausea and vomiting (PONV). ENT procedures, particularly of the middle ear, are associated with a high incidence of PONV.[19] Patients experiencing PONV are uncomfortable after surgery, their discharge may be delayed from the postanesthesia care unit (PACU), or they may have an unscheduled hospital admission. The accumulation of blood in the posterior oropharynx, which may drain into the stomach or be swallowed during the postoperative period, can lead to PONV. This frequently occurs during throat procedures such as tonsillectomy. Packing the back of the throat with surgical packs during the procedure can prevent some drainage into the stomach. Care must be taken that the patient is awake, all surgical packs are removed, and suctioning of the airway precedes the extubation process, producing a clear airway and ensuring the control of protective airway reflexes. A multimodal approach is advocated to attenuate PONV in ENT patients.[20,21]

Special Anesthetic Techniques Associated with ENT Procedures

Deliberate Controlled Hypotension

Extensive dissection is required for many head and neck tumors, with operative times extending to 12 or more hours. Considerable fluid replacement, blood loss, electrolyte imbalances, and cardiovascular and respiratory changes may occur during surgery. The surgeon may request deliberate controlled hypotension to reduce blood loss. Patients must be individually evaluated prior to controlled hypotension to determine a safe mean pressure.

TABLE 38-6 Common Intravenous Agents for Hypotensive Techniques

Drug and Dosage	Advantages	Disadvantages
Sodium nitroprusside Variable age- and anesthetic-dependent effects *Young adults:* 1-5 mcg/kg/min *Children:* 6-8 mcg/kg/min	Potent; reliable; rapid onset and recovery; cardiac output well preserved	Reflex tachycardia; rebound hypertension; pulmonary shunting; cyanide toxicity possible
Esmolol 200 mcg/kg/min to achieve 15% reduction of mean arterial pressure	Particularly useful to control tachycardia	Potential for significant cardiac depression
Nitroglycerin *Adults:* 125-500 mcg/kg/min *Children:* 10 mcg/kg/min	Preserves myocardial blood flow; reduces preload; preserves tissue oxygenation	Increases intracranial pressure; highly variable dosage requirements
Nicardipine 5 mcg/kg/min	Ca^{++} channel blocker Preserves cerebral blood flow	
Remifentanil with propofol Remifentanil: 1 mcg/kg IV then continuous infusion 0.25-0.5 mcg/kg/min Propofol: 2.5 mg/kg IV then infusion of 50-100 mcg/kg/min	Remifentanil reduces middle ear blood flow, creating a dry surgical field for tympanoplasty Propofol may help reduce PONV	No analgesic effect once remifentanil infusion discontinued

Modified from DeGoute CS. Controlled hypotension: a guide to drug choice. *Drugs*. 2007; 67(7):1053-1076.
PONV, Postoperative nausea and vomiting.

The effects of common intravenous controlled hypotensive techniques are compared in Table 38-6.[22,23] The practice of controlled hypotension focuses on reducing the mean arterial pressure to some predetermined level related to the limits of cerebral and systemic autoregulation. The mean pressure is not usually allowed to fall below 60 mmHg, maintaining cerebral and renal autoregulation, as well as adequate coronary artery blood flow. Patients with chronic hypertension may require a higher mean pressure to maintain adequate perfusion.[23] Regardless of the technique or medication chosen, it is imperative that urine output, mean arterial blood pressure, cerebral and cardiac perfusion pressure, and arterial blood gases be closely monitored and maintained. When using hypotensive anesthesia, an arterial line is required. Hypotensive techniques are also used with endoscopic sinus surgery. It has been noted that better operating conditions are achieved when moderate hypotension is produced with a vasoconstrictor such as a beta blocker than when vasodilating agents are used.[24]

SELECT TECHNIQUES COMMONLY USED IN ENT PROCEDURES

Laser Surgery

Anesthesia and laser surgery is also discussed in Chapter 43; however, some specific issues concerning lasers are relevant to ENT surgery. Laser technology has been used in medicine for more than 30 years. The two most common lasers used in ENT surgery are the CO_2 and Nd:YAG (neodymium-doped yttrium aluminum garnet); recently the argon laser has become a popular choice as well.[25] Laser light is different from standard light. Whereas standard light has a variety of wavelengths, lasers have only one wavelength (monochromatic). Laser light oscillates in the same phase, or all the photons are moving in the same direction (coherent), and its beam is parallel (collimated). The wavelength of the Nd:YAG laser beam is shorter as it passes through the garnet than that of the CO_2 laser. The shorter wavelength allows less absorption by water and therefore less tissue penetration. For example, the shorter wavelength of the Nd:YAG allows the laser light to pass through the cornea, whereas the longer wavelength of the CO_2 laser would burn the cornea. Laser light emits a small amount of radiation and can be infrared, visible, and ultraviolet in the spectrum. Lasers enable very precise excision, produce minimal edema and bleeding, and are favored by surgeons for resection of tumors and other obstructions of the airway. For operations in and around the larynx, the CO_2 laser is frequently used because of its shallow depth of burn and extreme precision.[13] The CO_2 laser produces a beam with a relatively long wavelength that is absorbed almost entirely by the surface of these tissues, vaporizing cellular water. Intermittent bursts of the CO_2 laser produce intense, precisely directed energy that results in a clean cut through the target tissue with a minimal amount of penetration of surrounding tissue. A low-energy helium-neon laser is commonly used to aim or direct CO_2 laser beams.

The holmium:yttrium-aluminum-garnet (Ho:YAG) laser is a fairly new laser. The Ho:YAG laser has a pulsed infrared output with a wavelength of 2.1 mm. The laser has excellent absorption in water-rich tissues, and in otolaryngology, it has been used for nasal surgeries and for tonsillectomies.

Laser light beams are primarily used for their thermal effect and can be used to cut, coagulate, or vaporize tissues. The exact tissue interaction of a laser is dependent on several variables, including the types of tissues being irradiated, the wavelength of the emitted beam, and the power of the beam.

The majority of surgical fires occur during head and neck surgery. This is due to the presence of oxygen and the extensive use of lasers. The use of laser technology mandates taking measures to ensure the safety of the patient and operating room personnel (Box 38-2). Specific concerns include eye protection with appropriate colored glasses, avoidance of the dispersion of noxious fumes, and fire prevention. Stray or reflected beams of the Nd:YAG laser are capable of traversing the eye to the retina; therefore, green-lensed eye protection for all personnel is mandatory during use of the Nd:YAG laser. All persons in the operating room must wear goggles specifically designed to absorb Nd:YAG laser beams. The required protective eyewear for CO_2 lasers can be any clear glass or plastic that surrounds the face. Orange-red eye protection is required for the potassium-titanyl phosphate (KTP) laser, and orange glasses are required for the argon laser.

When tissues are cut by a laser, the smoke and vapors that are formed are called laser "plume." This plume is an environmental

BOX 38-2

General Safety Protocol for Surgical Lasers

- Post warning signs outside any operating area: "WARNING: LASER IN USE."
- Patient's eyes should be protected with appropriate colored glasses and/or wet gauze.
- Matte-finish (black) surgical instruments reduce beam reflection and dispersion.
- Use the lowest concentration of oxygen possible.
- Avoid using nitrous oxide (N_2O), because it supports combustion.
- Lasers should be placed in STANDBY mode when not in use.
- Use an endotracheal tube specifically prepared for use with lasers.
- Inflate cuff of laser tube with dyed saline so that a cuff perforation is readily apparent.
- All adjacent tissues should be shielded by wet gauze to prevent damage by reflected beams.
- Plume should be suctioned and evacuated from the surgical field.

concern and potentially toxic to operating room personnel. When the tissues vaporized by the laser are malignancies or viral papilloma, the concern arises as to whether these vapors are even more dangerous to operating room personnel if not removed from the environment. Because this issue remains under investigation, it is judicious to suction the laser plume and not allow it to circulate into the room.

The prevention of combustion within the airway is of primary concern. Fire in the airway is relatively uncommon (0.4%), and it is usually due to penetration of the laser through the ETT, which exposes the beam to a rich oxygen supply. Nitrous oxide, although not flammable, also supports combustion and can propagate the flame.[26] Positive pressure ventilation in the presence of intraluminal combustion produces a blowtorch effect that causes serious damage to the respiratory tract of the unfortunate patient.[27] Many important steps should be taken to minimize the risk of laser fires.[28] Box 38-3 lists safety measures for preventing fires during ENT procedures.[13] Operating room fires are discussed further in Chapters 42 and 53.

The "perfect" ETT for use with lasers remains a major discussion. However, several manufacturers have attempted to produce a laser-compatible ETT that allows for adequate ventilation during the laser procedure but reduces the risk of airway fire injury. A few generalizations can be made. The necessity of an inflatable cuff is a point of debate, although the ability to better ventilate the patient and keep the field free of combustible gases is an advantage. When filled with air, the cuff becomes a generous reservoir of combustion-supporting gas. If a cuffed tube is used, inflation with methylene blue–tinged normal saline is encouraged to make it possible to detect penetration. If a laser beam contacts the cuff, the colored liquid will absorb and disperse heat, alerting the operating team to the penetration; the liquid also will reduce combustion.[29]

Fire safety policies, procedures, and practice guidelines are now routine and observed in every modern operating room.[30]

Endoscopy

Endoscopic surgery includes panendoscopy, laryngoscopy, microlaryngoscopy (laryngoscopy aided by an operating microscope), esophagoscopy, and bronchoscopy. All of these procedures can be performed using a rigid or flexible endoscope. If the rigid

BOX 38-3

Safety Measures for Preventing Fires During Ear, Nose, and Throat Procedures

- Use only air for open delivery to the face if the patient can maintain a safe blood O_2 saturation without supplemental.
- If the patient cannot maintain a safe blood O_2 saturation without extra O_2, secure the airway with a laryngeal mask airway or tracheal tube.
  - *Exceptions:* When patient verbal responses may be required during surgery (e.g., carotid artery surgery, neurosurgery, pacemaker insertion) and when open O_2 delivery is required to keep the patient safe, do the following:
  - Deliver the minimum O_2 concentration necessary for adequate oxygenation at all times.
  - Begin with a 30% delivery O_2 concentration and increase as necessary.
  - For unavoidable open O_2 delivery above 30%, deliver 5 to 10 L/min of air under drapes to wash out excess O_2.
  - Stop supplemental O_2 at least 1 minute before and during use of electrosurgery, electrocautery, or laser, if possible. Surgical team communication is essential for this recommendation.
  - Use an adherent incise drape, if possible, to help isolate the incision from possible O_2-enriched atmospheres beneath the drapes.
  - Keep fenestration towel edges as far from the incision as possible.
  - Arrange drapes to minimize O_2 buildup underneath.
  - Coat head hair and facial hair (e.g., eyebrows, beard, moustache) within the fenestration with water-soluble surgical lubricating jelly to make it nonflammable.
  - For coagulation, use bipolar electrosurgery, not monopolar electrosurgery.

During Oropharyngeal Surgery (e.g., Tonsillectomy)

- Scavenge deep within the oropharynx with a metal suction cannula to catch leaking O_2 and nitrous oxide (N_2O).
- Moisten gauze or sponges and keep them moist, including those used with uncuffed tracheal tubes.

During Tracheostomy

- Do not use electrosurgery to cut into the trachea.

During Bronchoscopic Surgery

- If the patient requires supplemental O_2, keep the delivered O_2 below 30%. Use inhalation/exhalation gas monitoring (e.g., with an O_2 analyzer) to confirm the proper concentration.

From Sheinbein DS, Loeb RG. Laser surgery and fire hazards in ear, nose, and throat surgeries. *Anesthesiol Clin.* 2010;28(3):485-496.

laryngoscope is used, the laryngoscope may be suspended from an arching support anchored to the patient's abdomen/chest or from a Mayo stand over the patient. One of the most common endoscopic procedures performed is the endoscopic sinus surgery. Over 250,000 endoscopic sinus surgeries are performed yearly in the United States alone.[31,32] Endoscopic sinus surgery is often associated with multiple and seasonal allergies leading to polyps. Patients undergoing surgery are often also being evaluated for pathology responsible for hoarseness, stridor, or hemoptysis. Other possible reasons for endoscopic examination include foreign-body aspiration, papillomas, trauma, tracheal stenosis, obstructing tumors, or vocal cord dysfunction. Several complications can arise with endoscopic surgery: eye trauma, epistaxis, laryngospasm, and bronchospasm; excessive plasma levels of local anesthesia

and epinephrine have been reported as well. Preoperatively, the patient should be examined for any signs of airway obstruction and proper measures should be taken to ensure safe and controlled airway management. Knowledge of the location and size of a mass is important, and discussion with the surgeon about chest roentgenogram, magnetic resonance imaging (MRI), and computed tomography (CT) scan results can be invaluable.[33]

Light sedation is suggested for premedication because older children and adults may experience respiratory depression and worsening of airway obstruction. The airway must be protected from aspiration of gastric contents, especially during prolonged airway manipulation and deeper sedation. Premedication with an antisialagogue to dry secretions and a full regimen of acid aspiration prophylaxis in aspiration-prone patients may be indicated. An awake oral or nasal intubation with minimal sedation and topical anesthesia of the oral cavity, pharynx, larynx, and nasopharynx is common. For shorter ENT procedures, anesthesia should be maintained with short-acting inhalation and intravenous agents to (1) avoid patient movement and vocal cord movement and (2) control sympathetic nervous system response to brief periods of extreme stimulation, as in laryngoscopy.

Good muscle relaxation of the vocal cords is an essential part of anesthesia management for microsurgery of the larynx. A single-dose short-acting relaxant such as succinylcholine may be considered for brief cases. If the procedure is expected to last 30 minutes or more, use of an intermediate-duration neuromuscular-blocking drug such as vecuronium, cisatracurium, or rocuronium for the initial tracheal intubation allows the return of muscle strength and spontaneous respiration to meet extubation criteria at the end of the surgical procedure. Emergence should include adequate oropharyngeal suctioning, humidified oxygenation, and observation in the PACU for laryngeal spasm or postextubation croup or stridor.

One of the greatest management challenges during endoscopic procedures is that of sharing the airway continuously with the surgeon. Several methods have been used to provide oxygenation and ventilation during the procedures. One method is to control the airway by using a small cuffed ETT (5.0 to 6.0 mm for an adult). Because the 5.0- and 6.0-mm ETTs are designed for smaller patients, a better ETT selection might include the microlaryngeal endotracheal tube (MLT). The MLT in similar sizes (5.0 to 6.0 mm) has a cuff that is larger than the small standard ETTs (5.0 to 6.0 mm), allowing for a larger cuff distribution across the surface of the trachea and creating a wider field of pressure on the tracheal surface. Distinct advantages of an ETT include a secure airway with easily controlled ventilation, a cuff to protect the lower airway from debris, monitoring of end-tidal CO_2, and the ability to administer inhalational anesthetics. Several drawbacks include the potential for extubation and loss of airway, complications during laser surgery, and interference with the operative field by the ETT.

Intermittent apnea is also used as a technique to ventilate patients in this shared space. The anesthetist or the surgeon repeatedly removes the ETT, operates during a brief period of apnea, and then allows the anesthesia provider to reintubate and ventilate the patient. One advantage of the technique is that no special equipment is needed to ventilate the patient. Many patients undergoing these procedures have a long history of heavy smoking and alcohol use, which predisposes them to cardiovascular disease and labile vital signs. Some of the disadvantages of this approach include difficulty in reintubation and the time allotment between ventilations while preventing desaturations. The procedure must be interrupted frequently to ventilate the patient, and the airway is unprotected while the ETT is removed. During this technique, the blood pressure and heart rate tend to fluctuate widely. The procedure resembles a series of stress-filled laryngoscopies and intubations, separated by varying periods of minimal surgical stimulation. Intravenous administration or topical application of agents such as lidocaine; small doses of alfentanil, remifentanil, sufentanil, or fentanyl; and/or β-adrenergic receptor–blocking drugs such as esmolol may help moderate the sympathetic response.

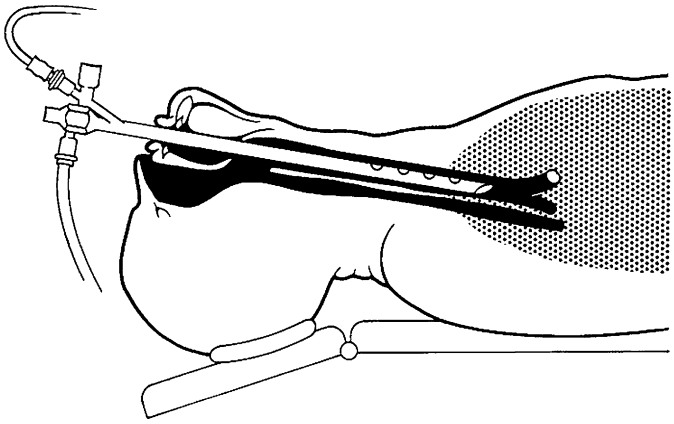

FIGURE **38-7** Rigid bronchoscope connected at its proximal end through an oblique side port to the jet line of the ventilator. (From Biro P. Jet ventilation for surgical interventions in the upper airway. *Anesthesiol Clin*. 2010;28[3]:397-409.)

Jet Ventilation

Jet ventilation has been used extensively for laryngeal surgery. When the trachea is not intubated, a metal needle mounted in the operating laryngoscope or passed through the cords can be used for jet ventilation. Jet ventilation may be performed manually, using a simple hand valve attached to an appropriate oxygen source, or together with various mechanical devices that allow for adjustment of rate and oxygen concentration. Because oxygen can support combustion, the lowest concentration of oxygen possible should be used. Many patients will tolerate an Fio_2 of 30% or less; however, oxygen requirements for each patient should be considered for his or her individual needs. Using lower levels of oxygen will decrease the likelihood of an airway fire.

High frequency is useful when access to the airway by the surgeon is limited by the endotracheal tube or the surgeon might interfere or ignite the tube. Jet ventilation does not require an endotracheal tube and requires only a narrow catheter with resistance to laser beams. There is no absolute contraindication to high-frequency jet ventilation (HFJV); however, it can be difficult maintaining oxygenation and/or CO_2 elimination in certain patients. These include patients who are morbidly obese, have a stiff thorax, or present with advanced forms of restrictive and/or obstructive lung disease, lung fibrosis, and reduced alveolar-capillary diffusion capacity, such as with pulmonary edema. Jet ventilation should be avoided in any situation in which an unprotected airway is a concern (e.g., full stomach, hiatal hernia, or trauma).[33]

Common types of HFJV include supraglottic, infraglottic, transtracheal, and via a rigid bronchoscope.[34] Figure 38-7 shows the commonly used rigid bronchoscope technique. HFJV was originally used as a technique to provide adequate oxygenation and alveolar ventilation for rigid bronchoscopy and laryngeal surgery. HFJV is typically ventilation at low tidal volumes with high respiratory rates. A needle connected to a high-pressure hose with a regulator to adjust rate and volume is used to deliver the ventilation. With the tip of the needle either above or below the

glottis, the anesthetist directs a high-velocity jet stream of oxygen into the airway lumen. The lungs are ventilated as the mixture of oxygen forces air into the lumen. Introduction of high-pressure (up to 60 psi) jet-injected oxygen entrains room air into the lung, allowing the jet stream of gases into the airway for ventilation.[35] Whereas inspiration is accomplished by HFJV pressurizing gas into the airway, the expiration is passive and adequate exhalation should be constantly assessed. Some pauses in ventilation may be necessary to provide adequate time for expiration, particularly in patients with severe respiratory disease.

If an airway mass lies above the level of delivery of the gas jet, it may be easy to force the gas down the trachea during inspiration, but the gases will be trapped during expiration. This air trapping can lead to increased airway pressure, subcutaneous emphysema, and pneumothorax, particularly in patients with bullae. The anesthetist or surgeon also may find it difficult to aim the jet into the airway lumen, leading to hypoxia. If the jet is not accurately aimed, gastric distention, subcutaneous emphysema, or barotrauma may result. Patients with decreased pulmonary compliance or increased airway resistance from bronchospasm, obesity, or chronic obstructive pulmonary disease (COPD) are at high risk for hypoventilation with jet techniques. Adequacy of ventilation is assessed by observing chest movement, auscultation with the precordial stethoscope, and a pulse oximeter. Intravenous anesthetic techniques are used with HFJV, because environmental contamination by leaking volatile agents is a concern.[34]

Foreign-Body Aspiration

Aspiration of foreign bodies is a common problem that carries high morbidity and mortality, particularly in children. Asphyxiation by an inhaled foreign body is a leading cause of accidental death among children younger than 4 years. Some common aspirants include peanuts, popcorn, jelly beans, coins, and bites of meat and hot dogs. The majority of aspirated items are food particles, with nuts and seeds being the most common. Aspiration of beads, pins, and parts of small toys are not unusual. A common site of foreign body aspiration is the right bronchus. If the patient is supine when the aspiration occurs, the object will most likely be found in the right upper lobe. If the patient is standing, the right lower lobe is most likely to be affected. Signs of aspiration include wheezing, choking, coughing, tachycardia, aphonia, and cyanosis. These signs indicate an obstructive severe irritation and swelling in the airway. As a result of the swelling, air may be trapped in the lungs, not allowing adequate expiration. Although rigid bronchoscopy is the traditional diagnostic "gold standard," the use of computerized tomography, virtual bronchoscopy, and flexible bronchoscopy is increasing. Reported mortality during bronchoscopy is 0.42%. Although asphyxia at presentation or initial emergency bronchoscopy causes some deaths, hypoxic cardiac arrest during retrieval of the object, bronchial rupture, and unspecified intraoperative complications in previously stable patients constitute the majority of in-hospital fatalities. Major complications include severe laryngeal edema or bronchospasm requiring tracheotomy or reintubation, pneumothorax, pneumomediastinum, cardiac arrest, tracheal or bronchial laceration, and hypoxic brain damage.[36]

Anesthetic management depends on the location of the airway obstruction, the size and location of the object, and the severity of the obstruction. If the foreign body is located at the level of the larynx, a simple laryngoscopy with Magill forceps should allow for easy removal of the object. Care must be taken not to dislodge the object and allow it to fall deeper into the airway. If the foreign body is located in the distal larynx or trachea, the patient should have an inhalation induction performed in the operating room, maintaining spontaneous respiration. With the patient spontaneously breathing, the surgeon will most likely use a rigid bronchoscope for extraction of the foreign body. Usually, a gentle mask induction without cricoid pressure or positive pressure ventilation is the preferred induction technique.[37] Attempts to assist respirations should not be made because that might cause the object to move farther into the airway and compromise ventilation with occlusion. Patients should be placed in the sitting position because it is known to produce the least adverse effect on airway symptoms. An antisialagogue, H_2 antagonist, and metoclopramide are often administered intravenously to decrease secretions and promote gastric emptying; the secretions may obscure the view through the bronchoscope. Patients with full stomachs who are induced with a rapid sequence must be prepared for complete occlusion of the airway.

Direct and sometimes rigid laryngoscopy is typically performed. A rigid bronchoscope is also used and passed through the vocal cords into the trachea. Ventilation is accomplished through a side port of the laryngoscope or bronchoscope that can be attached to the anesthesia circuit. If a foreign body is present, the telescope eyepiece within the bronchoscope is removed and optical forceps are inserted through the bronchoscope for retrieval of the item. When the telescopic eyepiece is being changed, a leak is present in the ventilation system, and protracted periods can lead to hypoxia. When an anesthesia gas machine circuit is used, high fresh gas flow rates, large tidal volumes, and high concentrations of inspired volatile anesthetic agents are often necessary to compensate for leaks around the ventilating bronchoscope. Coughing, bucking, or straining during instrumentation with the rigid bronchoscope may cause difficulty for the surgeon and result in damage to the patient's airway; these must be avoided. The best anesthesia technique for rigid laryngoscopy and bronchoscopy is total intravenous anesthesia, allowing greater control of cardiovascular stability and relaxation for short periods, as well as ventilation with 100% oxygen, allowing longer periods of hypoventilation without hypoxia.

A rigid bronchoscopy can lead to several complications, including damage to dentition, gums, and upper lips and chipped or damaged teeth, all of which can be prevented to some degree with the use of a mouth guard and vigilance. A good range of motion of the cervical vertebra is also evaluated and necessary for insertion of the rigid scopes. Vagal stimulation may be noted from the extreme head extension, and tracheal tears can occur with the introduction of the bronchoscope. Inadequate ventilation manifests as hypoxemia, hypercarbia, barotrauma, and dysrhythmias. The surgeon must be prepared to perform an emergency tracheotomy or cricothyrotomy if partial obstruction suddenly becomes complete.

At the conclusion of the procedure, patients can be intubated to provide ventilation until returning to consciousness. Allow the patient to return to consciousness as quickly as possible, with airway reflexes intact prior to extubation. Laryngeal and subglottic edema may occur for 24 hours after removal of a foreign body. To check for airway edema, the cuff of the ETT can be deflated if not contraindicated, and the lumen of the ETT should be occluded for one or two breaths during inspiration and expiration while listening for air movement around the tube. If there is no air escaping around the ETT, postoperative sedation and ventilation might be considered. Close observation and use of humidified oxygen are suggested during the recovery period. Some additional supportive measures that can alleviate some of the postoperative complications that occur include racemic epinephrine, bronchodilators, and steroids.

PROCEDURES INVOLVING THE FACE, EAR, HEAD, AND NECK

Some of the common surgical procedures for the ear and face include myringotomy with insertion of tubes, mastoidectomy,

acoustic neuroma, stapedectomy, and tympanoplasty. During ear surgery, the anesthetist must be concerned with four major issues: (1) nerve preservation, (2) the effect of nitrous oxide on the middle ear, (3) control of bleeding, and (4) PONV.

Nerve Preservation During Surgical Procedures

Surgical procedures of the ear and face require meticulous identification and preservation of the facial nerve and other cranial nerves, especially during resection of a glomus tumor or an acoustic neuroma. Intraoperative neuromonitoring is a relatively recent advance in electromyography (EMG) applied to head and neck surgery. Its purpose is to allow real-time identification and functional assessment of vulnerable nerves during surgery. The nerves most often monitored in head and neck surgery are the motor branch of the facial nerve (VII), the recurrent or inferior laryngeal nerves (X), the vagus nerve (X), and the spinal accessory nerve (XI), with other cranial lower nerves monitored less frequently. Morbidity from trauma to these nerves is significant and obvious, such as unilateral facial paresis. Although functional restorative surgery can be performed, the importance of preventing nerve injury in head and neck surgery is obvious.

The identification of these nerves requires the surgeon to isolate and verify function by means of an electrical stimulation. One method used for nerve isolation is the brainstem auditory evoked potential and electrocochleogram monitoring. Table 38-7 lists several types of intraoperative neurophysiologic monitoring used during ENT procedures and the effects of various anesthetic drugs on the monitoring modality.[38]

Patient movement during neck dissection and skull base surgery must be prevented, especially if a positioning device is used for craniotomy. Muscle relaxants should be used only at time of induction and intubation to prevent interference with the nerve monitors. The use of local anesthetics is also contraindicated because of their suppressant effects on muscle action potential amplitudes and muscle movement. Hemostasis during neck dissection is not as critical as during otologic or skull base neurosurgery, but the use of a short-acting opioid infusion such as remifentanil or sufentanil will help control blood pressure and aid hemostasis. The use of volatile anesthetic agents and nitrous oxide is acceptable only if the nitrous oxide is discontinued well before closing any cavity. Common anesthetic techniques include the use of remifentanil with short-acting volatile anesthetic agents with or without nitrous oxide. Midazolam preoperatively helps assure amnesia and rapid emergence. Selected use of deep extubation helps prevent straining during emergence; straining increases postoperative bleeding and may necessitate reexploration.[38]

Middle Ear Procedures

Middle ear procedures require a bloodless surgical field, specific head positioning, facial nerve monitoring, and management of postoperative nausea and vomiting. The term *middle ear* refers to the air-filled space between the tympanic membrane and the oval window. It is connected to the nasopharynx by the eustachian tube and is in close proximity to the temporal lobe, cerebellum, jugular bulb, and the labyrinth of the inner ear. The middle ear contains three ossicles—the malleus, incus, and stapes—which transmit sound vibration from the eardrum to the cochlea. This air-filled cavity is traversed by the facial nerve before it exits the skull via the stylomastoid foramen. The facial nerve provides motor innervation to the muscles of facial expression. Common surgeries in adults include tympanoplasty (reconstructive surgery for the tympanic membrane, or eardrum), stapedectomy or ossiculoplasty for otosclerosis, mastoidectomy for removal of infected air cells within the mastoid bone, and removal of a cholesteatoma. Common middle ear surgery in children includes tympanoplasty, mastoidectomy, myringotomy, grommet insertion, and cochlear implantation.[39]

Middle ear surgery can be done with either local or general anesthesia depending on the patient's ability to cooperate. Local anesthesia with sedation requires the patient to remain still under surgical drapes for extended periods. The main advantages of performing middle ear surgery under local anesthesia are the ability to test hearing during surgery and less bleeding. Most middle ear procedures can be performed as outpatient surgery; thus rapid recovery, good analgesia, and avoidance of nausea and vomiting are essential. Pain is a primary problem at the beginning of surgery when multiple injections of local anesthetic with epinephrine are given. The use of topical application of lidocaine and prilocaine (eutectic mixture of local anesthetics [EMLA]) may increase patient comfort. A bloodless surgical field is mandatory in microsurgery. A combination of physical and pharmacologic techniques is used to minimize bleeding. The patient's head is positioned to avoid venous obstruction and congestion.[40,41]

When general anesthesia is chosen, the airway can be maintained with a laryngeal mask airway (LMA) or endotracheal intubation. Intubation may be more appropriate if extreme neck extension or rotation is required. A nerve stimulator is often employed for intraoperative monitoring of evoked facial nerve electromyographic activity to aid preservation of the facial nerve. Muscle relaxants therefore are avoided after intubation. A smooth recovery without coughing or straining is important, especially in patients who have undergone reconstructive middle ear surgery to prevent prosthesis displacement.

Postoperative nausea and vomiting (PONV), a common problem after middle ear surgery, can be minimized by appropriate choice of anesthetic technique and antiemetic prophylaxis.[42] As noted above, a bloodless operative field is essential. Physical and pharmacologic techniques are used to minimize bleeding. They include a head-up tilt of 15 to 20 degrees, avoidance of venous obstruction, normocapnia, and controlled hypotension. An ideal blood pressure range is 80 to 90 mmHg or a reduction of mean arterial pressure to 30% of baseline in patients with hypertension. A slightly elevated position of the head reduces arterial and venous pressures in areas above the heart; however, it increases the risk of air embolism.

Pharmacologic agents used for controlled hypotension in ear, nose, and throat surgery include inhalation anesthetics, β-adrenoceptor antagonists (labetalol and esmolol), α_2-adrenergic agonists (dexmedetomidine), opioids (remifentanil), and more recently magnesium sulfate.[39,43] Dexmedetomidine has several advantages as an adjunct to lower blood pressure. It produces sedation, analgesia, and a modest reduction in heart rate and blood pressure without respiratory depression. Dexmedetomidine has been used successfully to lower blood pressure during general anesthesia or as the primary sedative with supplementary low-dose propofol and midazolam for intravenous sedation.[44,45] At the completion of the surgical procedure, the patient's head is lifted and usually wrapped with a bandage. The anesthetist will want to avoid excessive coughing and bucking of the patient during this period. Therefore, using a technique that limits coughing is desirable. Provided there are no contraindications, a deep extubation might be considered.

Nitrous Oxide and Middle Ear Surgery

Nitrous oxide (N_2O) is more soluble than nitrogen in blood and enters the middle ear cavity more rapidly than nitrogen leaves,

TABLE 38-7 Types of Intraoperative Neurophysiologic Monitoring and the Effects of Various Anesthetic Drugs

Type or Modality of Neurophysiologic Monitoring	Surgery Examples	Region	Volatile Agents (e.g., Isoflurane)	Neuromuscular Blocking Agents*	TOTAL INTRAVENOUS ANESTHESIA		Local Anesthetics*	Nitrous Oxide
					Opioids	Propofol		
Brainstem auditory evoked response	Acoustic neuroma, trigeminal neuralgia, facial nerve decompression, endolymphatic sac	Cerebellopontine angle, mastoid region, middle ear	1	0	0	1	0	0
Cortical somatosensory evoked potentials	Spinal fusion, tumor, decompression	Spine (posterior columns)	2 (affect amplitude and latency of waveforms)	0	0	0	2	1 Nitrous oxide (affects amplitude only)
Neuromuscular junction monitoring	Neuromuscular blockade in anesthesia	Ulnar nerve, facial nerve, posterior tibial nerve	0	2	0	0	2	0
IONM: spontaneous EMG†	Thyroid, parathyroid, parotid, neck dissection, skull base	Facial, vagal, recurrent laryngeal, other cranial nerves	0	2	0	0	2	0
IONM: evoked EMG†	Thyroid, parathyroid, parotid, neck dissection, skull base	Facial, vagal, recurrent laryngeal, other cranial nerves.	0	2	0	0	2	0
MEP	Spinal fusion, tumor, decompression	Spine (anterior columns)	2	2	0	0	2	0
EEG† (BIS)	All	All	2	0	1	2	0	1
EEG†	Carotid endarterectomy	Carotid	2	0	2	2	2	2

From Dillon FX. Electromyographic (EMG) neuromonitoring with otolaryngology-head and neck surgery. *Anesthesiol Clin.* 2010;28(3):434-442.

Scale: 0 = insensitive; 1 = somewhat sensitive; 2 = very sensitive.

*The two classes of drug to be avoided during monitoring of facial, recurrent laryngeal, vagal, and other cranial motor nerves are neuromuscular blocking agents and local anesthetics. Both may increase latency, decrease amplitude, and increase stimulus threshold of the evoked response, or may decrease the sensitivity of EMG to nerve injury.

†A conventional balanced anesthetic (opioid, nitrous oxide/oxygen, volatile agent) is suitable for surgery using EMG and EEG.

BIS, Bispectral electroencephalogram; *EEG*, electroencephalogram; *EMG*, electromyogram; *IONM*, intraoperative nerve monitoring; *MEP*, motor evoked potentials.

causing an increase in middle ear pressure if the eustachian tube is obstructed. Normally, pressure increases in the middle ear are vented via the eustachian tube into the nasopharynx. Yawning and swallowing actively open the eustachian tubes, but these equalizing maneuvers cannot occur in anesthetized patients. Additionally, pressure also may be increased in the middle ear with positive pressure ventilation by forcing air into the compartment through the eustachian tubes. During tympanoplasty, the middle ear is open to the atmosphere; thus there is no build-up of pressure, but once a tympanic membrane graft is placed, the continued use of nitrous oxide might cause displacement of the graft. At the end of surgery, when nitrous oxide is discontinued, the remaining N_2O is rapidly absorbed, which may then result in negative pressure, also possibly resulting in graft dislodgement, serous otitis media, disarticulation of the stapes, or impaired hearing. Some clinicians feel that discontinuation of the N_2O at least 15 minutes before closure of the middle ear is sufficient to prevent these adverse effects. Because N_2O is only a supplement to general anesthesia, avoiding it altogether during tympanoplasty is more reasonable. Nitrous oxide also may increase PONV, and its use in middle ear surgery may further increase the incidence of PONV above that already associated with this type surgery.[39]

Myringotomy and Tube Placement

Most often, patients scheduled for myringotomy are young, healthy patients. A myringotomy allows the pressure to equalize between the middle ear and the atmosphere, reducing the pressure in the middle ear compartment. Simple tubes with a lumen (grommets) are placed through the patient's tympanic membrane to alleviate the pressure created in the middle ear usually seen with chronic serous otitis media or recurrent otitis media. Chronic otitis media is manifested as fluid in the middle ear. Recurrent otitis media, a common pediatric disorder, is defined as either three or more acute infections of the middle ear cleft in a 6-month period or at least four episodes in 1 year. Untreated otitis media may lead to permanent middle ear damage and hearing loss; therefore, appropriate treatment is necessary. Children with chronic otitis frequently have accompanying recurrent upper respiratory infections (URIs). Intervals between URIs may be brief, and the patient is usually on a regimen of antibiotics. Scheduling surgery during these interludes is often impractical. Frequently, the eradication of middle ear fluid and inflammation resolves the URI; therefore, surgery should not be delayed.

Bilateral myringotomies with tube insertions are typically very short operations. Sedative premedications may outlast the procedure and are usually not necessary. Mask or IV induction and maintenance using oxygen, nitrous oxide, and a volatile inhalation agent such as sevoflurane is routine. If IV access is established, it is usually done after mask induction in children and may include fluid therapy or an injection cap for temporary access and administration of drugs. IVs are not usually necessary unless another procedure is performed at the same time.[46,47] N_2O is often avoided in surgeries that involve the middle ear, but given that the myringotomy surgical procedure is relatively short, and a tube will be placed through the tympanic membrane into the middle ear to relieve pressure, the effects of N_2O are not relevant. For bilateral procedures, the inhalation anesthetic is discontinued during the second myringotomy to facilitate prompt emergence. N_2O is continued until the completion of the surgery. Intubation is performed only if airway difficulties are anticipated or encountered, but airway equipment is always prepared and available. The procedure is typically without much risk of bleeding, but the patient's head must be held still, particularly when the myringotomy knife is being used.

The patient is supine with the head turned to expose the ear to the microscope. An ear speculum is inserted into the ear canal, cerumen is removed, and an incision is made in the tympanic membrane. Fluid is sometimes suctioned from the middle ear, and then a tympanostomy tube is inserted through the incision into the middle ear, straddling the tympanic membrane. Antibiotic and steroid eardrops frequently are inserted into the external auditory canal and mild pain medications given rectally, orally, or intravenously are administered in the perioperative period. The surgeon moves to the other side of the table, the microscope is repositioned, the head is turned, and the procedure is repeated in the other ear.[48,49]

Tonsillectomy and Adenoidectomy

The frequency of adenotonsillectomy in the United States has declined recently, although it remains the most common pediatric surgery.[50] The lateral tonsils, tonsillar tissue at the base of the tongue, and adenoids form a tonsillar "ring" around the oropharynx that can lead to significant airway challenges after surgical intervention. An adenotonsillectomy, although often considered a simple procedure, has the potential for significant airway challenges. Considerations of airway obstruction, shared airway, mechanical suspension of the airway, management of intubation and extubation, pain management, and the desire for a rapid awakening are all subtleties of anesthesia for this procedure. In adult patients, a tonsillectomy may also accompany a uvulopalatopharyngoplasty (UPPP) for pickwickian syndrome or obstructive sleep apnea (OSA). OSA is typically seen with obesity and redundant pharyngeal tissue. OSA patients can also present with significant comorbid conditions.[51,52]

The patient undergoing a tonsillectomy and/or adenoidectomy will probably have a higher incidence of airway obstruction because of the hypertrophied tissues. Chronic obstruction and infections of the tonsils can lead to systemic involvement, producing additional cardiac and respiratory anomalies. In the case of suspected airway obstruction, the clinician must choose wisely among routine intravenous induction, inhalation induction, awake intubation, or fiberoptic-assisted intubation before induction. Adult patients with severe obstructive sleep apnea may require awake intubation before the induction of general anesthesia. Surgical approaches to tonsillectomy include coblation, cold steel, snare, monopolar cautery, and hot knife techniques. Techniques differ with respect to operative times, intraoperative blood losses, postoperative pain scores, or time to resumption of oral intake.[53]

In children, anesthesia is induced with propofol or sevoflurane, oxygen, and N_2O by mask depending on the age of the child and intravenous access. Some institutions allow parental presence in the operating room during induction to prevent separation anxiety in the child. Laryngeal mask airway and endotracheal tube both may be used depending on the experience of the operating team.[54] A recent review noted that the use of the LMA during pediatric tonsil surgery does not appear to have any major disadvantages compared with use of the ETT. Analysis of safety, comfort, complications, and postoperative problems suggests that LMA may be superior for some outcome variables such as coughing and gagging. Use of spontaneous ventilation is more common among LMA patients.[55]

A cuffed tube is recommended in those older than 8 to 10 years of age,[4] with continued attention given to inflation pressures of the cuff. A properly sized pediatric ETT should allow a leak at 20 cm H_2O airway pressure, which reduces the likelihood of postoperative croup and edema. After the airway is secured, the mouth gag is inserted by the surgeon. An adequate depth of anesthesia is

needed to facilitate gag insertion. The gag, designed to maintain an open mouth and tongue retraction, is equipped with a groove for the ETT or LMA to rest in (Figure 38-8). The airway should be reevaluated at the time the gag is placed to ensure that the tube has not been moved from its original position and that occlusion of the tube has not occurred as a result of compression from the gag. The table is frequently turned 45 to 90 degrees away from the anesthetist just prior to incision.

The choice of maintenance techniques for anesthesia varies. Several major goals need to be considered when choosing an anesthetic: (1) provide a depth of anesthesia adequate to blunt strong reflex activity elicited by the procedure, (2) a rapid return of protective reflexes, (3) good postoperative analgesia, (4) reduced postoperative bleeding, and (5) minimal PONV. The use of intermediate-acting muscle relaxants is acceptable; however, they are usually not necessary. Judicious narcotic supplementation will reduce the total amount of inhalation agent required and provide analgesia with minimal postoperative respiratory depression. Disadvantages of opiates include increased sensitivity and desaturation in sleep apnea patients and PONV. Suggested techniques include modest opioids and acetaminophen doses for analgesia, dexamethasone and ondansetron for antiemetic prophylaxis, and deep extubation of the trachea to minimize coughing and airway stimulation when prudent.[54] Although an increase in postoperative bleeding has been a concern with the use of nonsteroidal antiinflammatory drugs (NSAIDs), a Cochrane review found that NSAIDs did not cause any increase in bleeding and there was significantly less nausea and vomiting compared to use of alternative analgesics.[56,57]

Blood loss during tonsillectomy is difficult to assess but has been estimated to average 4 mL/kg or 5% of blood volume.[7] Average blood loss during UPPP is slightly higher because the procedure frequently is performed in conjunction with adenotonsillectomy. Although younger, healthier patients can tolerate greater volumes of blood loss, transfusion should be considered if blood loss, laboratory values, and patient factors indicate the need.

At the end of the surgical procedure, the surgeon may release tension on the mouth gag to ensure that all bleeding has been controlled. The insertion of an orogastric tube and some irrigation may be used to remove blood and secretions from the stomach and oropharynx. This is thought to reduce the incidence of postoperative nausea and vomiting. Suctioning of the oropharynx and nares should be done very gently and briefly, avoiding the surgical beds to prevent disruption and mucosal bleeding. Vigorous suctioning may induce laryngospasm and bronchospasm.

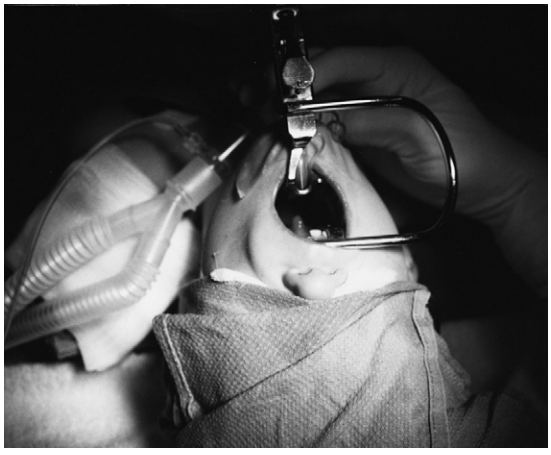

FIGURE **38-8** Superior view of the suspension technique for tonsillectomy using the Crowe-Davis mouth gag. Note use of preformed RAE orotracheal tube.

During emergence from anesthesia after tonsillectomy or UPPP, the anesthetist should ensure that all protective reflexes have returned, the airway is free of blood and debris, and an adequate breathing pattern is present before the removal of the ETT. A topical spray of 2% lidocaine (maximum 3 mg/kg) on the glottic and supraglottic areas before intubation prevents postextubation stridor and laryngospasm after adenotonsillectomy. This approach has proved as effective as administering lidocaine (1 mg/kg IV) before extubation but without higher sedation scores.[58]

The postoperative tonsillectomy patient should be transported to the recovery in the "tonsil position"—that is, on one side with the head slightly down. This allows blood or secretions to drain out of the mouth rather than flow back onto the vocal cords. Adults, however, frequently prefer a middle- or high-Fowler position after UPPP. This position aids in ventilation and lessens the feeling of asphyxiation in the immediate postoperative period. The patient must be awake enough to manage his or her own airway. To hydrate the airway, 100% oxygen with a high-humidity mist is given by facemask or face tent. The pharynx should be rechecked directly for bleeding and edema before discharge.

Routine tonsillectomy is generally performed as an outpatient procedure. A small subset of children are observed overnight if there are sufficient age, comorbidity, or perioperative concerns. Although postoperative bleeding is the most serious complication, persistent vomiting, poor oral intake, and persistent desaturation are the most common reasons for unscheduled overnight admission after ambulatory surgery. The incidence of postoperative nausea and vomiting can be as high as 70% during the first 24 hours after tonsillectomy.[59] This is due to swallowed blood, opioid administration, or pharyngeal stimulation, and significantly increases the risk of overnight admission, delayed oral intake, and lower patient satisfaction.[54,60,61] As discussed previously, it is important to develop anesthetic techniques that incorporate the use of antiemetics to minimize episodes of nausea and vomiting.

Bleeding Tonsil

Post-tonsillectomy hemorrhage (PTH) is the most common emergency pediatric airway surgery. PTH rates are between 0.5% and 7.5% and are most common in patients more than 15 years of age, boys, patients with frequent infectious tonsillitis, and after hot (electrocautery) versus cold (scalpel) techniques. Approximately 75% of the postoperative tonsillar hemorrhages that occur are within 6 hours of the surgical procedure. The remaining 25% of the postoperative bleeds occur within the first 24 hours of surgery, although bleeding may be noted up until the sixth postoperative day.[62] Slow oozing of the tonsillar bed is far more common than profuse bleeding. Patients may swallow large volumes of blood before bleeding is actually discovered. The patient may present with signs of hypovolemia evidenced by tachycardia, hypotension, and agitation. If the blood is swallowed, the patient may have nausea and vomiting. Appropriate laboratory tests including hemoglobin, hematocrit, and coagulation profile should be performed to determine patient status. Restoration of intravascular volume and/or blood based on the volume lost should precede induction. All patients should be assumed to have a significant amount of blood in the stomach and a rapid sequence induction is indicated. Care with laryngoscopy is necessary to prevent traumatic dislodgement of any clots. In some patients, an awake intubation to maintain reflexes may be necessary. At induction of anesthesia, an additional person should be available to provide suctioning of blood from the oropharynx. The patient should be placed

in a slight head-down position to protect the trachea and glottis from aspiration of blood. Gastric decompression is performed to assess for occult blood loss and decrease the risk of subsequent pulmonary aspiration. The induction agent selected is based on the hemodynamics and condition of the patient. Emergence and extubation of the trachea should occur after return of protective laryngeal reflexes.[54]

Thyroid Surgery

A thorough knowledge of the specific issues related to anesthesia case management for thyroidectomy is essential to provide high-quality care. Airway management may be difficult despite a normal airway examination because of impingement of a thyroid mass on the laryngeal and tracheal structures. Because sympathetic nervous system hyperactivity is associated with increased amounts of thyroid hormone, it is essential that all patients having an elective thyroidectomy be rendered euthyroid prior to surgery. There are multiple preoperative antithyroid medication regimens that effectively treat thyroid hormone hypersecretion. Although it is a rare event, thyroid storm can still occur during the perioperative period.

The thyroid gland is butterfly-shaped and composed of two lobes that are connected by a median tissue mass named the *thyroid isthmus*. It is located on the anterior and anterolateral aspect of the trachea immediately inferior to the larynx. The thyroid gland is the largest endocrine gland in the body, weighing 20 g in the healthy adult. Its major blood supply arises from the superior and inferior thyroid arteries, which are branches of the common carotid artery. Blood flow is approximately five times the weight of the gland, and therefore the thyroid receives one of the greatest blood supply per gram of tissue measures in the body.[63]

Motor function associated with movement of the intrinsic muscles of the larynx that abduct, adduct, and tense the vocal cords is supplied by the recurrent laryngeal nerve (RLN) and the external branch of the superior laryngeal nerve. These nerves lie in close proximity to the lateral lobes of the thyroid gland. During surgical resection, if these nerves are temporarily or permanently damaged, then vocal cord movement can be adversely affected and may result in airway compromise after extubation. Anatomic representation of the thyroid gland and its associated structures is presented in Figure 38-9.

Pathophysiology

Thyroid dysfunction can be treated medically or surgically. A thyroidectomy is performed as definitive treatment for thyrotoxicosis or malignancy. Thyrotoxicosis refers to a condition in which excessive amounts of thyroid hormone are present in a patient's system, whereas hyperthyroidism (the most common cause of thyrotoxicosis) describes states in which the excessive thyroid levels are due to a hyperactive thyroid gland.[64,65] Malignancies of the thyroid gland are the most common malignancies of the endocrine system and have been associated with prior exposure to radiation.[65,66] Thyrotoxicosis is a rare (2%) occurrence in thyroid malignancies.

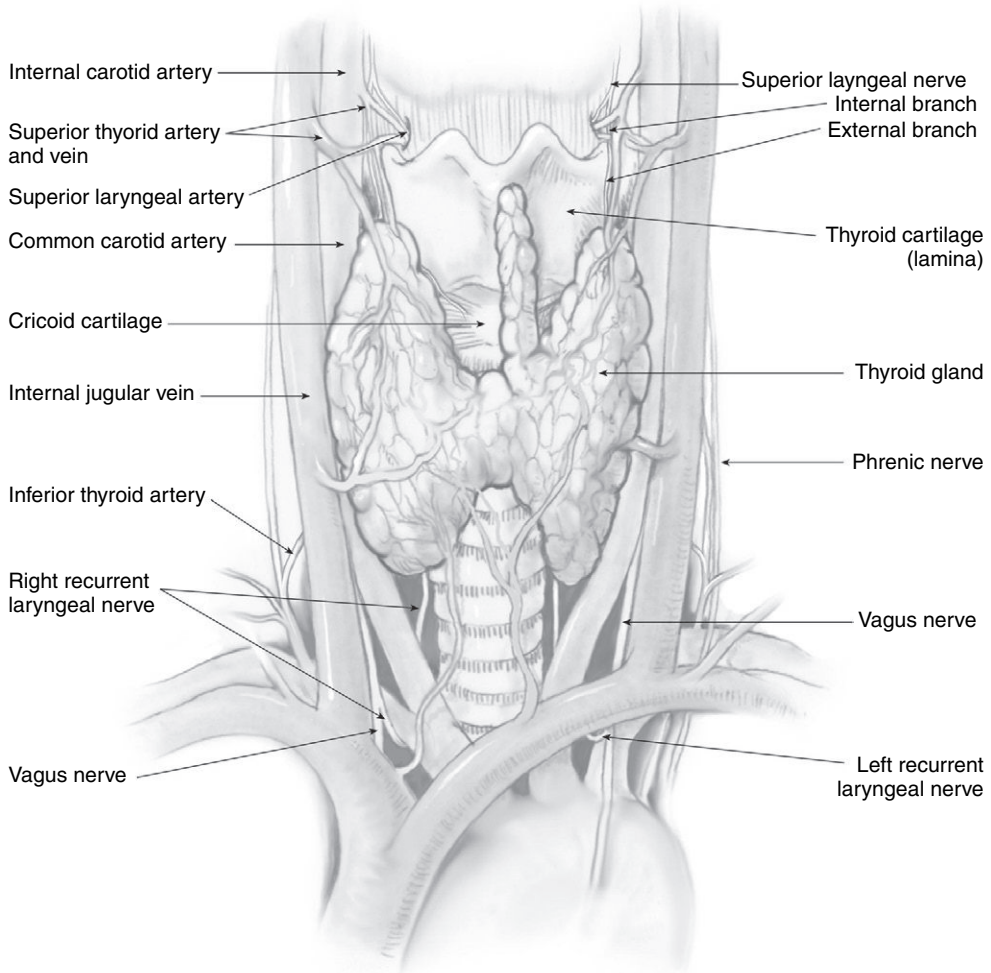

FIGURE **38-9** Thyroid gland and surrounding anatomic structures.

TABLE 38-8 Oral Drugs Used to Treat Hyperthyroidism

Drug	Daily Oral Adult Dose	Comments
Thionamides		
Methimazole (generic)	*Starting:* 10-40 mg once or divided *Maintenance:* 5-15 mg once or divided	Methimazole is preferred due to ease of dosing and a better side effect profile; continue up to the morning of surgery
Propylthiouracil (PTU) (generic)	*Starting:* 100-450 mg divided bid or tid *Maintenance:* 100-150 mg divided bid or tid	
Iodide		Iodide therapy added 1 week prior to surgery and continued through the day of surgery; decreases the production and release of thyroid hormone and reduces thyroid vascularity
SSKI	1-3 drops tid	
Lugol's solution	5 drops tid (dissolve in a full glass of water)	
Beta blockers		Beta blockers without intrinsic sympathomimetic activity are preferred; also used in emergency thyroid surgery for adrenergic suppression
Propranolol (generic)	20-40 mg qid	
Propranolol (Inderal)—long acting	80-160 mg once	
Atenolol (generic and Tenormin)	25-100 mg once or bid	
Metoprolol (generic and Lopressor)	50-200 mg divided bid or tid	

Adapted from Elisha S, et al. Anesthesia case management for thyroidectomy. *AANA J.* 2010;78(2):151-160.
bid, Twice a day; *tid*, three times a day; *qid*, four times a day; *SSKI*, saturated solution of potassium iodide.

Surgery is the principle treatment used to treat thyroid malignancies both for purposes of excision of the tumor as well as staging. Most thyroid malignancies (greater than 90%) are considered well differentiated and are categorized as papillary thyroid cancer (PTC) or follicular thyroid cancer (FTC). PTC accounts for 70% to 80% of thyroid cancer, usually presents at an early stage, and has an excellent prognosis (greater than 95% 10-year survival). FTC accounts for 10% of thyroid cancer and tends to present at a later stage than PTC. The 10-year survival rate for FTC is 85%.[64]

Preoperative Assessment and Preparation

The primary goals during preoperative assessment are ensuring that the patient is euthyroid, assessing the degree of end-organ complications, and determining the extent of airway involvement. Thyroid tumors or large goiters can impinge upon the tracheal cartilages and esophageal tissues, resulting in tracheomalacia and airway compromise. Preoperatively, the patient will be taking a combination of antithyroid medications to decrease the synthesis and release of thyroid hormone and to treat the hyperdynamic state associated with hyperthyroidism. The patient may have taken or be currently taking glucocorticoids, and thus require the administration of a steroid stress dose preoperatively or intraoperatively. Patients should continue their regimen of antithyroid medications and beta blockade through the morning of surgery. Preoperative use of antithyroid drugs has greatly decreased morbidity from thyroid surgery and rendered thyroid storm a rare event. The aim of preoperative management is to restore a normal metabolic state prior to surgical interventions. Patients with hyperthyroidism have increased T_3 and T_4 values and decreased or normal thyroid-stimulating hormone (TSH) levels. Beta-blocking drugs are widely used as an adjunct to the antithyroid thionamides for symptomatic control. Beta blockers are generally continued throughout the surgical period and may be incrementally withdrawn postoperatively. Drugs that are used to treat hyperthyroidism are listed in Table 38-8.[67]

All routine airway assessments should be performed as well as a full visualization and palpation of the patient's neck for a thyroid goiter. The patient's airway should be assessed in the supine position. If there is any indication for the potential for airway compromise, a chest radiograph and a CT scan of the neck and chest should be performed. Routine preoperative testing should include an electrocardiogram. Additional testing is dictated by the individual patient condition. Patients with hyperthyroidism have a higher incidence of myasthenia gravis and may present with skeletal muscle weakness and an increased sensitivity to muscle relaxants.[67]

Intraoperative Anesthetic Management

General endotracheal anesthesia is the technique of choice for thyroidectomy, and the standard induction and maintenance drugs are used. Paralysis may inhibit the surgeon's ability to assess the integrity of the recurrent laryngeal nerve (RLN), and relaxation is avoided after intubation if nerve testing is planned. Succinylcholine is used for intubation due to its short duration. Intraoperative neural monitoring (IONM) during thyroid and parathyroid surgery has gained widespread acceptance as an adjunct to the gold standard of visual nerve identification. Neurophysiologic monitory modalities and the effects of anesthetic drugs are given in Table 38-7.

A special endotracheal tube, Medtronic nerve integrity monitor (NIM) EMG endotracheal tube (NIM-EMG ETT), is frequently used to assess recurrent laryngeal and vocal cord function during surgery.[68] Injury during surgical procedures can lead to hoarseness, aphonia, and (although rare) difficulty with ventilation as a result of permanent adduction of the cords. The major advantage of using the NIM-EMG ETT is that it allows the surgeon the capability of identifying the recurrent laryngeal nerve prior to traction or severing the nerve. The NIM-EMG ETT is a flexible silicone elastomer endotracheal tube with an inflatable cuff. The tube is fitted with four stainless steel wire electrodes (two pairs) that are embedded in the silicone of the main shaft of the endotracheal tube and exposed only for a short distance, slightly superior to the cuff. The electrodes are designed to make contact with the patient's vocal cords to facilitate electromyographic (EMG) monitoring of the recurrent laryngeal nerve

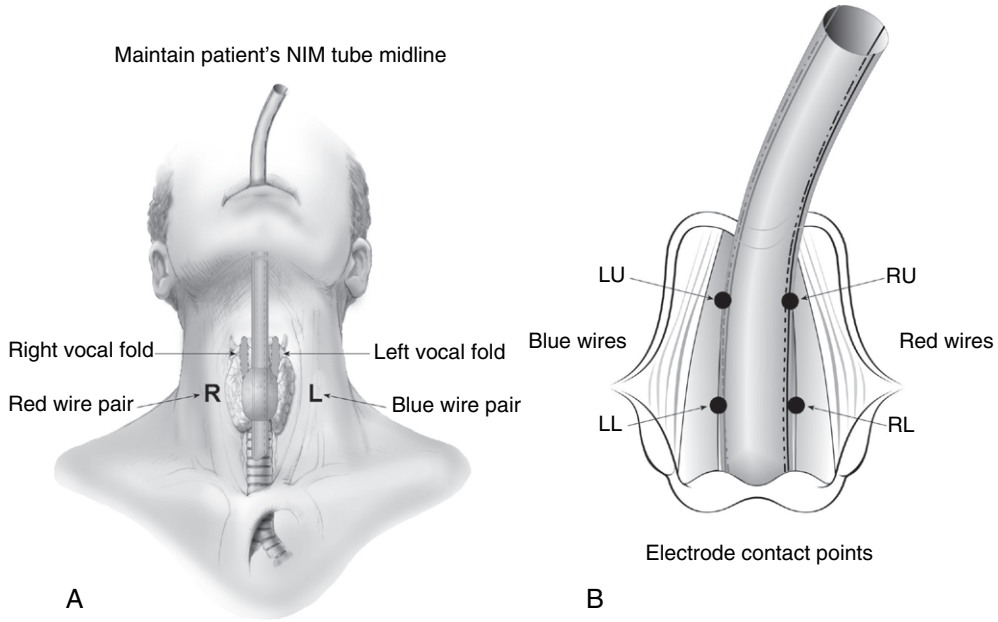

FIGURE **38-10** Nerve integrity monitor (NIM) endotracheal tube. **A,** Proper placement of the NIM endotracheal tube in relation to the thyroid gland. **B,** Four electrode contact points in relation to the vocal cords.

when connected to a multichannel EMG monitoring device. If monitoring correctly, the EMG should show a consistent sound signal and an action potential tracing. The red wire pair of the NIM tube should contact the anterior and posterior portion of the right true vocal cord, and the blue wire pair should contact the anterior and posterior portion of the left true vocal cord as shown in Figure 38-10. Paralysis and laryngeal tracheal anesthesia with lidocaine both inhibit accurate EMG readings. Research is ongoing regarding the efficacy of EMG; however, some studies have shown no statistically significant difference in outcome between a standard endotracheal tube and an NIM tube.[69,70]

Maintenance of anesthesia can be provided by inhalational anesthetics with or without nitrous oxide. A combined deep and superficial cervical plexus block can be considered for intraoperative and postoperative pain management.[71] The patient should be constantly monitored for an increase in core body temperature and hyperdynamic response. If hypotension occurs, it is best treated with a direct-acting vasopressor (phenylephrine) rather than an indirect-acting vasopressor (ephedrine), which stimulates the release of catecholamines.[67] The patient is positioned supine with the head elevated 30 degrees and the neck extended using a roll behind the neck and shoulders (Rose position). The arms are tucked at patient's sides with the ulnar nerves padded and protected. Hyperextension of the neck should be avoided in those patients with atlantoaxial joint instability and/or those with limited range of motion. Due to the limited access to the face, special care should be taken to protect the eyes from injury, especially in patients with exophthalmos.

Postoperative Management

The most common postoperative complications include hypocalcemia, recurrent laryngeal nerve damage, and hematoma at the surgical site. A complete list of the potential postoperative complications is presented in Box 38-4. Postoperative hypocalcemia can result from hypoparathyroidism. The four parathyroid glands are located on the posterior aspect of the thyroid gland and produce parathyroid hormone, which increases serum calcium. Inadequate release of parathyroid hormone is due to the inadvertent removal of the parathyroid glands during a total thyroidectomy. It can also occur secondary to parathyroid gland devascularization, injury, or "stunning" from dissection.[67,72]

Hypocalcemia causes neuronal excitability in sensory and motor nerves. Patients most commonly develop signs and symptoms associated with hypocalcemia 24 to 96 hours postoperatively. The degree of hypocalcemia coincides with the severity of the symptoms, which include perioral numbness and tingling, abdominal pain, paresthesias of the extremities, carpopedal spasm, tetany, laryngospasm, mental status changes, seizures, Q-T prolongation on the electrocardiogram, and cardiac arrest.[64,67,72] Neuromuscular irritability also can be confirmed by assessing for Chvostek's sign (i.e., facial contractions elicited by tapping the facial nerve in the periauricular area) and Trousseau's sign (i.e., carpal spasm on inflation of a blood pressure cuff). In addition, monitoring postoperative ionized calcium levels is recommended because these values are reflective of the physiologically active form of calcium.

Treatment for severe symptomatic hypocalcemia includes the administration of calcium gluconate or calcium chloride (10 milliliters of 10% solution) intravenously given over several minutes and followed by a continuous infusion (1-2 mg/kg/hr) until calcium levels normalize.[67]

Recurrent laryngeal nerve (RLN) damage is estimated to occur in 0% to 14% of cases. The surgical identification and preservation of the RLN is essential to avoid injury. RLN damage may be unilateral or bilateral; however, unilateral nerve injury is more common. Unilateral RLN damage causes the ipsilateral vocal cord to remain midline during inspiration, resulting in hoarseness. Bilateral RLN injury results in dysfunction of both vocal cords, which remain midline during inspiration. After extubation, biphasic stridor, respiratory distress, and aphonia occur due to unopposed adduction of the vocal cords and closure of the glottic aperture. Unlike unilateral nerve injury, bilateral nerve injury necessitates immediate intervention requiring emergent reintubation or tracheotomy.[67]

BOX **38-4**

Complications Associated with Thyroidectomy

- Hypocalcemia-hypoparathyroidism
- Recurrent laryngeal nerve injury—unilateral or bilateral
- Neck hematoma
- Thyroid storm
- Superior laryngeal nerve injury
- Infection
- Pneumothorax
- Tracheomalacia

Adapted from Elisha S, et al. Anesthesia case management for thyroidectomy. *AANA J*. 2010;78(2):151-160.

Postoperative bleeding of the surgical site results in a neck hematoma, which causes airway obstruction and asphyxiation. Common symptoms of neck hematoma include neck swelling, neck pain and pressure, dyspnea, and stridor. Initial treatment includes the emergent evacuation of the neck hematoma followed by airway management.[67,72]

Cleft Palate and Lip

Cleft Palate (Hard Palate and Soft Palate)

Cleft lip and palate is one of the most common craniofacial abnormalities, occurring in approximately 1:700 births.[73] During fetal development, the bones of the face develop between the fifth and ninth weeks and the growth of the palatal bones between the sixth and eleventh weeks. A cleft develops when the bones of the nasal and maxillary or the palatal bones fail to fuse. A fetus can develop both a cleft lip and palate or either alone. Up to 30% of these newborns have other congenital anomalies such as Down syndrome, Pierre Robin syndrome, and Treacher Collins syndrome.

The timing for surgery remains controversial. Generally, cleft lip repair with primary tip rhinoplasty is performed at age 3 months. This will enable the baby to feed and demonstrate normal facial expressions. The next repair involves closure of the posterior hard palate and the soft palate before the development of speech and is usually at 5 to 8 months of age depending on the exact defects. The patient's overall health status and the presence of other congenital anomalies are considerations as well. Widely followed preoperative guidelines include the rules of ten: weight at least 10 pounds, hemoglobin at least 10 g, white blood cell count less than 10,000/mm^3, and age more than 10 weeks. Others advocate for earlier repair, and in utero techniques are under investigation.[74,75]

Intubation may sometimes be difficult if the laryngoscope blade slips into the cleft. However, packing the cleft with gauze may prevent this from occurring. An oral RAE tube or flexible connector is used and secured at the midline of the lower lip. A specialized mouth gag is used to hold the mouth open and the ETT in place during cleft-palate surgery. All air bubbles should be carefully removed from IV lines to prevent air embolus, owing to the incidence of associated cardiac anomalies (e.g., atrioventricular defect [AVD]) that may lead to air crossing from the venous to the arterial circulation. Congenital heart disease may influence which drugs are selected for maintenance of anesthesia and infiltration of the operative site, particularly if epinephrine is selected. Care must be implemented to protect the child's eyes because accidental damage may occur during the surgical procedure. Before emergence, a suture is often placed through the tip of the tongue and taped to the cheek. This suture eliminates the need for an oral airway and prevents damage to the palatal repair. If soft-tissue obstruction occurs during emergence or recovery, traction on the suture can alleviate the problem. If edema occurs, a more aggressive and immediate airway management technique should be used. Copious secretions and blood may cause laryngospasm after extubation, and therefore a clear airway is imperative.

Cleft Lip

Management of unilateral cleft lip repair consists of routine induction followed by oral intubation using an RAE tube or a flexible connector. Secure the tube to the lower lip and midline via tape. To decrease tension on the surgical sutures at the end of the procedure, the surgeon may place a Logan bow across the upper lip of the patient.[76] When the Logan bow is placed, mask ventilation during emergence will become impaired or impossible. Extubation must be performed only with the patient fully awake and reflexes intact. The child's surgical site must also be protected from finger and hand manipulation. Some hospitals recommend the use of hand mittens or taping the extremities onto armboards during the postoperative period. Close monitoring of respiration should proceed into the postoperative period.

Dental Restoration Procedures

Dental restoration procedures are performed under general anesthesia for a multitude of reasons. These include rampant cavities, history of cerebral palsy or Down syndrome, and an uncooperative patient who would not be an appropriate candidate for local anesthetic and an office procedure.

Mentally disabled patients typically develop a close relationship with either a family member or their long-term health-care worker. It is often suggested that this individual accompany the patient to decrease anxiety and communicate a health history to the anesthesia provider. A thorough airway assessment should be performed before considering induction. Oral midazolam (0.5 mg/kg) or ketamine (3 to 4 mg/kg intramuscularly [IM]) is most effective in sedating children in the preoperative arena. Because many patients requiring dental restoration have congenital anomalies, it is not uncommon to find a small oropharynx, enlarged tonsils, a large tongue, and increased secretions. Atlantoaxial instability and congenital heart disease should also be considered in the preoperative preparation and anesthetic management.[77-79] Preparation and appropriate airway management must be planned and implemented for these patients. Patients who receive phenytoin to control seizures may have gingival hyperplasia. Because the gingiva is highly vascular, any surgical manipulation during restoration may lead to significant blood loss.

In patients with normal airways, a standard induction is appropriate, and a nasal intubation usually facilitates the dental procedure. The application of a topical vasoconstrictive nasal spray during the preoperative period reduces or prevents bleeding during the insertion of the nasotracheal tube. Following loss of consciousness, lubricated intranasal trumpets may be inserted into the most patent nasal airway. Starting with a smaller nasal trumpet, several are placed in increasing sizes to dilate the airway. When full dilation of the nares has occurred, a well-lubricated ETT is passed through the nose into the trachea, either blindly or assisted by Magill forceps under direct laryngoscopy. The nasal ETT is preferably placed on the side opposite where the surgeon will be working. The ETT is often sewn to the nasal septum by the surgeon. Throat packs may be placed to prevent blood from entering the stomach and causing nausea and vomiting; monitoring their removal is essential to preventing respiratory obstruction after extubation.

Sinus and Nasal Procedures

Nasal and sinus procedures for drainage of chronic sinusitis, polyp removal, repair of a deviated septum, or closed reduction of fractures

generally involves the young and healthy patient population. Many patients who undergo sinus and nasal surgery have chronic environmental and drug allergies; therefore, there is an increased incidence of reactive airway disease in these patients. Nasal polyp removal, for example, may be necessitated by Samter syndrome. A patient with Samter syndrome or triad presents with nasal polyps, asthma, and an aspirin allergy. The nasal polyps, if symptomatic, are removed surgically. The use of fiberoptics or functional endoscopic sinus surgery for nasal and sinus surgery has become a popular treatment for chronic sinusitis.

Nasal surgery may be successfully accomplished with local anesthesia, local combined with intravenous sedation, or general anesthesia. All three methods of anesthesia require vasoconstriction. The mucous membranes of the sinuses and nose are highly vascular, and blood loss may be significant if vasoconstriction is not used. The surgeon may select to control vasoconstriction with epinephrine or cocaine. Bizikas et al.[80] found when comparing cocaine and tetracaine that using tetracaine 2% with epinephrine produces superior anesthesia and vascular control for rhinoplasty. A hypotensive technique or slight head elevation (i.e., 10 to 20 degrees) may be used during the procedure. Using general anesthesia has been associated with increased blood loss, even with the use of an epinephrine injection. This exaggerated blood loss may be related to the vasodilatory properties of inhalation agents. Delivering general anesthesia for sinus surgery with propofol, as well as other intravenous anesthetic techniques for the maintenance of anesthesia, has been associated with less blood loss than occurs with the use of volatile agents for maintenance.[78] The placement of an oropharyngeal pack and light suctioning of the stomach at emergence may attenuate postoperative retching and vomiting. After all of the packing is removed, extubation should be performed on the awake patient who has regained control of protective reflexes.[79] The use of intravenous or topical lidocaine may reduce some of the coughing prior to extubation, leading to less bleeding in the postoperative period.

Trauma

Initial Assessment

Traumatic disruption of the bony, cartilaginous, and soft-tissue components of the face and upper airway require special consideration. It is imperative to create an anesthetic plan for securing the airway without promoting further damage or compromising ventilation. Possible mechanisms by which the upper or lower airway may become obstructed include edema, bleeding from the oral mucosa and palate, intraoral fracture sites, distortion of the nasal passages, injury of the pharynx and sinuses, open lacerations, and the presence of foreign bodies such as avulsed teeth, blood clots, or bony fragments.[81]

Initial management of the airway depends on the situation at hand. In the case of severe facial or neck trauma, alternative methods of tracheal intubation (e.g., fiberoptic laryngoscopy, retrograde wire placement, jet ventilation via cricothyrotomy, or emergent tracheostomy) may be necessary to secure the airway.

Injuries of the head and neck may include cervical spine or cranial injury. Although a complete evaluation of all cervical vertebrae is ideal, inspection of radiographs of the cervical spine is judicious to determine the presence or absence of dislocations and fractures. All seven cervical vertebrae must be visible in such studies. The seventh cervical vertebra is the most common site of traumatic fracture of the spine.[82] Vertebral artery injury must be suspected with a cervical injury, because these fractures can lead to vertebral artery tear or occlusion. If deteriorating respiratory function requires immediate airway management and intubation, the head should be maintained in a fixed position before any manipulation of the airway is performed. The use of manual axial in-line stabilization (MAIS) and/or a rigid cervical collar in place is recommended. The removal of the anterior segment of the collar can facilitate intubation and manipulation of the soft tissues of the neck.[82,83]

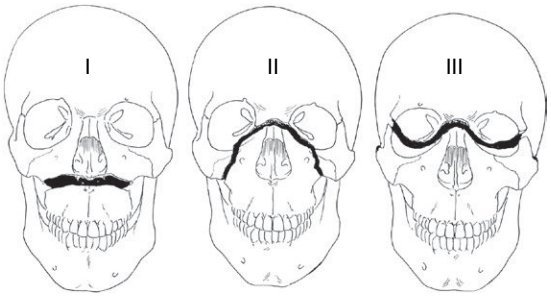

FIGURE **38-11** Examples of Le Fort I, II, and III facial fractures *(left to right)*.

Blunt trauma to the face or anterior neck may produce rapid airway occlusion secondary to soft-tissue edema or hematoma formation secondary to trauma of the vascular structures of the neck. The patient exhibiting smoke inhalation or blistering in the area of the mouth and nares or with a history of inhalation of toxic byproducts of combustion should be intubated immediately. Edema of the face and glottis, which may lack symptoms in the early stages, has the potential to produce serious airway compromise several hours after injury.

Maxillofacial Trauma and Orthognathic Surgery

Le Fort[84] determined the common fracture lines of the maxilla and face by experimentation on cadavers in 1901. The Le Fort classification is based on his finding that blunt trauma tends to cause fractures along three particular lines of the face. Fractures occurring in twenty-first–century, real-life situations (in particular, high-velocity motor vehicle accidents) often deviate from this classification system, and "pure" Le Fort fractures are rare. Nevertheless, the Le Fort classification system is widely known, and it provides a method for concise communication of fracture patterns between clinicians and radiologists. There are three types of Le Fort fractures that describe a pattern of fractures involving multiple facial bones.[85,86]

The fractures are divided into Le Fort I, II, and III (Figure 38-11). The Le Fort I fracture is a horizontal fracture of the maxilla extending from the floor of the nose and hard palate, through the nasal septum, and through the pterygoid plates posteriorly. The palate, maxillary alveolar bone, lower pterygoid plate, and part of the palatine bone are all mobilized. The Le Fort II fracture is a triangular fracture running from the bridge of the nose, through the medial and inferior wall of the orbit, beneath the zygoma, and through the lateral wall of the maxilla and the pterygoid plates. The Le Fort III fracture totally separates the midfacial skeleton from the cranial base, traversing the root of the nose, the ethmoid bone, the eye orbits, and the sphenopalatine fossa.[84,87]

A Le Fort I fracture generally causes little difficulty for the anesthesia provider. Patients may be intubated orally or nasally and the airway secured without a problem. The Le Fort II and Le Fort III fractures are of particular concern when contemplating nasal intubation. In both of these fractures, disruption of the cribriform plate may occur, opening the underside of the cranial cavity. The presence of cerebral fluid in the nose, blood behind a tympanic membrane, periorbital edema, or "raccoon-eyes" hematoma are indications that attempts to pass an endotracheal tube or nasogastric tube through the nares could lead to inadvertent intracranial placement.[87] Although the insertion of a nasal tube may aid the surgeon, an attempted nasotracheal intubation of a

patient with a basal skull fracture involves the very serious risk of introducing the tube into the skull, bringing contaminated material into the subarachnoid space and causing meningitis. The tube may also inflict damage to the brain itself.[88]

The forces required to produce facial fractures are considerable and may be associated with other trauma. It is important that cervical spine injury, subdural hematoma, pneumothorax, and intraabdominal bleeding be investigated. Soft-tissue injury to the airway and blood or debris in the oropharynx may make visualization impossible. If in doubt while in the emergency department, a tracheostomy under local anesthesia or an awake oral intubation with topical anesthesia should be considered. These patients should be treated with full stomach precautions.

As with any trauma victim, attention is first directed toward maintaining the ABCs: airway, breathing, and circulation. The repair of the facial fracture itself is not an emergency and may be carried out at a later time. Once the patient arrives in the operating room for surgery, it may be challenging to open the patient's mouth for intubation because of edema, pain, or trismus. It is necessary to differentiate the cause of the small mouth opening because it may be pain related or mechanical in nature. The administration of a short-acting narcotic or midazolam will sometimes assist the anesthesia provider in determining the cause of the restriction, which greatly influences the induction chosen. In mandibular or maxillary fractures, nasal intubation is usually best, because the patient's teeth are brought together via wires or rubber bands at the conclusion of surgery (intermaxillary fixation). Anesthesia is induced with an IV agent and maintained with narcotics, muscle relaxants, and inhalation agents. Blood loss from facial fractures can be extensive. The patient's blood should be typed and crossmatched so that blood is immediately available. The fixation process closes the teeth in proper occlusion and prevents access to the oropharynx. Masking the patient at emergence requires that the patient be awake with intact reflexes at extubation. It also requires that wire cutters or scissors be available to cut the wire or rubber bands fixing the mandible to the maxilla in case an airway emergency occurs in the recovery area.[89]

Orthopedic orthognathic procedures often require sagittal splitting of the mandible to move the lower jaw either forward or back. A Le Fort I or Le Fort II osteotomy may be purposefully performed to move the maxilla in any direction to correct anomalies. Many of these patients have anomalies of the mandible and maxilla, small mouth openings, and appliances that make intubation difficult and airway management challenging. Because many of the malocclusions are treated orally, a nasal endotracheal tube is usually preferred over an oral intubation. Securing the nasotracheal tube away from the surgical field without causing necrotic injury of the nares is vital. Because blood loss during these procedures can be extensive, the patient is typed and crossmatched. Deliberate hypotensive anesthetic techniques are often used if the patient remains stable. Rigid metal or plastic external or internal fixation devices are used to maintain stability in both the mandible and maxilla postoperatively; therefore, the proper cutting tools should be at the patient's bedside for emergency airway issues. Edema will often be extensive and progress over the first 24 hours after orthognathic surgery. To prevent postoperative respiratory problems, the patient may remain intubated for several days. If extubation is necessary, it should be done only when the patient is awake, in full command of protective reflexes, and can be carefully monitored in the postoperative period.

Radical Neck Dissection

Radical neck dissection is required when cancerous tumors have invaded the musculature and other structures of the head and neck. Neoplastic growths can occur anywhere within the upper airway and may achieve significant size with little evidence of airway penetration or obstruction. Such tumors are often friable and bleed readily. These patients are frequently heavy drinkers and smokers who have bronchitis, pulmonary emphysema, or cardiovascular disease. If the tumor interferes with eating, associated weight loss, malnutrition, anemia, dehydration, and electrolyte imbalance can be significant. Patients who have had radiation treatments of the neck and jaw prior to surgical intervention will have soft tissues that are less mobile, making intubation more difficult. Many of these patients are older and have the comorbidities associated with age.[90,91] Attempted tracheal intubation can induce significant hemorrhage and edema, causing severe compromise of the airway.

Determining the appropriate techniques for airway management entails consultation with the surgeon as to the nature, extent, and location of the tumor; therapy administered (radiation or chemotherapy); CT results; history and physical examination; and relevant preoperative laboratory values.

Head and neck reconstruction is an integral part of surgical removal of head and neck tumors. Traditional methods of reconstruction include regional pedicle flaps with microvascular reconstruction. Flaps include the pectoralis major myocutaneous flap, trapezius flap, and local rotational flaps (e.g., forehead flap). Additionally, small bowel may be harvested to reconstruct the oropharynx and esophagus. Successful anesthesia plays an important role in maximizing the overall success rate of a free flap and microvascular flow of the flap.[92] The planned donor site should be determined to plan for any limitation on the available sites to place lines necessary for monitoring and venous access. Although the choice of monitoring is largely dependent on the general condition of the patient, the placement of a central venous pressure (CVP) line, a Foley catheter, and an arterial line (beat-to-beat and arterial blood gas trends) is suggested, particularly if deliberate hypotension during anesthesia is used. The internal jugular approach should be avoided because of proximity to the surgical site. Sites commonly used for the CVP placement when the internal jugular is not accessible are the subclavian and femoral veins, respectively.

Maintenance of anesthesia is often performed with an inhalation agent and supplemental narcotics. The use of a nondepolarizing muscle relaxant must be discussed with the surgical team preoperatively because a nerve stimulator is frequently used (by the surgeon) to locate nerves distorted by the tumor during the procedure. Significant blood loss can be a problem; sometimes a controlled hypotension technique may be requested.[90,91] At least one and preferably two large-bore peripheral IV lines (16 to 14 gauge) should be in place. An arterial line, hemodynamic monitor, and central line are many times desirable. The patient's blood should be typed and crossmatched, with blood readily available. It is important to replace blood loss, but not to the point of overloading the patient. Monitoring estimated blood loss and measuring the hematocrit may provide some guidelines for replacement of blood. A positive fluid balance in the postoperative phase can result in edema and congestion of the flap, predisposing it to vascular compromise. Colloids may be used to help limit the amount of crystalloid required during the procedure. Patients undergoing a radical neck dissection are frequently hypovolemic and have electrolyte imbalances. This requires some fluid replacement and electrolyte balance intraoperatively to maintain cardiovascular stability. Cerebral blood flow can be compromised by the tumor, retractors, or blood flow; therefore it is important to maintain adequate perfusion.

In preparation for a tracheostomy or total laryngectomy to be performed during the surgical procedure, the patient should be well oxygenated. The trachea will be transected by the surgeon,

TABLE 38-9 Laryngectomy

Structures Removed	Structures Remaining	Postoperative Conditions
Total Laryngectomy		
Hyoid bone Entire larynx (epiglottis, false cords, true cords) Cricoid cartilage Two or three rings of trachea	Tongue Pharyngeal wall Lower trachea	Loses voice; breathes through tracheostomy; no problem swallowing
Supraglottic or Horizontal Laryngectomy		
Hyoid bone Epiglottis False vocal cords	True vocal cords Cricoid cartilage Trachea	Normal voice; may aspirate occasionally, especially liquids; normal airway
Vertical (or Hemi-) Laryngectomy		
One true vocal cord False cord Arytenoid One half thyroid cartilage	Epiglottis One false cord One true vocal cord Cricoid	Hoarse but serviceable voice; normal airway; no problem swallowing
Laryngofissure and Partial Laryngectomy		
One vocal cord	All other structures	Hoarse but serviceable voice; occasionally almost normal voice; no airway problem; no swallowing problem
Endoscopic Removal of Early Carcinoma		
Part of one vocal cord	All other structures	May have a normal voice; no other problems

From Odom-Forren J. *Drain's Perianesthesia Nursing: A Critical Care Approach*. 6th ed. St. Louis: Saunders; 2013:463.

which requires that the anesthesia provider suction the airway and remove the ETT only to a level above the tracheal incision. Once the tracheostomy tube has been placed by the surgeon and ventilation validated, the ETT can then be completely removed. A reinforced tube is usually placed in the distal airway by the surgeon and connected to the anesthesia machine. A reassessment of the ventilation should be performed, including the entire procedure of listening to bilateral breath sounds, observing chest excursion, and checking end-tidal CO_2 and positive inspiratory pressure (PIP) or negative inspiratory pressure (NIP). After the anesthesia provider has validated tube placement, the ETT is sutured to the chest wall for the entire surgical duration. At the end of surgery, the reinforced tube may be switched for a tracheostomy cannula.

During radical lymph node dissection of the neck for carcinoma, manipulation of the carotid sinus may elicit a vagal reflex, causing bradycardia, hypotension, or cardiac arrest. Small doses of local anesthetic injected near the carotid sinus or administration of an anticholinergic may block vagal reflexes. Owing to the long duration of the surgery and interruption of venous flow, venous thrombus is commonly seen in patients who are undergoing radical neck dissection. The head-up position and open neck veins during surgery may lead to venous air embolism. Careful monitoring with precordial Doppler sonography or transesophageal echocardiography (TEE) provides the best detection of air embolism. Immediate removal of the air through the CVP is essential. Laryngeal edema, vascular occlusion, and obstruction can also occur as a result of the venous stasis that follows major disruptions in venous flow during surgery or with trauma. Continual review of complications and follow-up treatments are necessary.[89-91,93]

Postoperative considerations consist of tracheostomy care, controlled ventilation, chest roentgenogram (to rule out pneumothorax, hemothorax, pulmonary edema), and monitoring for laryngeal edema induced by thrombosis. Postoperative characteristics of various surgical laryngectomy procedures are given in Table 38-9. It is suggested that these patients be admitted overnight in the intensive care unit because they have undergone major fluid and electrolyte shifts and altered ventilation-perfusion status and have spent an extensive time under the influence of anesthesia.[94,95]

SUMMARY

Administering anesthesia for ENT and maxillofacial procedures requires knowledge in both basic and advanced anesthesia techniques. Using these techniques demands the best skills of even a seasoned and experienced clinician. The usual tenets of safe practice must often be adhered to while remaining at a distance from the airway. Good preparation remains imperative. Cooperation and communication between the surgeon and anesthetist maintain a vital link for all concerned, especially those patients in their charge.

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39 CHAPTER Anesthesia for Ophthalmic Procedures

◆ *Randolf R. Harvey*

Ophthalmic anesthesia continues to be an exciting and challenging segment of anesthesia practice. Ophthalmologists recognize the value anesthesia practitioners provide to their patients and practice. The use of topical anesthesia for cataract surgery is now routine; however, the demand for eye blocks for other procedures continues. Retrobulbar block has been progressively phased out and replaced by peribulbar block, sub-Tenon's block, or topical anaesthesia with the use of phacoemulsification for cataract surgery, Advances in retinal surgical techniques have increased the demand by surgeons for injection eye blocks for select surgeries and replaced the use of general anesthesia except in rare circumstances. This trend is also growing for corneal transplants and adult eye muscle and glaucoma procedures. This is especially true for procedures requiring deep anesthesia and akinesia.

Today more than a million ocular blocks are performed annually for surgical procedures. Thanks to ophthalmic anesthesia educational programs, safer than ever ocular blocks are being administered, and more efficient patient care is being provided. This new expertise in eye anesthesia has spurred a high demand for such services, in part because of the proliferation of ambulatory surgical centers (ASCs) to meet the increased demand for ophthalmic surgery.

OPHTHALMIC ANATOMY

Extraocular Muscles

The eye is surrounded by six extraocular muscles (Figures 39-1 through 39-3). The *superior rectus muscle*, located at the 12-o'clock position on the globe, moves the eye upward, or *supraducts* the eye. The *inferior rectus muscle*, located at the 6-o'clock position on the globe, moves the eye downward, or *infraducts* the eye. The *medial rectus muscle*, located 90 degrees medially to the 12-o'clock position on the globe, moves the eyeball nasally, or *adducts* the eye. The *lateral rectus muscle*, located 90 degrees laterally to the 12-o'clock position on the globe, moves the eyeball *laterally*, or *abducts* the eye. The *superior oblique muscle*, located on the superior aspect of the eye, rotates the eyeball on its horizontal axis toward the nose, or *intorts* the eye and depresses the eyeball. The *inferior oblique muscle*, located on the inferior aspect of the globe, rotates the eyeball on its horizontal axis temporally, or *extorts* the eye and elevates the eyeball (Table 39-1).

All the ocular muscles except the inferior oblique originate in the orbital apex around the annulus of Zinn (Figure 39-4), which is a fibrinous ring that encircles the optic foramen. The four rectus muscles move forward in a conal pattern that forms the muscle cone around the globe. These muscles, which are about 40 mm long, insert into the globe just anterior to its equator.[1] The superior oblique muscle arises just superior to the annulus of Zinn and moves forward, becoming a tendon. This tendon passes through a cartilaginous ring called the *trochlea*, which is located on the medial supranasal orbital wall. After passing through the trochlea, the tendon is redirected in a posterolateral direction and inserts on the superolateral aspect of the globe under the superior rectus muscle. The inferior oblique muscle originates from the anterior nasal orbit and moves in a posterolateral direction to the globe, inserting along the lateral aspect of the globe. The arching of both the inferior and the superior oblique muscles around the globe allows for the torsional movements of the eye.

Eyelid Muscles

The levator muscle of the upper eyelid is the primary muscle used for raising the upper eyelids. This muscle originates near the annulus of Zinn (see Figure 39-1, *B*). It moves forward just superior and slightly medial to the superior rectus muscle, inserting into the upper eyelid. Because the levator muscle only retracts and does not contract the eyelid, akinesia of this muscle is not necessary.

The *orbicular muscle* of the eye (Figure 39-5) causes the eyelids to contract. This muscle has three divisions—*orbital*, *palpebral*, and *tarsal*—which are concentrically arranged around the eyelid. Akinesia of these muscles is generally desired for ocular procedures, because if the muscles were allowed to contract around the globe, intraocular pressure would increase. However, the recent success of cataract and glaucoma procedures performed with the use of topical and subconjunctival anesthesia has demonstrated that akinesia of the orbicular muscle of the eye is not always mandatory.

Cranial Nerves

The orbital portion of the *optic nerve* (cranial nerve II) (Figure 39-6) is from 25 to 30 mm long and travels posteriorly within the muscle cone from the globe into the cranial cavity. This distance is actually longer than that from the posterior portion of the globe to the orbital apex, giving the optic nerve an S-shaped configuration. This shape allows free movement of the nerve so that the many positions of the eye are accommodated. The optic nerve is myelinated and is about 4 mm in diameter.[2] The optic nerve extends through the *optic canal* and continues until it meets the *optic chiasm* intracranially. The optic chiasm is the junction of both optic nerve tracts. Here, suspended in and surrounded by cerebrospinal fluid, the optic nerve fibers partially decussate, sending visual fibers to the contralateral eye.

The optic nerve is not a true cranial nerve but is actually an outgrowth of the brain.[1] As a result, the optic nerve is also covered by the *meninges*, the fibrous wrappings of the arachnoid, dura, and pia mater, which envelop the central nervous system (CNS). Therefore any anesthetic agent injected into the optic nerve sheath can find its way back to the midbrain through the cerebrospinal fluid and result in CNS depression and even lead to respiratory arrest. The optic nerve also carries the central retinal artery and vein into the globe. The central retinal artery and vein exit the optic nerve about 8 to 15 mm posterior to the globe.[3]

The *oculomotor nerve* (cranial nerve III) innervates the following muscles of the orbit: the superior rectus muscle, the inferior rectus muscle, the inferior oblique muscle, the medial rectus muscle, and the levator muscle of the upper eyelid. The oculomotor

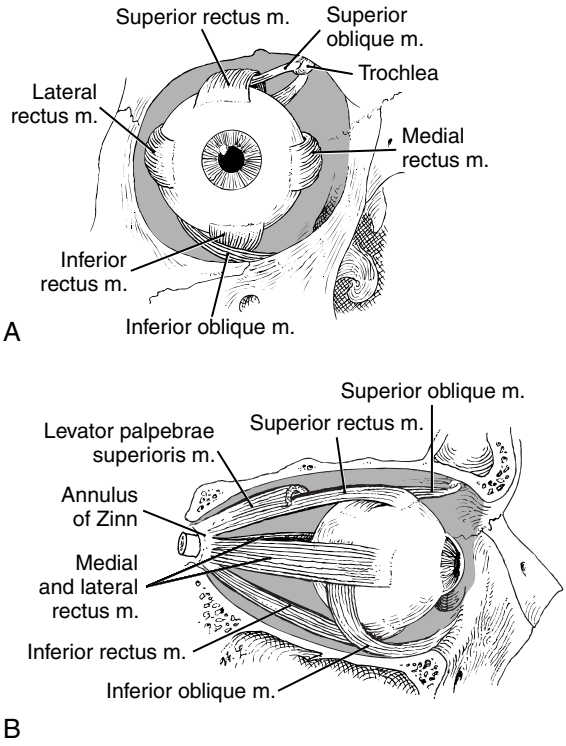

FIGURE **39-1** **A,** Frontal view of the orbit. **B,** Lateral view of the orbit. *m.*, Muscle.

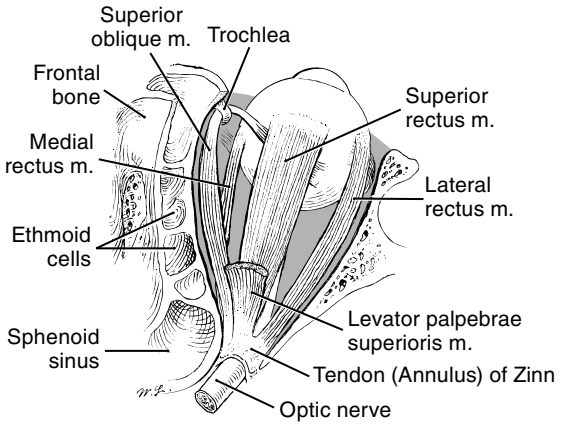

FIGURE **39-2** Superior view of the orbit. *m.*, Muscle.

nerve is the primary motor nerve to the extraocular muscles of the orbit; this nerve branches superiorly and inferiorly (Figure 39-7). The superior branch innervates the superior rectus muscle and the levator muscle of the upper eyelid. The inferior branch of the oculomotor nerve innervates the medial rectus muscle, the inferior rectus muscle, and the inferior oblique muscle. This nerve also sends parasympathetic fibers to the ciliary ganglion (Figure 39-8), which is located adjacent to the optic nerve in the posterior portion of the orbit. The ciliary ganglion receives parasympathetic fibers from the oculomotor nerve and also sympathetic fibers from the carotid artery plexus and a sensory branch from the nasociliary nerve, a branch of the ophthalmic nerve. The parasympathetic fibers move from the ciliary ganglion forward to innervate the iris sphincter muscles, which cause constriction of the pupil. The sympathetic motor fibers move forward to control the radial muscle of the iris for pupillary dilation.[1-3]

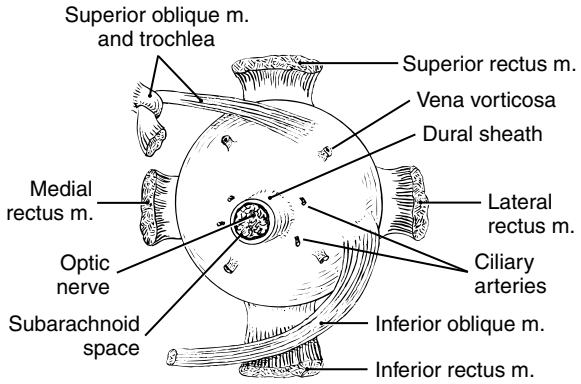

FIGURE **39-3** Posterior view of the globe. *m.*, Muscle.

TABLE **39-1** Orbital Muscles and Innervation

Muscle	Function	Cranial Nerve
Superior rectus	Supraduction	III
Inferior rectus	Infraduction	III
Medial rectus	Adduction	III
Lateral rectus	Abduction	VI
Superior oblique	Intorsion Depression	IV
Inferior oblique	Extorsion Elevation	III

The *trochlear nerve* (cranial nerve IV) (see Figure 39-7) provides the motor fibers for the superior oblique muscle. This nerve enters the orbit through the superior orbital fissure outside the muscle cone. It is the only orbital cranial motor nerve that enters the orbit from outside the muscle cone. Once inside the orbit, the nerve root moves in a medial direction to innervate the superior oblique muscle.

The *trigeminal nerve* (cranial nerve V) (see Figure 39-8) has sensory and motor components. In ocular anesthesia, the sensory component is of primary importance. The intracranial portion of the nerve forms the trigeminal ganglion, which has three main divisions: the ophthalmic, the maxillary, and the mandibular nerves. The ophthalmic branch provides for the sensation of pain, touch, and temperature to the cornea, ciliary body, iris, lacrimal gland, conjunctiva, nasal mucosa, eyelid, eyebrow, forehead, and nose. The maxillary branch provides for the sensation of pain, touch, and temperature to the upper lip, nasal mucosa, and scalp muscles.[4]

The *ophthalmic nerve* has three main branches: lacrimal, frontal, and nasociliary. The *lacrimal nerve branch* innervates the lacrimal gland in the superior lateral aspect of the orbit. The frontal branch is the largest branch of the ophthalmic nerve. This branch enters the orbit from outside the muscle cone through the superior orbital fissure and travels anteriorly outside the muscle cone superior to the levator muscle. The frontal nerve itself splits into two branches. The larger, supraorbital branch continues forward into the orbit and exits the orbit through the supraorbital notch; this branch innervates the forehead. The smaller branch is the supratrochlear nerve, which moves in a medial direction, supplying nerve roots to the forehead and the medial portion of the upper eyelid. The *nasociliary nerve branch* enters the orbit from inside the muscle cone and crosses over the optic nerve, sending nerve fibers medially and to the ciliary ganglion. The fibers to the ciliary ganglion form the short ciliary nerves, which continue anteriorly,

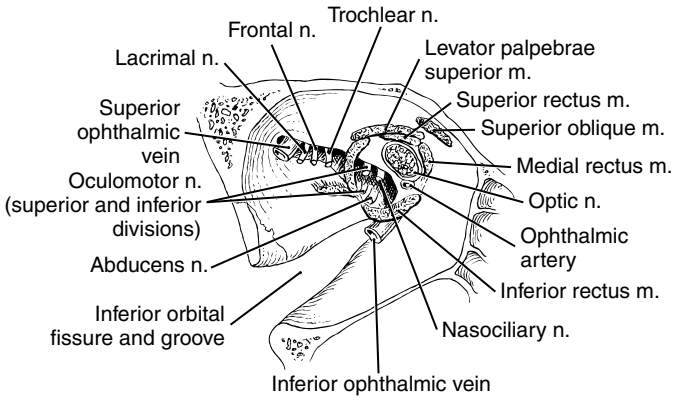

FIGURE **39-4** View of the orbital apex. *m.*, Muscle; *n.*, nerve.

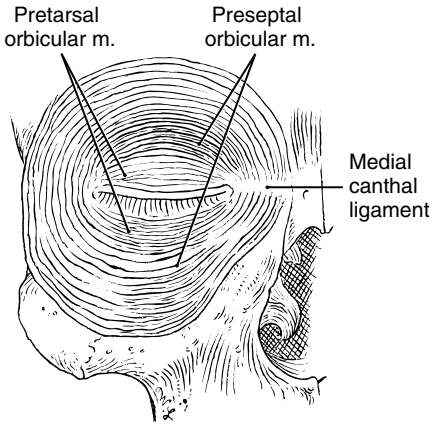

FIGURE **39-5** Orbicularis oculi muscles. *m.*, Muscle.

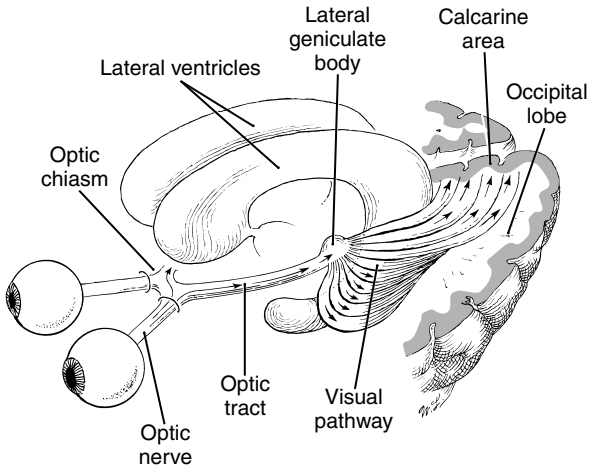

FIGURE **39-6** Intraorbital and intracranial view of the optic nerve.

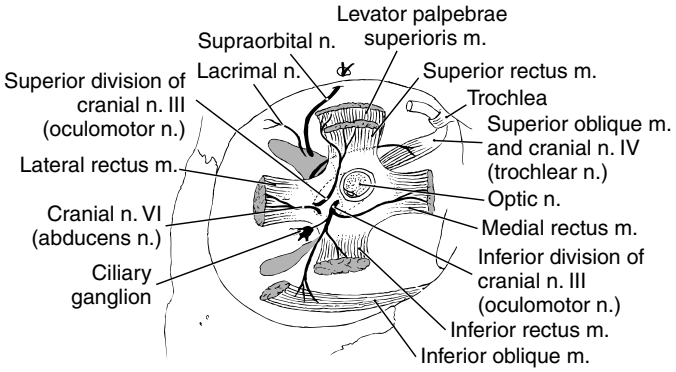

FIGURE **39-7** Frontal view of the posterior orbit with its motor nerves and the extraocular muscles. *m.*, Muscle; *n.*, nerve.

penetrating the posterior portion of the globe near the optic nerve. The nasociliary nerve also gives rise to the long ciliary nerves, which continue anteriorly and enter the posterior portion of the globe supplying the ciliary muscle, iris, and cornea. The long ciliary nerves also carry sympathetic fibers to the dilator muscle of the iris from the superior cervical ganglion. The nasociliary nerve continues along the medial aspect of the orbit just superior to the medial rectus muscle until it passes through the orbital septum to become the *infratrochlear nerve*. The infratrochlear nerve provides sensory input to the side of the nose, the medial aspect of the eyelids, the medial conjunctiva, the caruncle, and the lacrimal sac.[1-4]

The *abducens nerve* (cranial nerve VI) (see Figure 39-7) provides motor function to the lateral rectus muscle. The nerve enters through the superior orbital fissure within the muscle cone and continues along the conal surface of the lateral rectus muscle, eventually inserting in the posterior one third of that muscle.

The *facial nerve* (cranial nerve VII) (Figure 39-9) is predominantly a motor nerve for the muscles of the face. This nerve exits from the stylomastoid foramen. The facial nerve travels underneath the external auditory canal to the parotid gland, where it divides into an upper and a lower branch. Ocular anesthesia is more concerned with the upper branch of the facial nerve than with the lower. The upper branch further divides into the temporal and zygomatic branches, which innervate the orbicular muscle of the eye, the superficial facial muscles, and the scalp muscles.

The *vagus nerve* (cranial nerve X) provides motor function to the intrinsic muscles of the larynx and the heart; it provides major parasympathetic visceral innervation elsewhere. It is also the efferent pathway for the oculocardiac reflex, which can result in bradycardia and dysrhythmias.

Orbital Fossa

The *orbital fossa* has been described as pear shaped. The medial walls of the orbit extend almost straight back, whereas the lateral walls diverge at about a 90-degree angle to each other (Figure 39-10). The *superior* and *inferior orbital fissures* are in the orbital apex, which is located in the posterior orbit. These fissures are the entry portals for the orbital nerves and vessels (Figure 39-11). The *optic foramen* lies just medial to the superior orbital fissure and is the entry portal for the optic nerve and the ophthalmic artery from the intracranial to the intraorbital area. In the medial nasal aspect of the fossa, just behind the orbital rim, is the *lacrimal bone*, which is used as a landmark for the medial peribulbar block (Figure 39-12). The *ethmoid bone* is just posterior to the lacrimal bone.[4]

The *supraorbital nerve* exits the orbit in the supraorbital notch, which is in the superior nasal aspect of the orbital rim. The *infraorbital foramen*, where the infraorbital nerve and artery exit, is just below the infraorbital rim at about the 6-o'clock position. The *infraorbital nerve* is the sensory branch of the maxillary nerve. The *lacrimal*, *frontal*, and *trochlear nerves* all enter through the superior orbital fissure outside the muscle cone. The *oculomotor*, *abducens*, and *nasociliary nerves* all enter the orbit from inside the muscle cone.[4]

The *ophthalmic artery* (Figure 39-13), which is the first branch of the internal carotid artery, passes into the orbit through the optic canal. The ophthalmic artery usually lies just inferolateral to the optic nerve. The artery extends along the optic nerve for a short

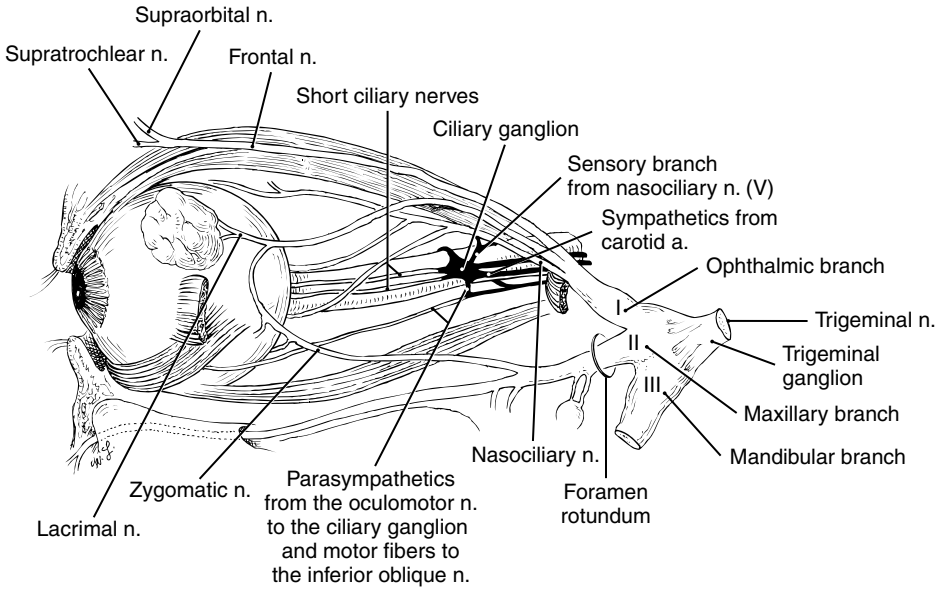

FIGURE **39-8** Lateral orbital view of sensory nerves and ciliary ganglion. *a.*, Artery; *n.*, nerve.

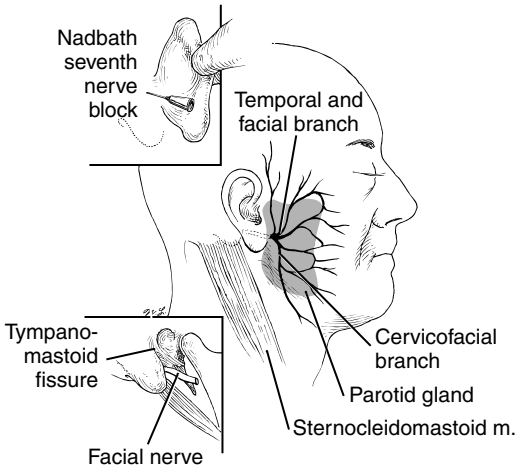

FIGURE **39-9** The origin and branches of the facial nerve. *Upper inset:* Needle placement for the Nadbath cranial nerve VII block. *m.*, Muscle.

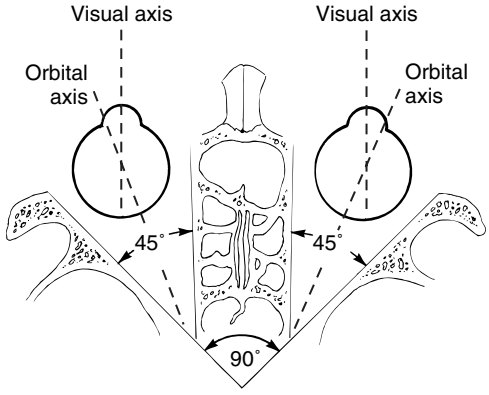

FIGURE **39-10** Superior view of the bony orbit, demonstrating the orbital and visual axes.

distance, crossing over it in most cases and continuing medially.[5] The first branch of the ophthalmic artery is usually the *central retinal artery*. The central retinal artery moves in an anterior direction underneath the optic nerve, usually entering the optic nerve on its inferomedial side 8 to 15 mm posterior to the globe.[3] The artery continues forward into the optic nerve head and branches into the retinal arteries. The ophthalmic artery gives rise to the long and short posterior ciliary arteries. The short posterior arteries move anteriorly and divide into many small branches that penetrate the globe close to the optic nerve and supply the choroid and the optic nerve head. The ophthalmic artery also provides branches to the optic nerve. The orbital branches of the ophthalmic artery include branches to the supraorbital arteries, the rectus muscles, and the lacrimal gland.[4]

The *lacrimal artery* moves anteriorly along the superior aspect of the lateral rectus muscle to the lacrimal gland. The *supraorbital artery* branches from the ophthalmic artery as it crosses over the optic nerve and extends just medial to the superior rectus and levator muscles. It continues forward on a superior nasal route and exits through the *supraorbital notch* or *foramen*.

The *dorsal nasal artery* is one of the terminal branches of the ophthalmic artery. It exits the orbital septum above the medial canthal tendon and joins with the *angular artery,* thus establishing communication between the internal and external carotid arteries.[1] The *external carotid artery* gives branches to the facial artery (the external maxillary artery). The *facial artery* originates near the angle of the mandible, extends toward the stylohyoid muscles, and then proceeds forward to the lower border of the mandible. The artery then turns upward and moves toward the nose, where it joins with the dorsal nasal artery in the medial canthal area. The inferior orbital fissure is the entrance site for the *infraorbital artery*. This artery moves anteriorly through the infraorbital canal and exits to the face through the infraorbital foramen.

The venous drainage system (see Figure 39-13) for the orbit includes the superior and inferior ophthalmic veins, which drain into the cavernous sinus that is located intracranially. Radiographic studies have demonstrated a unique characteristic of the orbital vascular system: the orbital veins are independent of the orbital arteries.[5] The venous system of the orbit is valveless, and blood flow in this area is determined by pressure gradients. The primary vein of the orbit is the *superior ophthalmic vein*. This vein travels posteriorly to the medial side of the superior rectus muscle, then beneath the superior rectus muscle inside a support hammock. The vein then emerges on the muscle's lateral aspect.

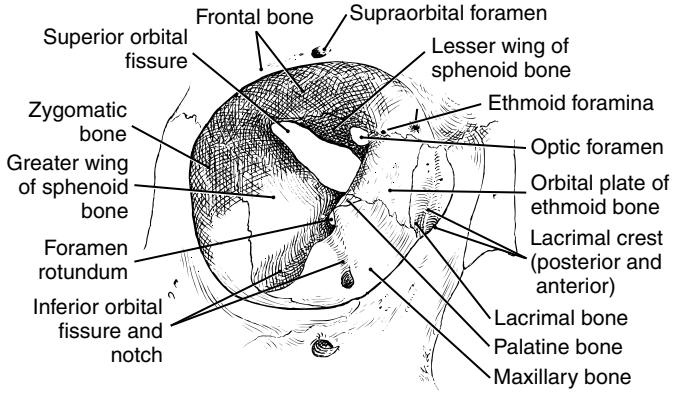

FIGURE **39-11** Frontal view of the orbital bones.

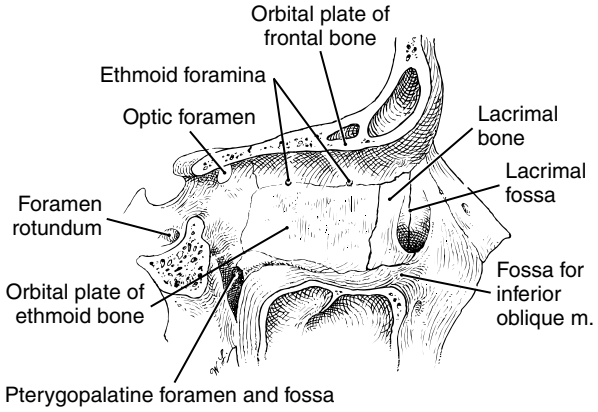

FIGURE **39-12** Lateral view of the orbital bones. *m.*, Muscle.

The vein continues its posterior direction along the lateral aspect of the superior rectus, exiting the orbit through the superior orbital fissure, and terminating in the cavernous sinus.[5]

Several veins enter into the superior ophthalmic vein: the *ciliary veins*, the *lacrimal veins*, and the *superior vortex veins*, which are located on the posterior quadrants of the globe and drain the choroid, or second layer, of the globe. The *inferior ophthalmic vein* originates from a diffuse plexus on the floor of the orbit. This vein receives several branches, including the extraocular muscles and the inferior vortex veins located on the inferoposterior quadrants of the globe. The primary branch of the inferior ophthalmic vein also drains into the *superior ophthalmic vein* before the entrance of the superior ophthalmic vein into the cavernous sinus. The *central retinal vein* exits the globe inside the optic nerve. The central retinal vein then exits the optic nerve and enters the orbit between 8 and 15 mm posterior to the globe[3] and usually passes directly to the cavernous sinus.[1]

Orbit

An evaluation of the patient's orbit and globe size is important before ocular anesthesia is conducted. The usual volume of the orbit is 30 mL (Box 39-1). The volume of a typical globe (which has a diameter of about 25 mm) is 6.5 to 7 mL.[5] The balance of the orbital volume is approximately 23 mL and is composed of muscles, vessels, nerves, and fat. Katsev et al.[6] measured 120 orbits from 60 adult skulls and found an average orbital depth of 48 mm. The distance from the middle third and lateral third of the infraorbital rim to the superior aspect of the optic foramen was also measured and ranged from 42 to 52 mm. This distance should not be confused with the depth of the orbital floor. Because of the pear shape of the orbit, the orbital floor does not extend directly to the orbital apex.

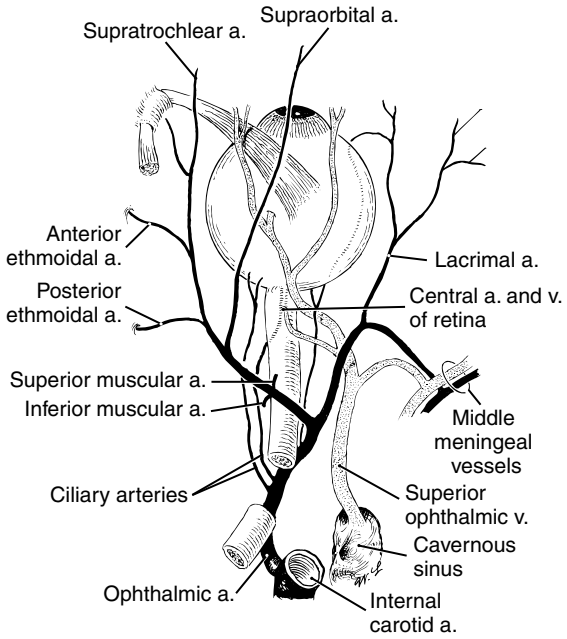

FIGURE **39-13** Superior view of the orbital arteries and veins. *a.*, Artery; *v.*, vein.

BOX **39-1**

Orbital Measurements

- Height of the orbit: 40 mm
- Width of the orbit: 35 mm
- Depth of the orbit: 42-52 mm
- Approximate orbital volume: 30 mL
- Approximate globe volume: 6.5-7.0 mL
- Balance of orbital volume: 23 mL

The orbital floor extends only to the posterior wall of the maxillary sinus, about two thirds of the depth of the orbital apex.

Orbital fat is contained in both the extraconal and the intraconal areas. The orbital fat encircles and encapsulates all these areas of the orbit.

The *orbital septum* is a fibrinous tissue that defines the anatomic anterior boundary of the orbit and keeps the adipose tissue from protruding forward. The *visual axis* (also known as the *optic axis* or the *geometric axis*) is an imaginary line from the midpoint of the cornea (anterior pole) to the midpoint of the retina or macula (posterior pole) (Figure 39-14). The horizontal (anteroposterior) diameter of the globe is an important consideration for ocular blocks. This measurement of the visual axis is referred to as the *axial length*. The axial length is measured preoperatively to determine the appropriate intraocular lens that should be placed in the eye after cataract removal. The axial length of the globe can be used *only* when measurements for intraocular lens implants are performed by the ophthalmologist. Normal axial lengths range from 23 to 23.5 mm. In the hyperopic (farsighted) eye, the globe is less than 22 mm long. This shorter eye length may allow a little more working area behind the eye during an ophthalmic block; however, this advantage may be offset by a smaller overall orbit.[4,6]

The main concern regarding ophthalmic blocks involves the longer, myopic (nearsighted) eye, whose axial length is greater than 24 mm. As the globe stretches, it is believed that the fibrinous scleral layer thins, making the globe easier to penetrate by the

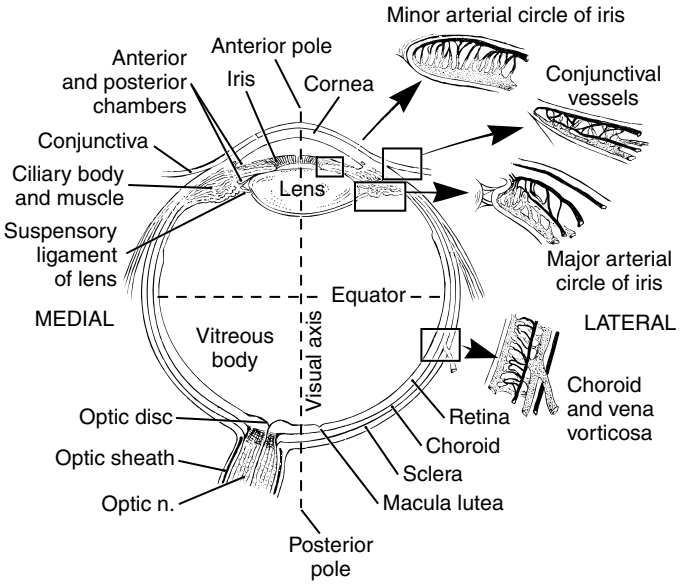

FIGURE **39-14** Cross-sectional view of the globe. *n.*, nerve.

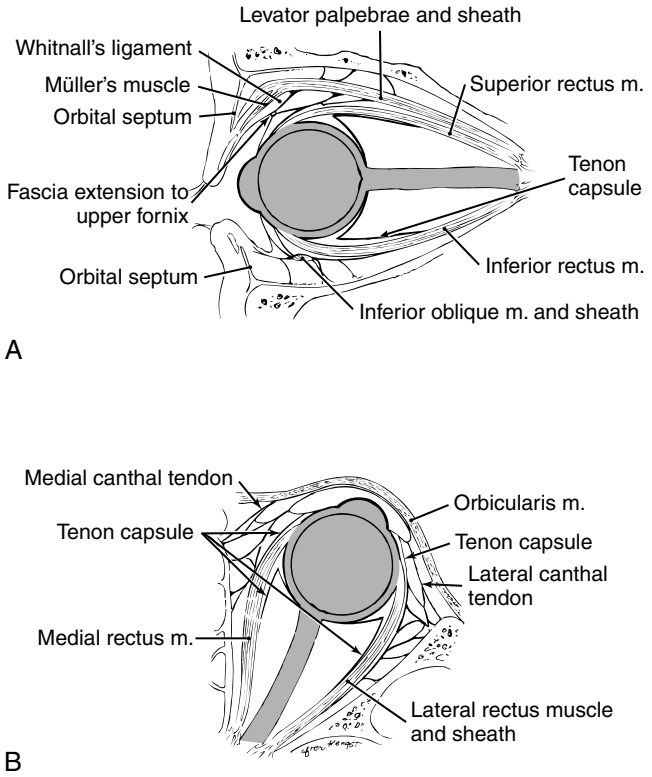

FIGURE **39-15** **A,** Lateral view of the orbital connective tissue. **B,** Superior view of the orbital connective tissue. *m.*, Muscle.

needle. This increased posterior length of the globe also increases the chance of globe puncture. Therefore, because of a greater chance of contact in the posterior aspect of the orbit, the axial length of the eye (if this measurement is available) should be considered in the planning for ocular block. If the axial length is unknown, which may be the case in glaucoma surgery, corneal transplants, retinal procedures, or muscle surgery, the practitioner's preoperative questions should include a history of nearsightedness or previous retinal procedures.

The separate *coats*, or *tunics*, of the eyeball (see Figure 39-14) start with the *sclera*, which is the outer, fibrinous protective layer. The sclera is white and opaque and lies just posterior to the cornea. The *cornea* is the outer, fibrinous protective layer located anteriorly, and it is transparent and colorless. The middle, or vascular, layer is called the *choroid*. The *retina* is the inner layer of the posterior half of the eye. The *limbal area* is defined as the area at the junction between the cornea and the sclera.[1] The *conjunctiva* is a thin, transparent mucous membrane that covers the posterior surface of the eyelids and the anterior surface of the sclera.

A *staphyloma* is a bulging of the uvea, which comprises the iris, the ciliary body, and the choroid, into a thin and stretched sclera. Staphylomas may occur in the anterior, equatorial, and posterior areas.[2]

Tissue Systems of the Orbit

Three connective tissue systems within the orbit have been defined by Koornneef.[7] They are the Tenon capsule, the orbital connective tissue, and the fascial sheaths of the extraocular muscles (Figure 39-15).

Tenon Capsule. The *Tenon capsule* (bulbar fascia) consists of fibrous connective tissue that covers the eyeball from near the corneal limbus, where it is fused to the conjunctiva, and extends behind the eye, with openings for the extraocular muscles and the optic nerve. The Tenon capsule serves primarily as a cavity in which the eye moves.

Orbital Connective Tissue. Koornneef demonstrated the presence of *connective tissue* attachments between both the globe and the periorbital area. The connective tissue begins at the orbital apex and continues anteriorly, becoming more complex and more clearly defined at the level of the globe. Koornneef[7] also noted that the tissue septa are in a 360-degree encapsulation of the globe (Figure 39-15). These connective tissue septa encircle and support the globe within the bony orbit. Connective tissue septa were also noted between the superior and inferior oblique muscles, the Tenon capsule, the rectus muscles, and the ligaments stabilizing the globe within the orbit. This connective tissue septa meshwork limits displacement of the globe.

Fascial Sheaths. The *intermuscular membrane* is a fibrous membrane that connects the four rectus muscle sheaths. Numerous extensions from these muscle sheaths form an intricate system of fibrinous attachments that interconnect the muscles into the orbit, support the globe, and check the ocular movements.

In the posterior orbit, the fascial sheaths of the extraocular muscles are not as well defined as they are immediately behind the globe.[8] Koornneef was not able to identify a common muscle cone throughout the orbit (Figure 39-16). The muscle sheaths themselves contribute fibrinous septa to the periorbit; these septa serve as ligaments for the extraocular muscles. These fascial extensions promote the efficiency of the extraocular muscle functions.[7-10]

PHARMACOLOGY: OCULAR MEDICATIONS AND ANESTHETIC AGENTS

A number of drugs are used in ophthalmology practice including mydriatics, miotics, cycloplegics, antibiotics, anti inflammatory drugs, viscoelastics, and glaucoma therapies. Ocular medications are listed in Table 39-2. The local anesthetics and hyaluronidase are covered in detail in Chapter 10.

Systemic Absorption of Eye Drops

The *lacrimal apparatus* includes the lacrimal gland, the puncta, the inferior and superior canaliculus, the common canaliculus, the lacrimal sac, and the nasolacrimal duct (Figure 39-17).

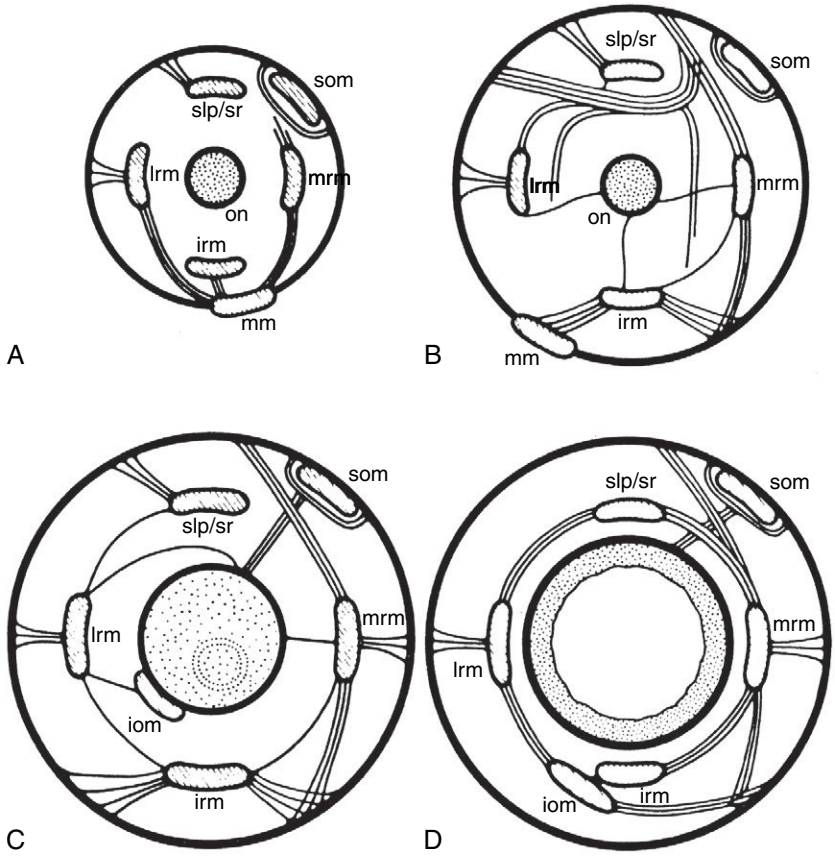

FIGURE **39-16** Extraocular muscle connective tissue system. Highly schematic representation of the connective tissue system of the extraocular muscles. **A,** Coronal section near the orbital apex. **B,** Coronal section near the posterior portion of the globe. **C,** Coronal section lying just anterior to the posterior portion of the globe. **D,** Coronal section near the equator of the globe. *iom*, Inferior oblique muscle; *irm*, inferior rectus muscle; *lrm*, lateral rectus muscle; *m*, Müller's muscle; *mrm*, medial rectus muscle; *on*, optic nerve; *slp/sr*, levator palpebrae superioris–superior rectus complex; *som*, superior oblique muscle. (From Koornneef L. Orbital septa: anatomy and function. *Ophthalmology.* 1979;86:876.)

The lacrimal gland is located in a depression of the frontal bone in the superior temporal orbit.[1-2] The gland has several ducts that lead to the conjunctival surface of the upper eyelid. Tears pass from the lacrimal gland through the ducts, over the cornea and conjunctiva, keeping the eye moist. Near the medial canthus, tears enter the puncta, travel through the canaliculus to the lacrimal sac, and drain into the nasolacrimal duct before entering the nasal mucosa.

Topical eye medications enter the bloodstream through the outer eye membrane and the lacrimal apparatus. The following measures reduce the amount of topical medications that enter the bloodstream:

- Have the patient close the eyes for 60 seconds after drops are instilled to encourage absorption by the eye and minimize drainage to the nasal mucosa.
- Have the patient avoid blinking, which rapidly moves the medication into the tear outflow canal and the systemic circulation.
- Block the tear outflow canal by placing the index finger over the medial canthus after the eye is closed.[2]

Patients may complain of a metallic taste after the administration of ocular anesthetics. This precursor to a toxic anesthetic level needs further evaluation. However, it is usually the result of the local anesthesia passing into the nasal mucosa.

SELECT OCULAR ANESTHESIA TECHNIQUES

Ophthalmic Block Techniques

Topical/Intraocular Anesthesia

Cataract and vitreoretinal surgeries are the most frequently performed intraocular surgical procedures.[11,12] Topical anesthesia for cataract surgery (e.g., 2% lidocaine) has proved to be effective in providing adequate analgesia for the surgical procedure and is commonly used with phacoemulsification. Topical anesthesia is applied as drops or gels and may be supplemented by intracameral injection by the surgeon for better intraoperative pain control. Vitreoretinal surgery usually requires at least a sub-Tenon block and more frequently injection anesthetic techniques.[12] Today's smaller-incision surgical techniques with foldable intraocular lenses provide a safer surgical experience for the patient and a more rapid recovery. Intraocular anesthesia can further enhance the analgesia for the surgical procedure; lidocaine (preservative free) has been studied and recognized as safe for intraocular administration.[13] However, topical anesthesia may not be appropriate in all cases for the surgeon or the patient, because it provides a lesser degree of analgesia and no akinesia of the ocular muscles or eyelids. There is wide variability in operative conditions, sensations, and pain relief, depending on the type of local anesthesia administered for intraocular surgery. Using data that present the strength of evidence as "strong evidence," "weak evidence," or "no evidence," the differences between local/regional

TABLE 39-2 Ocular Medications

Class	Generic Name (Trade Name)	Comments
α_2-Agonist	brimonidine tartrate (Alphagan P) apracionidine (Lopidine)	Glaucoma: Reduces aqueous humor production Contraindicated with MAO inhibitors
Cholinesterase inhibitors	ecothiophate iodide (Phospholine Iodide)	Glaucoma: Produces miosis by allowing acetylcholine to continually stimulate iris and ciliary muscles, improving uveoscleral outflow of aqueous humor May prolong effects of succinylcholine; however, rarely used
β-Blockers	timolol (Timoptic) levobunolol (Betagan Liquifilm) betaxolol (Betoptic) metipranolol (OptiPranolol) carteolol (generic)	Glaucoma: Reduces aqueous humor production Caution in patients with asthma, COPD, heart block, heart failure, and hypotension
Carbonic anhydrase inhibitors	acetazolamide (Diamox) dorzolamide (Trusopt) brinzolamide (Azopt)	Glaucoma: Reduces aqueous humor production
Cholinergic agonists	pilocarpine, topical carbachol (Miostat), intraocular acetylcholine chloride (Miochol-E), intraocular	Miotics; used to constrict pupil for surgical procedures
Cycloplegics	atropine homatropine cyclopentolate	Pupillary dilators; cause temporary paralysis of ciliary muscle and muscles of accommodation
Intraocular gases	sulfur hexafluoride perfluoropropane	Retinal detachment: Intravitreal insufflation to tamponade retina in place *Avoid nitrous oxide for up to 3 months*
Mydriatics	phenylephrine tropicamide epinephrine	Pupillary dilators; cause either a direct or indirect effect on dilator muscle of iris
Nonsteroidal antiinflammatory agents	flurbiprofen sodium (Ocufen)	Preserves pupillary dilation during surgical procedure by inhibiting prostaglandins, which cause miosis
Osmotic diuretics	glycerin (oral agent) mannitol	Reduce intraocular pressure
Prostaglandins	latanoprost (Xalatan) bimatoprost (Lumigan) travoprost (Travatan) tafluprost (Zioptan)	Glaucoma: Promotes uveoscleral outflow of aqueous humor
Viscoelastics	hyaluronate sodium (Healon, Amvisc)	Protect endothelial cells of cornea during surgical procedures

COPD, Chronic obstructive pulmonary disease; *MAO*, monoamine oxidase.

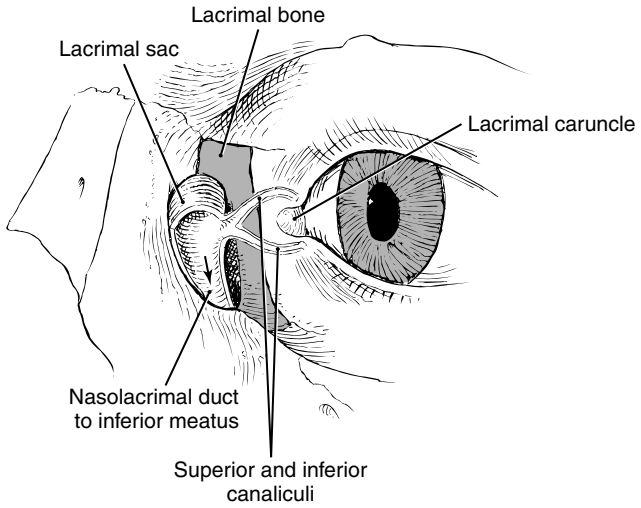

FIGURE 39-17 Frontal view of the lacrimal drainage system.

anesthetic techniques for variables such as pain (during placement of the block and during the surgery), eye akinesia, eyelid sensation, and visual sensations were quantified on a + or − scale, and the conflicts of evidence are presented as a range in Table 39-3.[12]

Sub-Tenon Block

The sub-Tenon block will produce a more profound analgesia; however, motor movement of the globe may still be present. The Tenon tissue, as described earlier, encapsulates the globe posteriorly and fuses with the conjunctiva anteriorly. Anteriorly it is inferior to the conjunctiva. The sub-Tenon block is a procedure performed between the rectus muscles of the globe. The conjunctiva is incised, the Tenon tissue is elevated and incised, and a short cannula is inserted into the sub-Tenon space. Local anesthetic is injected with the objective of a posterior spread of the agent. The dose is usually 3 to 4 mL to achieve analgesia; however, larger doses of up to 10 mL have been reported to achieve some degree of akinesia.[14]

OCULAR REGIONAL ANESTHESIA

The ocular regional needle block still remains the most common and effective way to consistently produce a profound analgesia and akinesia of the eye and eyelids.

TABLE 39-3 Comparisons of Local/Regional Anesthesia Techniques

	Topical	Sub-Tenon Block	Peribulbar Block	Retrobulbar Block
Pain on administration	0 or –	+ or ++	++ or +++	+++
Surgical pain prevented	– –	+++	++	++
Eye akinesia	– – –	0 or +	++	++
Eyelid sensation blocked	– – –	+	+	+
Visual sensations experienced	+++	++ or +	+	+

From Vann MA, et al. Sedation and anesthesia care for ophthalmologic surgery during local/regional anesthesia. *Anesthesiology.* 2007;107(3):502-508.
+ Represents strength of affirmative evidence; 0 represents insufficient evidence; − represents strength of contrary evidence.

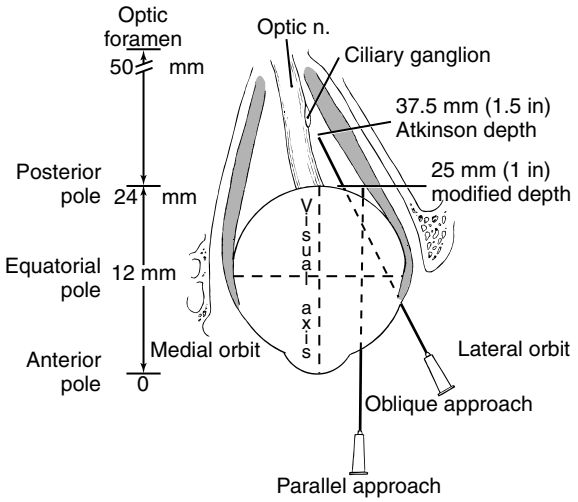

FIGURE **39-18** Superior view of the parallel and oblique approach to retrobulbar anesthetic blocks. *n.*, nerve.

The term *ocular local anesthesia* has been used to refer to retrobulbar or peribulbar blocks. More correctly, local anesthesia should be defined as *superficial, topical,* or *cutaneous anesthesia,* used, for example, when skin-laceration suturing is performed that poses minimal risks both to the body as a whole and to proximate vital organs.

Retrobulbar and peribulbar injections are categorized under regional anesthesia methods. These blocks are designed to anesthetize multiple cranial nerves (III, IV, V, VI, and VII). As described earlier, the optic nerve is a continuation of the brain. The dura mater divides at the entrance of the optic nerve into the orbit. The visceral layer of the dura covers the intraorbital part of the optic nerve, and the parietal layer blends into the periosteum of the orbit.[1] Therefore, by anatomic definition, this procedure is performed in the orbital epidural space. As has been demonstrated in the anatomic reviews by Koornneef, no true muscle cone exists, especially in the posterior portion of the orbit.[7-10] Therefore, old anatomic concepts such as the image of an intact muscle cone must be set aside in favor of concepts that illustrate a communication throughout the orbit.

Techniques and Modifications

The term *retrobulbar block* refers to an ophthalmic block technique originally described by Atkinson in 1936. The patient is instructed to look up and nasally (supranasal position). A 23-gauge retrobulbar (dull) needle is inserted through the skin in the infratemporal area, just above the inferior orbital rim and advanced toward the orbital apex 35 mm (1.38 inches) deep into the muscle cone (retrobulbar space). After negative aspiration, 2 to 4 mL of anesthetic solution is injected into the muscle cone. After the injection is completed, the eyelids are closed, and digital pressure is applied over the globe to the orbit. A few minutes later, the eyelids are opened, and the globe is inspected for akinesia.[15] The popularity of the retrobulbar block for ophthalmic procedures grew, with more than 1 million blocks performed annually in the 1940s.[16] Unfortunately, so also did the complication rates.

The reported complications from retrobulbar anesthesia include trauma to the optic nerve, the blood vessels, and the globe, all of which can lead to loss of vision. Respiratory arrest may result when anesthetic agents enter the cerebrospinal fluid of the optic nerve. Seizures may occur when even small amounts of local anesthetic are injected intravascularly.

As a result of the increasing number of complications being reported, practitioners began to alter the Atkinson retrobulbar technique in an effort to increase the margin of safety for ocular anesthesia.[17] Three major problem areas in the Atkinson technique are identified in this chapter, and technique modifications are discussed (Figure 39-18).

Eye Position

The position of the eye during retrobulbar block anesthesia is an important consideration. When the patient looks upward and nasally, the optic nerve and blood vessels are placed in the path of the needle. Tension is created on the optic nerve and the surrounding vasculature, making the orbital structures more susceptible to trauma. In this position, the posterior pole of the globe also moves into the needle path. As a means of avoiding this problem, the following modification in technique has been recommended.

The primary gaze position, in which the patient is looking directly forward, allows the optic nerve to maintain its S-shaped curvature and also releases the tension on the blood vessels. The down-and-out gaze position allows the optic nerve and vessels to rotate toward the optic foramen and farther away from the needle path. Both of these eye positions have the potential disadvantage of needle visualization by the patient. The upward-gaze position should only be used as described by Gills and Lloyd.[16] Their technique allows the use of the upward-gaze position because the needle is placed lateral and parallel to both the optic nerve and the vessels.

Needle Depth

A second problem is the depth of the needle insertion. The vital structures in the ocular anatomy are more crowded in the posterior orbit. Deep needle penetration in the orbit increases the likelihood of trauma to the optic nerve and vessels. If the depth of the needle insertion is decreased to approximately 25 mm (1 inch),[17] the needle would lie just posterior to the globe, thereby reducing the risk of puncture of the vital structures. Studies have demonstrated that because of the wide variation in orbital and globe sizes, a needle depth of 19 to 31 mm (0.75 to 1.25 inches) is the safest.[6]

Needle Tip Shape

A pertinent issue debated in the literature is the use of sharp versus dull needles for ocular blocks. Dull or flat-grind needles

made specifically for retrobulbar anesthesia are touted by some clinicians as the only safe needles for use in ocular blocks. It is not so much the type of needle but where the needle is placed that increases the risk.[18] Dull retrobulbar needles may not be tolerated as well by awake patients because of the sensation of pressure they create on insertion. Other needles proposed for ocular blocks include a curved retrobulbar needle[19] and a dull pinhead needle, in which the injection port is proximal to the head of the needle.[20]

Needle Angle

The angle of the needle is a third very important area that should be considered for modification. The original Atkinson technique uses an oblique approach; that is, the needle is inserted in the infratemporal area just above the inferior orbital rim and is directed toward the orbital apex**,** a pathway that tracts the needle tip toward the posterior pole of the globe, arteries, and the optic nerve.

Gills and Lloy[16] developed a technique that takes into consideration not only the aforementioned changes but also the length and spherical shape of the globe. This technique changes the oblique approach to a parallel approach. The lateral limbic margin, corneoscleral junction, is identified, and the needle is inserted in the inferotemporal area transconjunctivally, just lateral and parallel to the lateral limbic margin. The needle is inserted to a depth of approximately 25 mm (1 inch), entering the muscle cone just behind the globe. The advantages of this technique result from the needle position, which lies lateral and parallel to the optic nerve, the vasculature, and the posterior pole of the globe. However, the technique does not address the question, When does the needle tip pass the equator of the globe? The needle tip must pass the equator of the globe before it may be safely redirected cephalad and inserted into the intraconal space.

The original retrobulbar block technique described by Atkinson can be made safer by modification of the technique. Modifications that decrease the risk of adverse effects are as follows:

- Position the globe to decrease tension on the vital orbital structures and position them farther away from the needle—for example, the primary gaze position.
- Use a depth of needle insertion of about 25 mm (1 inch), which places the needle just behind the globe itself and avoids the structures deep in the orbit.
- Consider using a more lateral to parallel approach to the orbit than was originally demonstrated by Atkinson.

Some practitioners, in an effort to further improve the safety of ocular blocks, have advocated the use of extraconal peribulbar blocks.[21-25] The literature describes these techniques as directing the needle outside the muscle cone, or *extraconal.* The anesthetic is injected, creating a positive extraconal pressure that spreads the agent inside the muscle cone to anesthetize the cranial nerves. To accomplish this, the needle is inserted parallel to, or is angled away from, the visual axis of the globe in an effort to remain outside the muscle cone. Peribulbar injections may be performed in the superior temporal, medial, and inferior temporal orbital areas. Peribulbar anesthesia requires larger volumes of anesthetic agents (8 to 12 mL). Owing to the many septal divisions of the orbit, the anesthetic flow may not adequately diffuse into the intramuscle cone. Therefore, extraconal peribulbar anesthetic injections, as described in the literature, may not consistently produce adequate akinesia and may necessitate multiple repeat injections.[22]

Patients who may benefit from the extraconal peribulbar approach are those at increased risk for globe puncture, such as those with high myopia resulting in long axial lengths, significant

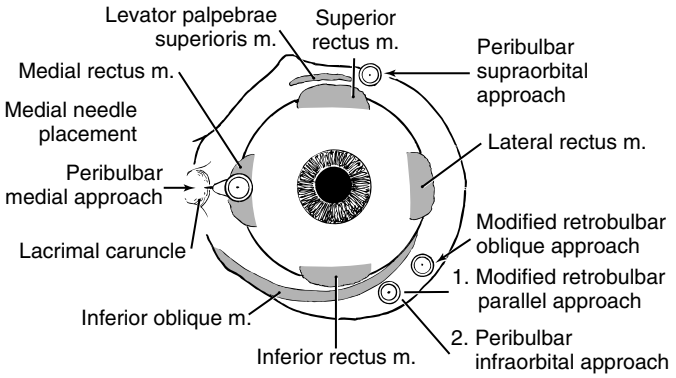

FIGURE **39-19** Frontal view of needle placement for retrobulbar and peribulbar anesthetic blocks. *m.*, Muscle.

enophthalmos, previous scleral buckling procedures, and staphylomas. However, peribulbar blocks have also been used in patients with globe punctures.[26]

The primary goal of extraconal peribulbar blocks is the avoidance of the muscle cone and its vital structures. With modified retrobulbar blocks, the goal is not only to avoid the vital structures but also to enter the muscle cone just posterior to the globe.

The least vascular areas in which ocular blocks can be performed were described by Koornneef and Kramer[9] (Figure 39-19). The inferotemporal area can be used for both the intraconal modified retrobulbar and the extraconal peribulbar technique. The superior orbital area just lateral to the 12-o'clock position through the skin and the medial orbital area through the caruncle conjunctiva may be accessed for the extraconal peribulbar technique.

The most important considerations for ocular blocks are the position of the eye and the depth and angle of the needle. Needle placement should avoid the optic nerve, arteries, veins, extraocular muscles, and the globe itself**.** At what insertion depth does the needle tip reach the equator of the globe, a spherical tangential point, beyond which it can be safely redirected into the retrobulbar space is addressed in an abstract that was accepted and presented at the 23rd annual meeting of The Ophthalmic Anesthesia Society, "A Geometrical Method Applied to an Orbital Block." The author introduces the measurement of the dynamic orbital-globe relationship and uses the measured axial length to calculate the distance to the equator of the globe, beyond which the needle may be safely redirected cephalad and inserted into the retrobulbar space. The calculation mathematically demonstrated that a 0.5-inch (12.5-mm) needle insertion was usually beyond the equator of the globe, but recommended calculating the distance to the equator on each patient for safety.[27]

Anesthesia Techniques

Gills-Lloyd Modified Retrobulbar Technique[16]

Equipment List.

- One 3-mL syringe
- One 6-mL or 10-mL syringe
- One 25-gauge 1-inch needle
- 1-inch paper tape
- One 4 × 4 gauze pad

Description. Figures 39-20 and 39-21 and Box 39-2 present valuable reference aids for the Gills-Lloyd modified retrobulbar technique.

The patient should be in a comfortable, reclining position. Anesthetic drops are placed in the conjunctiva, the eyelids are closed, and the outer eyelids are cleansed. The patient is asked to look directly overhead and to stare at a finger or other object.

The eye should not look inward but may look somewhat outward. Needle insertion through the skin is preferably avoided in this technique so that patient discomfort is minimized. The lateral limbic margin, corneoscleral junction, is identified. The lower eyelid is everted and controlled with a finger. The needle is placed with the bevel toward the globe, just above the inferior orbital rim, just lateral and parallel to the lateral limbic margin. The needle is then inserted through the conjunctiva and directed toward the orbital floor until the orbital septum is penetrated. The needle is then redirected parallel to the visual axis of the globe to a depth of 25 mm (1 inch). At this time, 1 to 1.5 mL of lidocaine, 1% to 2%, is injected after negative aspiration is performed. This initial extraconal peribulbar technique is effective in reducing the potential discomfort from the needle and the anesthetic injection of the modified retrobulbar block in the awake patient.

The eye is closed briefly in preparation for the modified retrobulbar injection. The lower eyelid is again everted and controlled with a finger. The needle is placed with the bevel toward the globe, just above the inferior orbital rim, just lateral and parallel to the lateral limbic margin. The needle is then inserted through the conjunctiva and directed toward the orbital floor until the orbital septum is penetrated. The needle is then redirected parallel to the visual axis of the globe past its equatorial plane, about 0.5-inch (12.5 mm)[27] deep. At this point, the needle is redirected cephalad between the lateral and inferior rectus muscles. Resistance may or may not be felt as the needle enters the muscle cone. The needle should be inserted about 25 mm (1 inch), depending on the size of the orbit and the globe (range, 19 to 31 mm). After negative aspiration, the anesthetic agent is injected slowly, 1 mL/10 sec, until the orbit is filled. Orbital size governs the total amount of anesthetic injected; however, about 6 mL usually suffices. Once the orbit is full of anesthesia, as indicated by orbital tension, the needle is withdrawn. The eyelids are closed, a 4 × 4 gauze is placed over the eye, and positive digital pressure is applied. The pressure helps spread the anesthetic and detect any increasing orbital pressure, which might indicate a retrobulbar hemorrhage.

The initial needle insertion is directed away from the globe so that the risk of globe puncture is decreased. Resistance may or may not be felt as the needle enters the muscle cone, depending on the presence or absence of the fibrinous connective tissue in the area behind the globe, as described by Koornneef and Kramer.[9] The sharper the needle, the less resistance felt by the practitioner and the less discomfort felt by the patient. By comparison, use of dull needles results in more resistance, potentially resulting in greater patient discomfort. Patients have described this resistance to the needle as *pressure pain*. Because a pop may or may not be felt as the needle enters the muscle cone, attention to needle depth is important for the avoidance of deep penetration into the orbit.

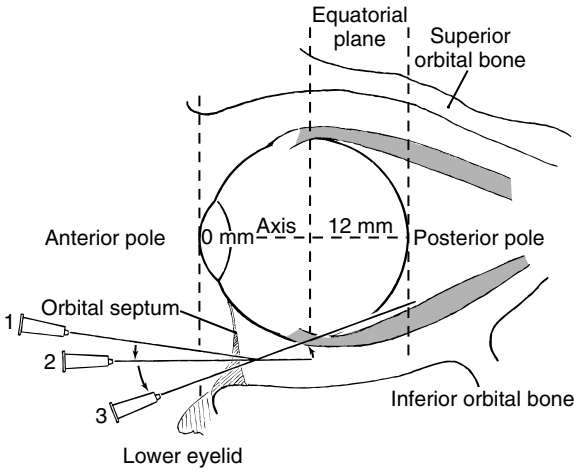

FIGURE **39-20** Lateral view of needle angles for a modified retrobulbar block.

During injection, the patient is told to inform the practitioner if any discomfort, such as stinging or a mild headache, is experienced. If this occurs, the injection should be stopped to allow the agent to take effect. The pressure sensation appears to result from the spread of the local agent throughout the orbital area. The stinging is noticed more when the agent moves into the peripheral area along the upper and lower eyelids. This slow injection process is continued until the orbit is filled with the anesthetic agent. When the anesthetic is placed into the muscle cone, the effects are seen rapidly, and the block can be evaluated for akinesia after about 2 minutes. Generous traction must be applied to the lower eyelid, because this technique is performed before the orbicular muscles of the eyelids are anesthetized (i.e., seventh nerve block). Seventh nerve blocks can be very painful and are not well tolerated by patients. These blocks generally precede retrobulbar or peribulbar blocks but may not be necessary, because the anesthetic agent from the modified retrobulbar or peribulbar block spreads randomly throughout the orbit and eyelids, providing adequate akinesia of the eyelids.[16,26]

Peribulbar Extraconal Techniques

Description. Figures 39-22 and 39-23 and Box 39-3 serve as valuable reference aids for the peribulbar technique.

Extraconal peribulbar blocks may be performed using different techniques. One is a supraorbital-only technique of injecting a large volume (10 to 12 mL) of anesthetic agent, which should distribute throughout the orbit for completion of the block. An inferotemporal-only technique also involves injection of a large volume (10 to 12 mL) of anesthesia, which should distribute throughout the orbit and anesthetize the eye. A more reproducible approach to extraconal peribulbar anesthesia is the use of both the inferior and superior approaches. Each of these injections may be performed with a 6-mL syringe for a total volume of 10 to 12 mL. The combination technique generally provides a more consistent result.

Infraorbital and Supraorbital Extraconal Peribulbar Anesthesia

Equipment List.

- One 10-mL syringe or two 6-mL syringes
- One or two 25-gauge needles
- One 4 × 4 gauze pad
- 1-inch paper tape
- One alcohol or povidone-iodine (Betadine) wipe

Description. For the *infraorbital peribulbar technique*, the lateral limbic margin is identified, and the patient is asked to look directly overhead. The lower eyelid is everted and controlled with a finger. The needle is placed, with the bevel toward the globe, just above the inferior orbital rim, lateral and parallel to the lateral limbic margin. The needle is then inserted through the anesthetized conjunctiva and directed toward the orbital floor until the orbital septum is penetrated. The needle is then redirected parallel to, or angled away from, the visual axis of the globe to a depth of about 25 mm (1 inch). After the syringe is secured and negative aspiration is performed, 6 mL of the anesthetic agent is slowly (1 mL/10 sec) injected. The rate of injection is determined by patient comfort. After the injection, the eyelids are closed, and positive pressure is applied for dispersal of the medication.

The *supraorbital peribulbar injection* is performed just inferior to the supraorbital rim, just lateral to the 12-o'clock position and superior to the globe. The needle is inserted with the bevel

toward the globe through the skin. This area is generally anesthetized from the original inferotemporal injection. The needle is inserted parallel to, or angled away from, the visual axis of the globe to a depth of about 25 mm (1 inch). After negative aspiration is performed, the anesthetist may begin a slow injection of 4 to 6 mL of anesthetic solution until a tense orbital area is observed. A more tense orbit should be expected to result from the peribulbar technique because of the increased extraconal pressure necessary to move the anesthetic intraconally.

Once this technique is completed, the eyelids are closed and taped shut. A 4 × 4 gauze pad is placed over the closed eye. A positive-pressure device is now placed over the eye to help distribute the agent throughout the orbit and achieve the desired analgesia and akinesia. The positive-pressure device also decreases intraocular pressure to an acceptable surgical level. To avoid corneal abrasion, the eyelids must completely cover the eye. It may take up to 10 minutes for satisfactory surgical anesthesia to be established from an extraconal peribulbar block. If the peribulbar block fails

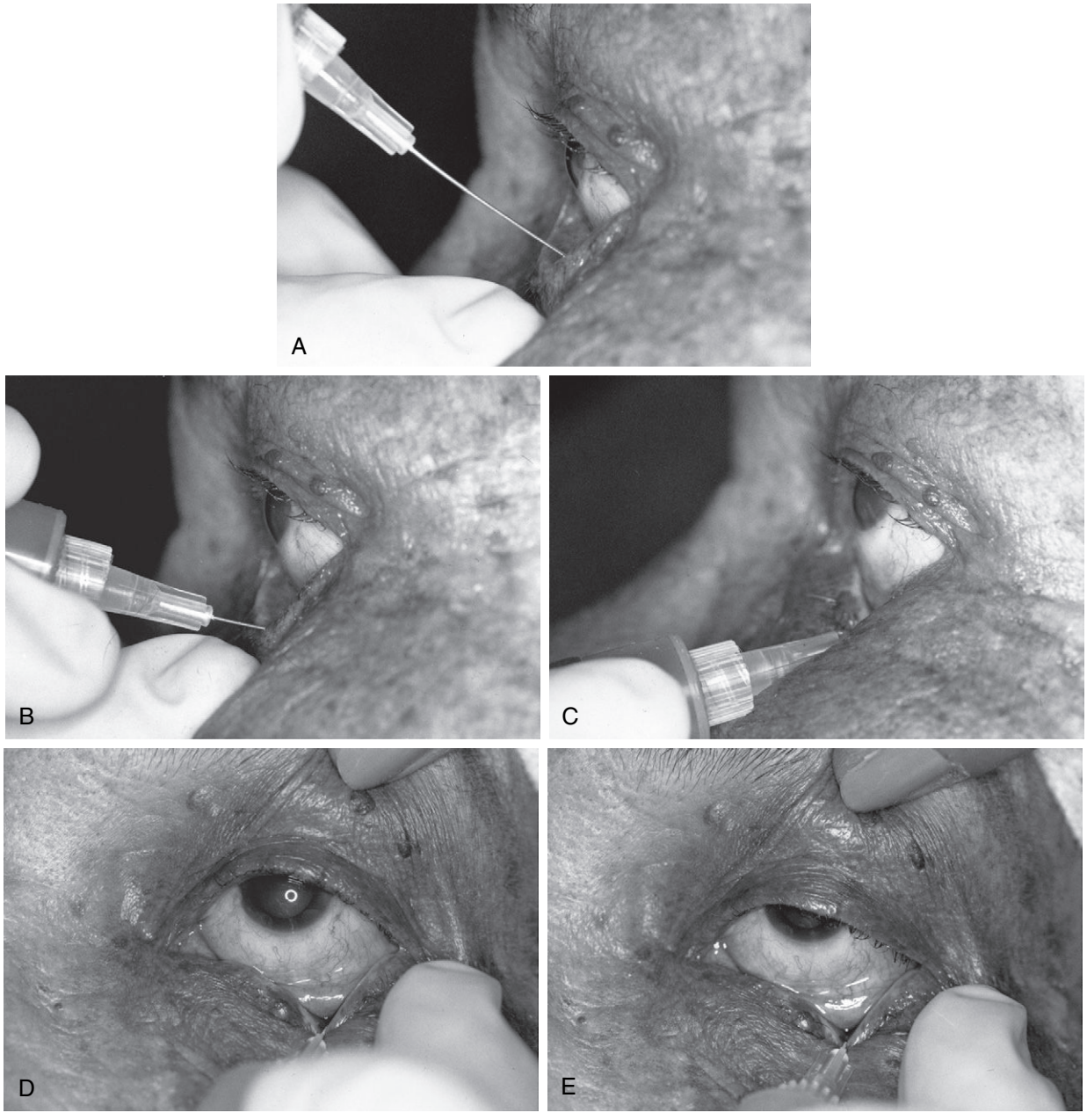

FIGURE **39-21** **A,** In the Gills-Lloyd modified retrobulbar technique, the needle should be inserted transconjunctivally or transcutaneously, angled away from the visual axis of the globe toward the orbital floor until the orbital septum is penetrated. **B,** After penetrating the orbital septum, the needle should be redirected parallel to the visual axis to a depth of about 12 mm (0.5 inch) passing the equatorial plane of the globe. **C,** After passing the equatorial plane of the globe, the needle should be redirected cephalad to a depth of about 25 mm (1 inch). At this point, the needle enters the muscle cone, and the medication is injected. **D,** Needle placement, which is lateral and parallel to the lateral limbic margin. **E,** Completion of the modified retrobulbar block. Some degree of globe proptosis and drooping of the upper eyelid should be expected.

to attain adequate akinesia within 10 minutes, the appropriate muscles must be reblocked by use of the inferior technique for the inferior rectus, inferior oblique, and lateral rectus muscles. The superior technique is used for the superior rectus, superior oblique, and medial rectus muscles. The supraorbital approach should not be attempted through the conjunctiva because of the potential for damage to the levator muscle of the upper eyelid; such damage may result in upper eyelid ptosis.

BOX **39-2**

The Gills-Lloyd Modified Retrobulbar Technique: Parallel Approach

- Insert the needle transconjunctivally or transcutaneously, with the bevel toward the globe, lateral to the lateral limbic margin and angled away from the visual axis of the globe toward the orbital floor, until the orbital septum is penetrated (see Figure 39-21, *A*).
- After penetrating the orbital septum, redirect the needle parallel to the visual axis to a depth of about 12 mm (0.5 inch) past the equatorial plane of the globe (see Figure 39-21, *B*).
- Past the equatorial plane of the globe, redirect the needle cephalad to a depth of about 25 mm (1 inch), entering the muscle cone while remaining lateral to the lateral limbic margin, and inject the medications (see Figure 39-21, *C*).

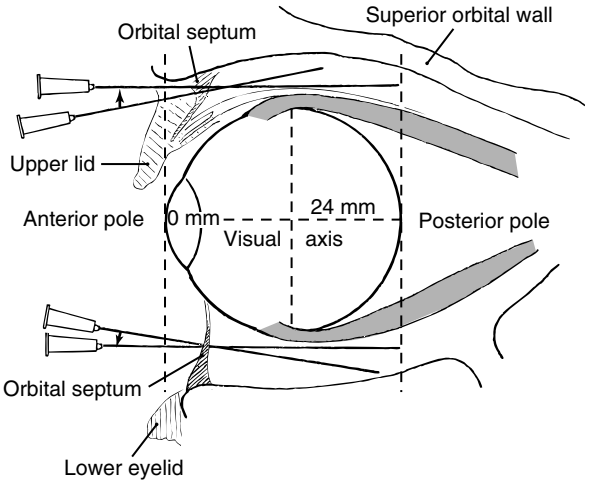

FIGURE **39-22** Lateral view of needle angles for peribulbar block.

Medial Extraconal Peribulbar Block

Equipment List.

- One 3-mL syringe
- One 30-gauge, ½-inch needle

Description. Figures 39-24 and 39-25 and Box 39-4 serve as valuable reference aids for medial peribulbar anesthesia.

The *medial peribulbar area* is a rather avascular fatty compartment that lies just medial to the medial rectus muscle. This area narrows significantly as it approaches the posterior surface of the globe, with the medial rectus muscle lying next to the bony orbit. Superior to the medial peribulbar area is the supranasal area. This area contains a portion of the superior ophthalmic vein and branches of the ophthalmic artery and should be avoided when ophthalmic blocks are performed.

The medial area also has herniated orifices within the connective tissue that communicate anteriorly to the posterior surface of the orbicular muscle of the eye. Therefore, the anterior spread of the anesthetic agent blocks cranial nerve VII, resulting in satisfactory akinesia of the eyelids for surgery. The medial peribulbar technique also can be used with minimal discomfort to provide eyelid akinesia before a modified retrobulbar block is performed; in this case, proparacaine drops are applied to the caruncle before the block is administered. The anesthetic agent is injected into the periorbital space that exists between the medial wall of the bony orbit and the medial rectus muscle. The technique is very effective as a secondary block both for incomplete akinesia of the medial rectus muscle and the superior oblique muscle and as a primary block for the orbicular muscles of the eyelid.

To avoid needle injuries to the medial rectus muscle, a modified insertion site, needle length, and angle may enhance the ease of needle placement and safety. The landmark for the modified technique is the *caruncle*, a small mound at the inner canthus of the eye formed by a conjunctival fold at its junction with the skin. The needle is inserted through the caruncle conjunctiva, tangential to the globe, and is directed medially and posteriorly toward the lacrimal bone, which is just posterior to the lacrimal sulcus. Care must be taken to avoid trauma to the puncta, the lacrimal cuniculi, and the lacrimal sac. To avoid contact with the medial

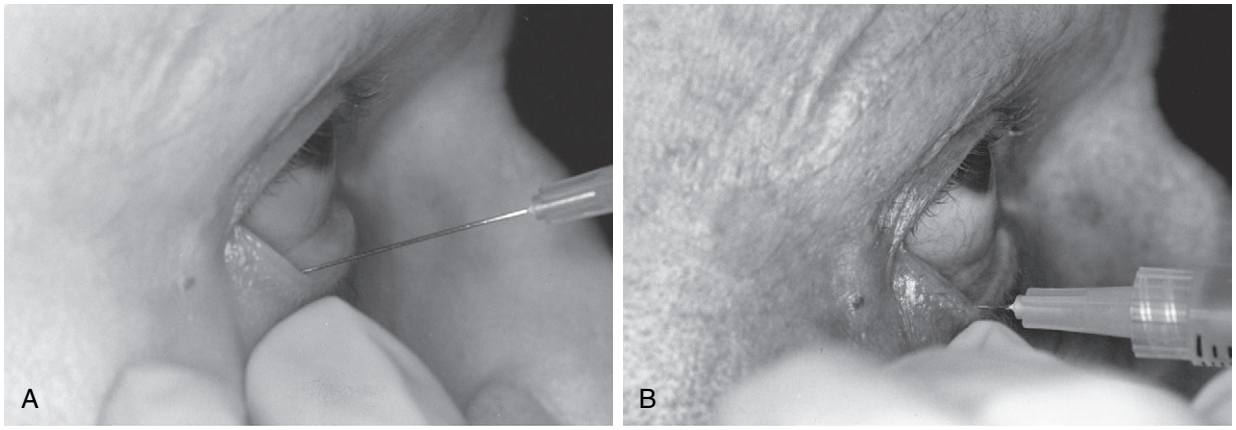

FIGURE **39-23** **A,** In the infraorbital approach, the needle is inserted transconjunctivally or transcutaneously and angled away from the visual axis of the globe toward the orbital floor to a depth of about 25 mm (1 inch), and the medications are injected. **B,** After penetration of the orbital septum, as shown in **A,** the needle is redirected parallel to the visual axis to a depth of about 25 mm (1 inch), and the medications are injected.

rectus muscle, it is important to keep the needle angled toward the lacrimal bone and away from the visual axis. Insert the needle, bevel toward the globe, to a depth of about 12 mm (0.5 inch). After negative aspiration is performed, 3 mL or more of anesthetic agent may be injected for facilitation of the desired effect. After the block is completed, the eyelid should be closed and light pressure applied to reduce the incidence of bleeding.

Ocular Block Evaluation

After an ophthalmic block is performed, partial movement of one or more of the ocular muscles may occur. Residual movement should be assessed to determine which muscles are involved and whether additional anesthesia is required. Analgesia of the globe generally precedes akinesia of the eye muscles. Therefore, analgesia of the globe may be assumed, but not guaranteed, in the presence of an akinetic muscle. The effectiveness of a modified retrobulbar block may be evaluated 2 minutes after it is administered, and an extraconal peribulbar block 10 minutes after it is administered, by observing for eye movement in all four quadrants.

BOX 39-3

Peribulbar Techniques

Infraorbital Approach

- Insert the needle transconjunctivally or transcutaneously, with the bevel toward the globe, lateral to the lateral limbic margin and angled away from the visual axis of the globe toward the orbital floor, to a depth of about 25 mm (1 inch), and inject the medications (see Figure 39-23, *A*).

  or
- After penetrating the orbital septum, as described above, redirect the needle parallel to the visual axis to a depth of about 25 mm (1 inch), and inject the medications (see Figure 39-23, *B*).

Supraorbital Approach

- Insert the needle only transcutaneously, with the bevel toward the globe, just inferior to the supraorbital rim, just lateral to the 12-o'clock position and superior to the globe. Angle away from the visual axis of the globe toward the orbital ceiling, to a depth of about 25 mm (1 inch), and inject the medications.

  or
- After penetrating the orbital septum, as described above, redirect the needle parallel to the visual axis to a depth of about 25 mm (1 inch), and inject the medications.

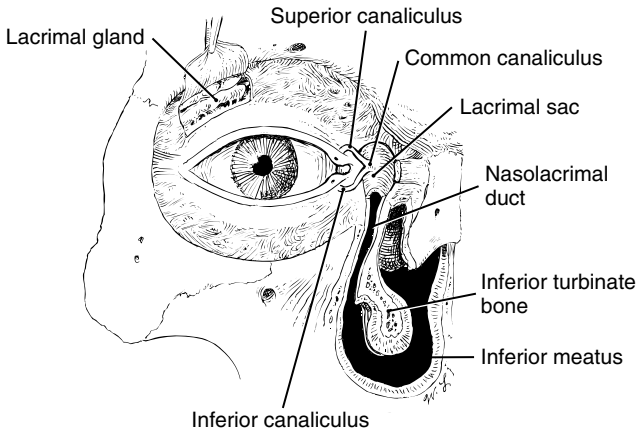

FIGURE **39-24** Frontal view of the lacrimal drainage system.

Eyelid Block

Once satisfactory akinesia of the globe is established, evaluation for movement of the eyelids is necessary. Partial to complete akinesia of the orbicular muscle is generally found after the ocular block. If incomplete akinesia of the orbicular muscle persists, perform a medial peribulbar to complete the block of nerve VII. Several blocks of nerve VII are described in the literature, including those by Van Lint, O'Brien, Nadbath, and Hustead.[24,28,29]

The O'Brien and Nadbath techniques block cranial nerve VII proximally, resulting in unilateral facial paralysis. The O'Brien and Nadbath techniques are still used; however, their popularity is decreasing because of their systemic side effects and patient discomfort. The Van Lint technique more appropriately addresses the need for eyelid akinesia, with less potential for adverse effects, by blocking the temporal and zygomatic branches of the facial nerve to the orbicular muscles. However, it is very painful. A variation of these techniques may be used for *orbicularis oculi block*. This technique has the advantage of being safer, less painful, and better accepted by the awake patient than the Van Lint block, but it requires injections through the skin and has the potential for causing patient discomfort and eyelid ecchymosis. The preferred technique for eyelid akinesia remains the medial peribulbar block.

Orbicularis Oculi Block

Equipment List.

- One 6-mL syringe
- One 30-gauge, ½-inch needle
- One alcohol wipe

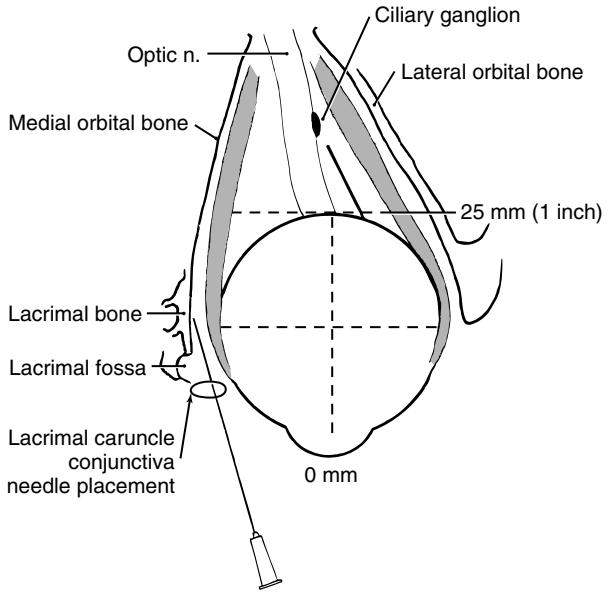

FIGURE **39-25** Superior view of the needle angle for a medial peribulbar block. *n.*, Nerve.

BOX 39-4

Medial Peribulbar Block

- Penetrate the caruncle conjunctiva with the bevel of the needle toward the globe and the needle angled toward the lacrimal bone, to a depth of approximately 12 mm (0.5 inch), and inject the medications.

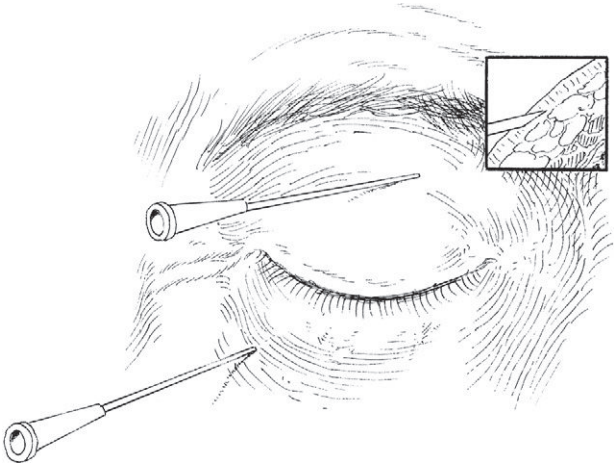

FIGURE **39-26** Frontal view of the needle placement for an orbicularis oculi block.

Description. Figure 39-26 and Box 39-5 serve as valuable reference aids for the orbicularis oculi block.

This technique is performed after a modified retrobulbar or peribulbar block in which residual eyelid movement remains. The first injection is made inferotemporally in the lower eyelid. The needle is inserted bevel down, subcutaneously and tangentially to the lower eyelid, and 1 to 2 mL of the anesthetic agent is injected just under the skin of the eyelid. After the needle is removed, the local anesthesia should be digitally spread to the medial and the lateral canthi; this measure avoids running the needle across the lower eyelid. The second injection is made supranasally in the upper eyelid. A finger should be placed over the closed eyelid, slightly depressing the globe. The needle is again inserted, bevel down, subcutaneously and tangentially to the eyelid, and 1 to 2 mL of the agent is injected just under the skin of the eyelid. After the needle is removed, the local anesthetic is digitally spread to the medial and lateral canthi. Once the anesthetic is spread throughout the eyelids, light to moderate pressure is applied over the eyelids for prevention or reduction of superficial bleeding.

Van Lint Technique

Equipment List.

- One 6-mL syringe
- One 25- or 27-gauge, 1.5-inch needle
- One alcohol or povidone-iodine wipe
- One 4 × 4 gauze pad

Description. A 37.5-mm (1.5-inch) needle is inserted inferotemporally into the subcutaneous tissue of the lateral canthus. The first injection of 1 to 2 mL of anesthetic agent is directed nasally along the lower margin of the orbit and then withdrawn to its origination point. The second injection of 1 to 2 mL of anesthetic agent is directed upward along the supratemporal margin of the orbit. After the block is completed, light pressure is applied over the closed eyelids to disperse the medication and decrease ecchymosis.

POSITIVE ORBITAL PRESSURE

The increased volume of local anesthetic required for both modified retrobulbar and peribulbar anesthetics causes an increase in orbital and intraocular pressures. The anesthetic agent not only tracks along and penetrates the fascial sheaths behind the globe, it also moves anteriorly underneath the conjunctiva, producing chemosis (i.e., subconjunctival edema) of the eye. These events may make the surgical procedure more difficult to perform. However, the random diffusion of the orbital anesthetic cannot be controlled. The agent merely tracks along the path of least resistance. Clinically, chemosis can begin with the injection of as little as 1 to 2 mL of anesthetic. In other instances, chemosis has not been seen even after the injection of as much as 12 mL of anesthetic agent.

Positive-pressure devices are used to reduce increased intraocular/intraorbital pressures and chemosis. Such devices are placed directly over the globe and orbit to enhance the orbital spread of anesthetic agent and return the orbital anatomy to a softer, more normal state for surgery. Positive-pressure devices deepen the anterior chamber by further reducing the intraocular pressure, thus allowing greater room for surgical intervention.

BOX **39-5**

Orbicularis Oculi Block

- *Lower lid:* Insert the needle subcutaneously, bevel down and tangential to the lid in the infratemporal area, and inject the medications.
- *Upper lid:* While slightly depressing the globe, insert the needle subcutaneously, bevel down and tangential to the lid in the supranasal area, and inject the medications.

Positive-Pressure Device

Honan Intraocular Pressure Reducer

The Honan intraocular pressure reducer, or Honan balloon, is an inflatable pneumatic device used to apply ocular compression after retrobulbar or peribulbar anesthetic injection. A rubber head strap is placed behind the head. The eye is taped closed, and a folded 4 × 4 gauze pad is placed over the eye. The Honan cuff is placed over the gauze pad and secured with the Velcro head strap. The pressure gauge is inflated to 30 mmHg, a value marked in yellow on the gauge.

ANESTHESIA MANAGEMENT

Preoperative Preparation

Ophthalmic procedures are most commonly performed on young children and elderly persons. Each age group has a unique set of physical problems. For the young child, the questions regarding the patient's history should include any congenital, metabolic, and musculoskeletal abnormalities, such as malignant hyperthermia, that may affect anesthesia care. In the elderly patient, multisystem medical problems may be present, and drug interactions from multiple medication regimens may exist. A thorough patient history is therefore paramount.

Admissions on the Day of Surgery

Anesthesia practitioners must not forget how stressful a surgical procedure on the eye can be for patients. A kind and professional attitude on the part of all those providing care will help patients deal more effectively with personal stress. The proper use of progressive relaxation and hypnotic techniques further helps alleviate their anxiety. Establishing a good patient-provider relationship works synergistically with pharmacologic agents in promoting the best possible surgical environment. On admission, the patient's mental and physical status, vital signs, and electrocardiogram (ECG) should be reviewed for any changes that may require postponement.

Regional Versus General Anesthesia

Patients undergoing regional block, in which they are awake for the procedure, must be evaluated for claustrophobia, severe

arthritis, tremors, and any other physical derangements that may make it difficult for them to lie supine. Patients' mental status also must be evaluated so that their degree of cooperation and ability to follow commands can be determined.

Elderly patients often take multiple medications and may not remember all of them. Patients should be instructed to bring their medications to the surgery center the day of surgery. A preoperative visit to the primary care physician is advised to confirm that the patient's overall medical condition is optimized for the planned surgical procedure.

The attending surgeon, in collaboration with the anesthesia practitioner, will make the final evaluation as to the patient's fitness on the day of surgery. An ECG performed within the past year should augment medical evaluation. The preoperative ECG assessment furnishes a baseline of what is optimal for the individual patient. Comparing the baseline ECG against the patient's ECG on the day of surgery helps determine whether any further preoperative testing is warranted.[30] For patients receiving regional anesthesia, routine laboratory tests are not ordered unless they are medically necessary. Appropriate laboratory data may be necessary when general anesthesia is planned.[31,32]

After the patient history and physical examination are completed, the appropriate anesthesia plan can be formulated. General anesthesia should be used for infants and young children. General anesthesia is also indicated for patients with severe claustrophobia, a history of uncontrolled acute anxiety attacks, or inability to cooperate, communicate, or lie flat (Box 39-6). It is also a consideration for procedures of greater than 2 hours' duration.[33] Most adults tolerate ophthalmic procedures well when regional anesthesia is used. Given the potential risks associated with general anesthesia (Box 39-7), regional anesthesia should be considered the anesthetic of choice in adults, especially the elderly, for ophthalmic procedures.

BOX 39-6

Indications for General Anesthesia

- Pediatric patient
- Patient's lack of cooperation
- Severe claustrophobia
- Inability to communicate
- Inability to lie flat
- Open-eye injuries
- Procedures with durations greater than 2 hours

BOX 39-7

Disadvantages of General Anesthesia

- Nausea/vomiting
- Retching/bucking
- Increased intraocular pressure
- Aspiration
- Complications secondary to other medical problems (e.g., cardiovascular disease)
- Time and expense

Regional Anesthesia

Regional Block with Minimal Sedation

Nothing-per-Mouth Status. The views of anesthesia practitioners vary on the advisability of nothing-per-mouth (*nil per os*; NPO) status prior to ocular procedures, especially cataracts. Some practices allow patients undergoing surgery in the morning to eat a light breakfast the day of surgery. Those undergoing surgery in the afternoon may be told to eat a light lunch.[34] Patients also may be encouraged to consume clear fluids until they are admitted to the facility.[35] However, practitioners also may mandate a strict NPO protocol.

Patients are requested to take their medications as usual on the day of surgery. An exception may be patients who complain of a frequent need to urinate after taking diuretic medications. Antiglycemic agents may be reduced or withheld when patients are NPO according to usual practice.[36] Evaluation and management of any anticoagulant medications are required for certain eye procedures to decrease the likelihood of bleeding. A medical consult with discontinuation several days prior to surgery may be necessary for certain anticoagulants. An increase in bleeding has been reported following vitreoretinal surgery in patients taking antiplatelet drugs.[37] Others note discontinuation is not necessary.[38] It is generally not required that antiplatelet drugs (e.g., aspirin, Clopidogrel) and anticoagulants (e.g., warfarin [Coumadin]) be discontinued. The risk of systemic complications, such as cardiovascular accidents and myocardial infarctions, is potentially greater if administration of these products is discontinued. Continuing anticoagulant administration, however, requires consultation and agreement between the anesthesia practitioner and the surgeon.[17,39] If bleeding occurs, it may be more severe; therefore, patients also need to be made aware of the risk and benefits of continuing their anticoagulants. Patients who are receiving or have previously been treated with chemotherapy also may have prolonged bleeding times.

Regional Block Environment

Ocular blocks are commonly performed outside the operating room. This method facilitates a more efficient case flow and a more comfortable environment for the patient. The potentially life-threatening effects of orbital epidural blocks require that appropriate resuscitative equipment and trained personnel are available to monitor the patient. The area used for performing ocular blocks should have the following:

- Oxygen
- Bag-valve mask
- Suction
- Airways
- ECG equipment
- Blood pressure cuff
- Oxygen saturation monitor
- Intravenous access tubing
- Canthotomy set
- Ammonia capsules
- Nitroglycerin tablets
- Atropine
- Glycopyrrolate

Additional resuscitative equipment and medications as recommended by advanced cardiac life support guidelines should be available.

Sedation for Regional Blocks and Ophthalmic Procedures

The goal of conscious sedation is to help patients gain and maintain control by reducing their heightened state of anxiety. This enhances their cooperation and ability to tolerate the awake surgical procedure.

Many techniques have been advocated to relax the patient prior to the ocular block and during the surgical procedure.[40,41] Conscious sedation techniques have included the use of benzodiazepines,

BOX 39-8

Sedation Techniques

- Good rapport between patient and clinician—minimizes medications necessary
- Intravenous benzodiazepine administration
- Intravenous narcotic administration
- Intravenous propofol or narcotic administration

BOX 39-9

Causes of Discomfort Resulting from Regional Blocks

- Needle injection through the skin
- Needle penetration of the conjunctiva
- Needle penetration of the intermuscular membrane
- Rapid injection of anesthetic
- Stinging from peripheral spread of anesthetic

narcotics, and nonbarbiturates. When these medications are properly tailored they are tolerated well by the elderly patient. Sedation techniques should be designed to decrease anxiety (Box 39-8) and reduce the discomfort of the block (Box 39-9). When the block is less painful, patients require less sedation for comfort. The surgeon's preference for an awake, relaxed, or sleeping patient during the procedure also should be considered. Sleeping patients often snore and may have sudden head movements on awakening.

If the patient is to be asleep during the block, fasting before the procedure consistent with the facility's criteria for general anesthesia should be followed (Box 39-10). Propofol is an excellent choice for this technique because of its short duration of action.[42]

Sedation is typically effective and safe for ocular blocks and intraoperative use but necessitates provider vigilance and monitoring to recognize and treat any of the adverse medical events that may occur.[43]

Monitoring for Regional Anesthesia

Communication is the cornerstone of interacting with the patient who is awake. Informing the patient regarding what to expect and what to do if he or she experiences any problems is mandatory. Questions and instructions must be clear and specific, especially if the patient is hearing impaired or if a language barrier exists.

The positioning of the patient is very important. Pillows may be used under the knees to decrease back strain. The patient with severe arthritis must be carefully padded and positioned. The patient's head and neck should be placed in a satisfactory surgical position. The practitioner should ensure that the patient is warm and as comfortable as possible. Nasally administered oxygen may be considered. Monitoring equipment should consist of the standard monitors used for all procedures. Observing the surgical procedure on a television monitor is preferable to not seeing the surgery. This allows the anesthetist to follow the surgical progress and visualize critical points in the procedure at which patient movement would be most detrimental.

The surgical draping placed over the patient's face should be tented, and high-flow air may be used to dissipate expired carbon dioxide more quickly. Claustrophobia can be a problem for awake patients, and some patients experience it for the first time during this procedure. Techniques for dealing with claustrophobia include

BOX 39-10

Procedure for Patient Who Is Asleep During Regional Block

- Tilt head to maintain patent airway
- Open patient's eye in primary gaze position
- Administer regional block
- Administer incremental sedation as required

taping the nonsurgical eye or adjusting the drape so that the patient can see the room with the nonsurgical eye. If a patient experiences a claustrophobic attack, the surgical drapes should be tented away from the face immediately, while the sterile field is maintained, and verbal control of the patient is gained. At this point, the anesthetist must determine whether the patient can proceed with surgery under regional block. Rarely, the patient may experience incomplete ocular analgesia, even in the presence of muscle akinesia. This problem responds well to 2% lidocaine MPF (methylparaben-free) drops or subconjunctival anesthetic injection.

Acute increased intraocular pressure during the surgical procedure can be catastrophic and cause loss of ocular contents. This problem can be created by coughing or a choroidal hemorrhage. The increased intrathoracic pressure created during coughing is reflected through the valveless orbital veins, resulting in an acutely increased intraocular pressure of 40 mmHg or greater.[44] A choroidal hemorrhage occurs when a vessel in the vascular choroidal layer of the eye ruptures, bleeding into the closed cavity and creating an acute rise in intraocular pressure with potential expulsion of eye contents unless the eye is closed quickly. In the acute phase, medications that lower intraocular pressure may be of minimum benefit.

If the patient has a history of postnasal drip, vasoconstrictive nose drops may be given preoperatively. If the patient complains of a dry throat, small amounts of water may be given. These two remedies are helpful in reducing the incidence of coughing intraoperatively. The patient must also be instructed to give notice before he or she coughs. Instructing the patient to clear his or her throat effectively reduces the forcefulness of the cough. Quick, shallow breaths have been reported to help suppress the cough reflex.[44] Sedating the patient or using intravenous lidocaine to prevent further coughing can help but has minimal effect during an active coughing episode.[45]

After the surgery is completed, the patient is transported from the operating room to postanesthesia recovery (PAR). Postoperative recovery time should be in accordance with the individual patient's physical and mental status and the amount of medication administered.

In a meta-analysis of regional verses general anesthesia for ambulatory anesthesia, patients who received peripheral nerve blocks, such as orbital regional eye blocks, experienced less postoperative pain, nausea, and a decreased postanesthesia care time.[46] If postoperative nausea is noted immediately after surgery, it may result from the sedative medications, increased intraocular pressure, or ocular pain.[47] On the afternoon or evening after their surgery, patients are generally called at home to evaluate their status. A sudden onset of nausea at home after the procedure is more likely associated with increased intraocular pressure than anesthetic medications. Patients are usually examined the following day by the surgeon and are requested to fill out questionnaires regarding their experience on the day of surgery.

General Anesthesia

For general anesthesia, preoperative patient preparation should include the appropriate fasting guidelines for the patient's age and physical condition (e.g., diabetes). The patient should be reminded that the surgical eye will be patched when he or she awakens. Sedation should be administered as needed to help the patient relax. Benzodiazepines such as midazolam are effective in low doses. For reduction in the incidence of postoperative nausea, the use of 5-HT3-receptor antagonists, histamine-2 antagonists, metoclopramide, and other antiemetics should be considered. Induction of general anesthesia with propofol or etomidate is recommended because they decrease intraocular pressure. In infants and children, inhalation induction also decreases intraocular pressure. Because of their emetic effect, narcotics should be used in low doses. Other than during examinations under anesthesia, endotracheal intubation is indicated for maintenance of the airway.

Succinylcholine causes a transient increase in intraocular pressure; however, it can be used safely for ocular procedures. Some caveats include the following:

- The sustained contracture of the extraocular muscles after succinylcholine could cause an expulsion of the intraocular contents. This assumption is theoretic, and it is now felt that succinylcholine may be safely used in eye surgery. See full discussion later.
- In eye muscle surgery, the sustained contraction may interfere with the forced duction test used by the surgeon for the treatment plan.

Nondepolarizing muscle relaxants are satisfactory for induction and have the advantage of decreasing intraocular pressure.[48] Laryngoscopy, especially with light anesthesia, increases intraocular pressure, but intravenous lidocaine (1.5 to 2 mg/kg), given 1 to 1.5 minutes before laryngoscopy, helps attenuate this response. Inhalation anesthetics, which also decrease intraocular pressure, are commonly used for the maintenance of general anesthesia.

For intraocular procedures, the continued use of nondepolarizing muscle relaxants is recommended for the maintenance of an akinetic eye and a satisfactory intraocular pressure. The anesthetist must be aware of the adverse ECG changes that may result from the oculocardiac reflex, which may be elicited when traction is exerted on the extraocular muscles and orbital structures. Patients undergoing eye-muscle surgery have an increased incidence of malignant hyperthermia and postoperative nausea. In retinal procedures in which sulfur hexafluoride or perfluoropropane is used as an intraocular gas, the use of nitrous oxide should be discontinued 15 minutes before injection.

When spontaneous ventilation returns after neuromuscular blockade is reversed, the patient may be extubated while receiving deep anesthesia with 100% oxygen and placed in the lateral position until he or she awakens. In the patient with a difficult airway, full stomach, or incompetent esophageal sphincter, gastric suction and intravenous lidocaine (1.5 to 2 mg/kg) may be given before the patient is extubated awake. This method helps reduce the incidence of coughing and vomiting, along with their deleterious effects.

The laryngeal mask airways (LMAs) also have their respective place in ophthalmic procedures. They may be inserted without muscle relaxants and removed with less risk of coughing in the awake patient. Along with the usual risk assessment for gastric aspiration, the practitioner should also consider that the lack of access to the airway during the procedure, intraoperative malposition of the LMA, and light anesthesia in the absence of muscle relaxants may result in laryngospasm or coughing. The LMA is gaining popularity in extraocular procedures such as strabismus and scleral buckles.[42]

Postoperative care, with attention paid to the alleviation of pain and control of nausea, will help maintain a satisfactory intraocular pressure. The ophthalmologist should be made aware of continued postoperative nausea, because it may be the result of acute increased intraocular pressure.[47]

Open-Eye Injury and the Use of Succinylcholine

Traumatic eye injuries can be categorized as either open- or closed-globe injuries. Open-eye injury in a patient with a full stomach is at best a difficult situation for the anesthesia provider. These injuries are commonly considered emergencies requiring general anesthesia. The clinician must protect the patient from aspiration and yet avoid increased intraocular pressure that could result in expulsion of intraocular contents. Authors have traditionally debated the risks and advantages of using succinylcholine for this procedure.[49,50] Normal intraocular pressure (IOP) is 10 to 22 mmHg, with slight diurnal and positional changes of 1 to 6 mmHg. It is physiologically determined by aqueous humor dynamics, changes in choroidal blood volume, central venous pressure, and extraocular muscle tone. The most important determinant of IOP is the balance between production and elimination of aqueous humor, maintaining an average volume of 250 mL. Aqueous humor is formed in the ciliary process from capillaries by diffusion, filtration, and active secretion. It flows through the posterior chamber, around the iris, and into the anterior chamber. It is eliminated through the spaces of Fontana and canal of Schlemm at the iridocorneal angle, where it flows into the episcleral venous system. Any increase in venous pressure (e.g., cough, strain, head-down position) will increase IOP. Additionally, any decrease in cross-sectional area of the spaces of Fontana (e.g., mydriatic drugs) will increase IOP.[51-55] Administration of succinylcholine increases IOP within 1 minute and peaks at an increase of 9 mmHg within 6 minutes after succinylcholine administration. The exact mechanism of this increase is unknown. Some feel that tonic contractions of the extraocular muscles may explain this IOP increase. It is now thought, however, that succinylcholine-induced IOP increase is a vascular event, with choroidal vascular dilation or a decrease in drainage secondary to elevated central venous pressure, temporarily inhibiting the flow of aqueous humor through the canal of Schlemm.[52]

It is clear that succinylcholine raises IOP. However, at induction of general anesthesia, there are many activities that raise IOP to a much greater degree than succinylcholine, including crying, Valsalva maneuver, forceful blinking, rubbing of the eyes, and coughing or bucking during poor intubating technique. Therefore, the increase in IOP due to succinylcholine may be inconsequential if optimal intubating conditions are not provided.

Moreno wrote: "This observation, coupled with the lack of any documented cases of extrusion of intraocular contents in open globes of humans when succinylcholine is used, causes us to question the traditional teaching that succinylcholine should be avoided in all cases when open globe is suspected or known."[51]

Chidiac and Raiskin[52] have stated that two questions need to be asked before the decision about the use or avoidance of succinylcholine in open-globe surgeries is made: Is this an easy airway; and is the eye viable? If the airway assessment shows that intubation should be easy, then regardless of the patient's aspiration risk, and regardless of the viability of the eye, succinylcholine can be avoided and replaced with rocuronium. If the airway assessment shows that this could be a difficult intubation, regardless of the patient's aspiration risk, then the second question becomes important: Is the eye viable? If the ophthalmologist feels that the eye is viable, use of succinylcholine is recommended. Pretreatment with drugs that attenuate the intraocular pressure effect of

succinylcholine, such as a small dose of nondepolarizing agent and lidocaine, should be used.

Choosing or avoiding succinylcholine is a matter of balance of risk. To control IOP at induction, there must be adequate dosing of drugs timed appropriately to coincide with the three potent stimuli: the administration of succinylcholine, the laryngoscopy, and the endotracheal intubation. It is clear that succinylcholine increases IOP, but this increase can be attenuated with various pretreatments, is less than increases seen with inadequate paralysis at the time of laryngoscopy and intubation, and is unimportant when weighed against the risk of loss of the airway. Therefore, in the situation of "difficult airway, eye viable," one should use succinylcholine.

Closed-globe injuries require significant planning and preparation to prevent further damage to the eye by an increase in IOP. They also require smooth induction and emergence because patient coughing or bucking will cause a detrimental increase in IOP.[53]

OPHTHALMIC ANESTHESIA COMPLICATIONS

Anxiety coupled with underlying cardiovascular disease may promote marked hypertension, cardiac dysrhythmias, or angina in the patient before surgery. Vasovagal responses (e.g., fainting) secondary to anxiety are not unusual. Ammonia capsules are effective in preventing and treating fainting episodes.

Chronic coughing secondary to chronic obstructive pulmonary disease, asthma, or postnasal drip must be evaluated. Vasoconstrictive nose drops effectively decrease postnasal drip. Coughing and deep breathing before surgery help clear the lungs of excess mucus in patients with chronic pulmonary disease. Proper evaluation and treatment help reduce undesired perioperative systemic and ocular sequelae.

Most complications of regional ocular anesthetics can be attributed to direct traumatization of the orbital vessels, the globe, and the optic nerve. Trauma to these structures can result whenever a needle is placed near the eye. Frequently, the cause of complications during general anesthesia is patient movement.

Retrobulbar Hemorrhage

Retrobulbar hemorrhage results from trauma to an orbital vessel. The retrobulbar bleeding moves the eyeball forward (proptosis), and a subconjunctival hemorrhage is usually present. Venous hemorrhages are typically slow in onset, but arterial hemorrhage has a rapid onset and more pronounced proptosis and subconjunctival hemorrhage. Ecchymosis of the eyelids and orbit is usually present. The pressure caused by the bleeding in the bony orbital cavity produces increased orbital pressure on the optic nerve, vessels, and globe. This pressure usually resolves without problems but may result in an occlusion or spasm of the central retinal artery or vein, resulting in partial to complete loss of vision.[56] One may detect a progressively increasing orbital pressure when digital pressure is applied over the eye after an ocular block. Continuous digital pressure may be all that is required for stopping a venous hemorrhage.[17] If the orbital pressure continues to increase in the presence of digital pressure, a lateral canthotomy is indicated and may be performed by the ophthalmologist or the anesthesia practitioner, who should then notify the ophthalmologist. *Canthotomy* is a procedure performed to increase the orbital space by cutting the lateral canthus and reducing the orbital pressure that results from a retrobulbar hemorrhage.

Anesthesia practitioners who perform ocular blocks should consider being instructed in the performance of a canthotomy, and a canthotomy set should be readily available (Box 39-11). The ophthalmologist should examine the central retinal artery and vein for patency. Occlusion of these vessels may warrant further surgical intervention for reduction of elevated orbital pressure.

BOX 39-11

Canthotomy Procedure

Equipment

1 straight hemostat
1 plastic scissors

Procedure

1. If possible, inject lidocaine along the lateral canthus.
2. Place the hemostat in a temporal direction along the lateral canthus 4-6 mm, and clamp the hemostat.
3. Remove the hemostat.
4. Use the plastic scissors to incise only in the crush marks left by the hemostat.
5. Control local bleeding with the hemostat or with digital pressure.

A localized episcleral hemorrhage also causes subconjunctival bleeding. In this situation, however, no proptosis of the globe or increase in orbital pressure is noted. These episcleral vessels are the same ones the ophthalmologist cauterizes after a conjunctival incision. The vessels break as a result of the spread of local anesthesia through the subconjunctival area and are of no consequence. However, the ophthalmologist should be notified of their presence before the procedure begins.

Retrobulbar hemorrhage remains the most common sequela for ocular blocks (Box 39-12). Peribulbar injections also can cause orbital hemorrhages.[26] Retrobulbar hemorrhages have been reported to occur in 1% to 3% of cases.[57]

Intravascular Injection

Grand mal seizures have been reported to occur after retrobulbar injections with lidocaine and lidocaine-bupivacaine combinations.[58,59] Seizures may result from a less-than-toxic dose of local anesthesia by direct intraarterial injection, resulting in retrograde flow to the cerebral circulation (Box 39-13). Mathers[60] surveyed 200 ophthalmologists. Sixty-six responded and reported three seizures occurring after retrobulbar injections. From these data, it appears that seizures after retrobulbar anesthesia may occur more frequently than reported in the literature. A reaction after an orbital vein injection also has been reported: the patient experienced uncontrolled shivering and rigor approximately 15 seconds after the retrobulbar injection. These symptoms resolved within 2 minutes of onset.[61]

Globe Puncture

Multiple reports have been published regarding globe perforations. Both sharp and dull needles have either penetrated or perforated the eye during retrobulbar and peribulbar injections. Although rare, globe punctures have occurred in the hands of experienced practitioners who have performed many thousands of ophthalmic blocks. The literature also notes that patients may or may not exhibit signs and symptoms of a puncture immediately, and the diagnosis has been made anywhere from 1 to 14 days after the event.[18,62-65] The most devastating globe injury reported, fortunately rare, is an ocular explosion. The globe can literally burst apart from the intraocular pressure exerted by the local anesthesia injection.[66,67]

The myopic eye has an increased axial length of greater than 24 mm. Scleral thinning may result from this increased

BOX 39-12

Measures for Preventing Retrobulbar Hemorrhage

- Choose least vascular areas for needle placement.
- Avoid deep orbital injections.
- Avoid supranasal position of gaze.
- Use primary gaze position.
- Use upward-gaze position (Gills-Lloyd technique only).
- Insert needle slowly.

BOX 39-13

Measures for Preventing Seizures Resulting from Intravascular Injection

- Choose least vascular areas for needle placement.
- Avoid deep orbital injections.
- Avoid supranasal position of gaze.
- Insert needle slowly.
- Aspirate gently before injection; negative aspiration is no guarantee that you are not in a blood vessel.
- Avoid injection against resistance.
- Avoid forceful rapid injections.

BOX 39-14

Measures for Preventing Globe Puncture

- Use caution in patients with increased axial length.
- Avoid supranasal position of gaze.
- Direct needle away from axis of globe during insertion through the orbital septum.
- Observe globe movement with needle insertion.
- Insert needle slowly, with the bevel toward the globe.
- Never forcefully inject anesthetic.
- Use modified retrobulbar and peribulbar techniques (although globe punctures have also been reported with these).

BOX 39-15

Signs and Symptoms of Globe Puncture*

- Increased resistance to injection
- Immediate dilation and paralysis of the pupil
- Rapid increase in intraocular pressure with edematous cornea
- Pain and agitation
- Hypotony of the globe
- Intraocular hemorrhage

*Patient may or may not exhibit signs and symptoms of a puncture immediately.

anteroposterior diameter. A previous scleral buckling procedure also increases the anteroposterior diameter of the eye. *Staphyloma*, a bulging of the sclera, also may predispose the patient to globe puncture. The risk of puncture increases when this abnormality is located inferoposteriorly on the globe. *Enophthalmos* is a recession of the eyeball into the orbit. This condition decreases the distance between the posterior pole of the globe and the posterior orbital wall. The supranasal gaze position rotates the posterior pole of the globe in line and closer to the retrobulbar needle path. Multiple orbital injections also have been cited as a factor in globe punctures, along with unexpected patient movement (Box 39-14).

The choice of sharp versus dull retrobulbar needles is highly debated. The literature reviewed appears to draw conclusions based more on opinion than on fact. A review of the literature confirmed a lack of safety with the use of blunt needles. Optic nerve penetration, ocular perforation, and CNS complications result from the use of blunt needles.[18] The surgeon should be notified if a globe puncture is suspected (Box 39-15).

Optic Nerve Sheath Trauma

To review, the *optic nerve sheaths* surround the optic nerve and are composed of the meninges of the brain. The outer sheath contains the *dura mater* and the inner sheath consists of the *arachnoid mater* and *pia mater*. The subarachnoid space contains cerebrospinal fluid and is continuous with the optic chiasm. The dura splits into two layers at the optic foramen. The outer dural layer becomes continuous with the orbital periosteum. The inner layer forms the dural covering of the optic nerve, creating the orbital epidural space.[1] Anesthetic agents injected into the subdural or subarachnoid space may track back to the optic chiasm. Here, the anesthetic can affect the contralateral eye by blocking cranial nerves II and III as they proceed through the subdural or subarachnoid space; this block can result in contralateral amaurosis.[68-70] The condition can be a precursor to the continued migration of the anesthetic to the respiratory centers of the midbrain, resulting in respiratory arrest.[56,71,72]

The anesthetist should observe the contralateral pupil before an ocular block is performed. The pupil may be dilated from accidental administration of preoperative eye drops, a preoperative examination, or existing pathology. If the contralateral pupil is constricted before the ocular block and dilates after the ocular block (contralateral amaurosis), one must assume that subarachnoid or subdural injection has occurred and be prepared to treat a respiratory arrest.

The onset of *respiratory arrest* is usually within 2 to 5 minutes after injection; however, it may occur as late as 10 to 17 minutes after injection. Spontaneous ventilation usually returns in 15 to 20 minutes but may take up to 55 minutes for complete recovery. Treatment includes appropriate ventilatory and cardiovascular support, supplemental oxygen with oxygen saturation monitoring, ECG monitoring for cardiac dysrhythmias, and blood pressure monitoring. The surgeon should be notified immediately so the eye can be examined for any optic nerve trauma that may require surgical intervention.

A retrobulbar hemorrhage resulting in increased extravascular pressure may result in occlusion of the central retinal artery or vein, or both. Also, direct trauma to the ophthalmic artery or the optic nerve by the retrobulbar needle may cause artery or vein occlusion without causing retrobulbar hemorrhage[73] (Box 39-16).

Ocular Ischemia

Retinal vascular occlusion or thrombosis has been reported after ocular blocks.[74,75] Studies have also reported a decrease in the pulsatile ocular blood flow after ocular blocks, secondary to the pressure exerted by the volume of local anesthesia injected into the orbit. However, the same orbital injection volume did not cause a significant rise in the intraocular pressure. Even though not contraindicated, caution should be exercised in patients with preexisting compromised ocular circulation.[76-79] Some authors have advocated not using epinephrine in the local anesthetic solution.[80,81]

BOX 39-16

Measures for Preventing Optic Nerve Sheath Trauma

- Avoid supranasal eye position.
- Choose least vascular area for needle insertion.
- Avoid deep orbital injection.
- Insert needle slowly.
- Avoid forceful injection of anesthetics.
- Use modified retrobulbar or peribulbar techniques.

Optic nerve atrophy has been reported after intraocular surgery with either *regional block* or *general anesthesia*.[56] Direct trauma to the optic nerve may result in transient symptoms, such as contralateral amaurosis or respiratory arrest, or it may result in vascular occlusion or thrombosis, or both, with partial to complete loss of vision.

Extraocular Muscle Palsy and Ptosis

Inferior muscle palsy has been reported after retrobulbar anesthesia. Segmental inferior rectus muscle enlargement was noted posterior to the globe deep in the orbit.[82] The complication has not been reported to occur after general anesthesia.[83] The initial signs and symptoms of this problem manifest after surgery as persistent vertical diplopia. Surgical intervention is indicated for correction of this condition. Trauma to the superior oblique tendon–trochlea complex also has been reported to occur with peribulbar anesthesia[84] (Box 39-17).

Carlson et al.[85] performed experiments on the rectus muscle of monkeys and humans and demonstrated minimal myotoxic damage to ocular muscles after retrobulbar administration of local anesthetics. Typically after the injection of local anesthesia, the surface muscle fibers degenerate, then regenerate. However, direct injections of local anesthesia into the rectus muscle resulted in massive internal muscle lesions that were large enough to produce noticeable functional deficit. The myotoxicity of local anesthetics also may play a role in postoperative ptosis, especially in the elderly, because regeneration of their muscle fibers may not be as complete as that in younger patients. However, ptosis is also associated with the superior rectus stay suture and the eyelid speculum. Postoperative ptosis may take as long as 6 months to resolve.

Facial Nerve Blocks

Patients commonly experience discomfort as a result of blocks of cranial nerve VII. Prolonged Bell's palsy has been seen after Nadbath and O'Brien blocks, probably secondary to direct nerve trauma.[86] Several authors have reported cases of dysphagia, hoarseness, coughing, and respiratory distress after Nadbath blocks (Box 39-18). They noted that these symptoms were consistent with paresis of the vagus, glossopharyngeal, and spinal accessory nerves. These nerves exit the skull about 10 mm medial to cranial nerve VII. Therefore, anesthesia injected for a cranial nerve VII block could also reach these nerves and result in unilateral vocal cord paralysis.[87,88]

Patients have also complained of jaw ache with movement for several weeks after a cranial nerve VII block. Grand mal seizure has rarely occurred (1 report) when 3 mL of 2% lidocaine with epinephrine (1:200,000) was injected using the Nadbath technique.

Zaturansky and Hyams[89] reported an ocular perforation that occurred when a modified Van Lint procedure was performed after a retrobulbar block. The needle penetrated the proposed eye just under the insertion of the lateral rectus muscle.

BOX 39-17

Measures for Preventing Extraocular Muscle Trauma

- Avoid needle contact with extraocular muscles.
- Avoid deep orbital penetration.
- Avoid angling needle toward visual axis of the globe when parallel to an extraocular muscle.

BOX 39-18

Prevention and Treatment of Complications from the Nadbath Block

- Avoid using the Nadbath technique in patients weighing less than 45 kg.
- Avoid using large volumes of anesthesia and hyaluronidase.
- Avoid using the Nadbath technique when patients have a preexisting unilateral vocal cord dysfunction.
- Place the patient in seated or lateral position to maintain a patent airway and patient comfort.
- The patient with an unsatisfactory airway should be intubated.

Oculocardiac Reflex

The *oculocardiac reflex* is a trigeminal-vagal reflex that was first described in 1908 by Aschner. The stimulus for this reflex is generated by pressure on the globe, the orbital structures (e.g., the optic nerve), or the conjunctiva, or by traction on the extraocular muscles (particularly the medial rectus muscle). The afferent pathway for the stimulus is via the long and short ciliary nerves to the ciliary ganglion and then through the gasserian ganglion along the ophthalmic division of the trigeminal nerve terminating in the main trigeminal sensory nucleus in the floor of the fourth ventricle. The efferent pathway consists of the vagus nerve to the cardio-inhibitory center.

The reflex may be elicited during local infiltration anesthesia, retrobulbar or peribulbar blockade, and general anesthesia. The occurrence of the reflex in ocular procedures is variable, but it is commonly seen in muscle procedures performed in children. The oculocardiac reflex reveals itself most often as an acute sinus bradycardia. However, it also may cause a wide variety of other cardiac dysrhythmias, such as nodal rhythms, atrioventricular block, ventricular ectopy, idioventricular rhythm, and asystole. Continuous ECG monitoring is essential for the diagnosis of dysrhythmias that result from the oculocardiac reflex. If cardiac dysrhythmias are observed, the surgeon must be instructed to immediately cease all pressure or traction on the orbit. Simultaneously, the patient should be assessed for adequate oxygenation and ventilation and for adequate anesthetic depth because one or more of these may be an underlying cause for the dysrhythmia. The aberrant rhythm usually resolves without intervention within a few seconds.

However, if the aforementioned measures are taken and the dysrhythmia continues, thus threatening to cause hemodynamic instability, intravenous atropine should be administered. Atropine, 2 to 3 mg, may be required for complete vagal blockade. Caution should be exercised with the administration of atropine, because atropine itself may induce cardiac dysrhythmias. Glycopyrrolate may be given for less severe bradycardic episodes. The surgeon may proceed only after the dysrhythmia is resolved. If the reflex recurs, the aforementioned process should be repeated. The oculocardiac reflex, however, appears to fatigue with continued manipulations.

The use of intravenous atropine or intravenous glycopyrrolate just before surgery may help reduce the incidence of the reflex, especially in children.[90,91]

Other Complications

Corneal abrasion is the most common injury occurring after general anesthesia. It is believed to result from the drying of the exposed cornea or from direct trauma, such as an anesthesia-mask injury. Ensuring that the eyelids are closed and secured with tape should provide satisfactory protection of the cornea. *Movement during ocular surgery was identified as the single most common mechanism of injury*. Movement was described as coughing and bucking, which resulted in poor visual outcome. In these reported cases, muscle relaxants were used less than 50% of the time, and nerve stimulators were omitted. Chemical injury can result from spillage of cleaning materials or preparatory solutions into the eye. In these cases, the eye should be flushed immediately with saline.[92]

Central retinal artery occlusion may result from prolonged pressure on the eye.[93] This type of injury may result with the patient in the prone position. Careful attention to padding and periodic checks of the eyes are necessary, especially for long procedures. Eye protectors, along with foam headrests or gel donuts for the face, may help prevent eye trauma. It is prudent to request an ophthalmic examination immediately after surgery if the patient complains of any eye problems or if the anesthesia provider suspects a problem. Ocular positioning injuries are discussed in detail in Chapter 21.

SUMMARY

Anesthesia management for ophthalmic procedures has changed rapidly in the last few years. As an anesthesia practitioner you will be challenged with the increasingly complex comorbidities and multiple pharmacologic agents used in the care of the elderly patient. The pediatric patient also presents anesthetic challenges, many associated with the preterm infants and chronic upper respiratory infections**.** Newer surgical techniques for cataract surgery have increased the popularity of topical anesthesia for such procedures; however, the advances in retinal surgical techniques, corneal transplants, and adult eye muscle and glaucoma procedures are fueling an increased demand by surgeons for anesthesia practitioners to perform ophthalmic eye blocks versus general anesthesia. Orbital regional blocks have the further advantage of minimizing postoperative pain, requiring minimal to no opioid administration, with significant reductions in postoperative nausea and vomiting. General anesthesia will continue to be the technique of choice for the pediatric patient, patients with ocular trauma, and patients who are not candidates for topical or orbital regional blocks.

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Anesthesia for Orthopedics and Podiatry

CHAPTER 40

◆ *Patricia Tuttle*

The Merriam-Webster dictionary defines orthopedics as "a branch of medicine concerned with the correction or prevention of deformities, disorders, or injuries of the skeleton and associated structures (as tendons and ligaments)".[1] Evidence of such "corrections" dates back many centuries. Egyptian artifacts have been found that demonstrate the use of splints for patients, and some of the earliest documented orthopedic interventions came from the battlefields of the gladiators. Jean-Andre Venel established the first orthopedic institute in 1780. Much progress in orthopedics has been made in recent decades including the development of better arthroscopic techniques, total hip and knee replacements, ligament repairs using minimally invasive techniques, spine surgeries, and more. As the baby boomers born after World War II reach retirement age, the demand for orthopedic repair and the incidence of degenerative joint disease are expected to increase.[2]

Anesthesia and orthopedics are described time and again in historical accounts, the earliest being events usually occurring on battlefields throughout history. Although the initial encounters involved anesthetic techniques that were rather primitive, anesthesia for orthopedics has evolved into a highly specific set of choices that are deemed to be safe for patients . Modern techniques must account for complicated, sometimes lengthy procedures requiring significant postoperative pain control.

The anesthetic plan can vary greatly; the administered anesthetic can be regional, general, a combined technique, or involve intravenous sedation. The anesthetic choice is based upon many factors: What type of surgery is the patient having? How long will the procedure take? Does the patient have preferences? Does the patient's airway present any challenges? In what position will the patient be placed for surgery? What comorbidities are present? Answers to all of these questions and others carry weight in the decision-making process when determining care of orthopedic patients.

Preoperative assessment for orthopedic patients follows much the same guidelines used for any other surgical candidate. A thorough review of systems, review of home medications and the last date taken, current anticoagulant status, and baseline laboratory values are only some of the components of a preoperative assessment of these patients. Often for patients scheduled for total joint replacement, a baseline complete blood count (CBC), a pregnancy test (for females of childbearing age), and a urinalysis may be completed. Also, most orthopedic surgeons prefer to evaluate their patients for the presence of infection before committing to joint replacement surgery.[3] Surgical site wound infection is a serious and potentially catastrophic complication after joint arthroplasty.[4] Pathogens in the urinary tract are common, and their presence can create a potential reservoir of resistant pathogens and increase patient morbidity.

One of the ways all surgeons attempt to decrease the chance for surgical site infection includes the administration of appropriate preoperative antibiotics in a timely fashion. For cefazoline (a first-generation cephalosporin), the preoperative time allotment is within 1 hour of incision time; for vancomycin, within 2 hours of incision time. In 2006 the Centers for Medicaid and Medicare Services (CMS) introduced a program called the Surgical Care Improvement Project, often abbreviated SCIP. The goal of the group was to find common opportunities for improving surgical care and to provide definitions of these measures and the appropriate guidelines that would decrease risks to patients when instituted. These risks may include surgical site infection, postoperative thromboembolism, intraoperative and postoperative glucose management, and most recently, maintenance of core body temperature. The list of inclusions is fluid, based upon research findings and performance related to the measures.

Many institutions require their health care providers to be responsible for implementing appropriate interventions under the SCIP guidelines and, just as important, require them to document these interventions. These data are abstracted at hospitals across the country, and the data are then fed into a website called *Hospital Compare*. The *Hospital Compare* website allows patients and their families to view how a particular hospital participates in the guidelines and how the outcomes of that hospital compare to other hospitals in the area, specific to those guidelines. In addition to creating a best practice environment, and better patient outcomes, compliance with these measures are often incentivized financially through private insurers as well as the CMS. All anesthetists should familiarize themselves with the guidelines their institution has in place and should strive to fulfill their responsibilities accordingly.[5] The most up-to-date guidelines related to SCIP can be found at *www.jointcommission.org/surgical_care_improvement_project*.

Advances in technology are yielding a much higher rate of arthroscopic procedures. Outpatient surgery is now the routine for many orthopedic procedures. Outpatient surgery is being used for everything from shoulder repair to orthopedic repair in the knee, ankle, wrist, and elbow. The advantages of today's surgical techniques are readily apparent. Smaller incisions mean less pain. Patients who have arthroscopic procedures experience faster recovery from anesthesia, have shorter lengths of stay, use fewer narcotics for pain relief, and return to work more quickly than those undergoing open procedures.[6] From an anesthesia standpoint, it means more patients are being managed on an outpatient basis.

PNEUMATIC TOURNIQUET

One of the ways blood loss can be diminished in the operating theater is through the application of the pneumatic tourniquet. The advantages of a bloodless field are important for the surgeon. Pneumatic tourniquets maintain a relatively bloodless field during extremity surgery, minimize blood loss, aid identification of vital

structures, and expedite the procedure.[7,8] The components of the pneumatic tourniquet consist of the inflatable cuff, connective tubing, a pressure device, and usually, a timer. Specialized training and understanding of the application and management of the pneumatic tourniquet is required for proper management of the device intraoperatively. Safety considerations for use of a tourniquet are noted in Box 40-1.

Tourniquets are generally applied after the initiation of anesthesia. The time of inflation should be documented in the anesthesia record and should be in parallel with the time documented in the operating room (OR) record. Interruption of blood supply leads to tissue hypoxia and acidosis.[9] The degree of hypoxia and acidosis is partially influenced by the duration of insufflation. For this reason, the inflation device also comes with a built-in timer, generally set for 60-minute increments, with an alarm that will sound as a warning when the allotted time has been exhausted. A maximum of 2 hours is generally considered safe.[10] The pressure to which the tourniquet should be inflated depends on the patient's blood pressure and the shape and size of the extremity.

Deflation of the tourniquet results in the release of metabolic waste into the systemic circulation. The release of these substances can cause metabolic acidosis, hyperkalemia, myoglobinemia, myoglobinuria, and renal failure.[11,12] The deflation of the tourniquet may be marked by transient changes in the hemodynamics or pulse oximetry readings for the patient. Most of these resolve quickly, except in those patients with extreme conditions related to their cardiac or vascular status. Box 40-2 lists common physiologic changes that occur with pneumatic tourniquet.

Tourniquet Pain

One of the greatest concerns when the tourniquet is in use is the patient perception of tourniquet pain. In 1944 Denny-Brown and Brenner[13] reported the first investigation into the cause of tourniquet discomfort. They listed characteristic anatomic changes associated with tourniquet ischemia that were due to acute compression of the nerves under the inflated cuff. Compression of the intraneural blood vessels caused a secondary ischemia of the nerve fibers. Similar reports of "tourniquet discomfort" or "aching" despite adequate spinal anesthesia prompted considerable attention being directed toward discovering ways to minimizing subjective discomfort. Based on their discoveries and subsequent measurements of "occlusive pressure" in 1979, Klenerman and Hulands[14] suggested using tourniquet pressures of two times the patient's systolic blood pressure to minimize the subjective discomfort and destruction of tissues. Klenerman[15] modified this

BOX 40-1

Safety Measures for Preventing Tourniquet Complications

- The tourniquet should be applied where the nerves are best protected in the underlying musculature.
- Proper functioning of the equipment should be tested before it is operated.
- The tourniquet should be used for no longer than 2 hours.
- The widest cuff possible should be chosen (wide bladders can occlude the blood flow with the use of a lower cuff pressure).
- A minimum of two layers of padding should be placed around the extremity of loose fibers/lint that can become embedded in the contact closures. The best results for the protection of the skin occurs with the use of an elastic stockinette.
- The tourniquet size should be half of the limb diameter. The cuff should overlap between 3 to 6 inches. Large areas of overlap result in rolling and wrinkling of the underlying skin and increased pressure in that area.
- The tourniquet choice size should allow placement of two fingers between the cast padding and the cuff.
- When possible, the extremity should be exsanguinated prior to the inflation of the cuff. An Esmarch bandage is most commonly used.
- Only the minimally effective pressure should be used for occluding blood flow to the extremity. For the upper extremity, 70 to 90 mmHg more than the patient's systolic blood pressure should be used. For the lower extremity, twice the patient's systolic pressure should be used. For Bier block anesthesia, a minimum standard tourniquet pressure of 300 mmHg should be used unless the tourniquet is on the upper leg. In that case, twice the patient's systolic pressure should be used unless that amount is less than 300 mmHg.
- The pressure display must accurately reflect the pressure in the tourniquet bladder.

BOX 40-2

Physiologic Changes Caused by Limb Tourniquets

Neurologic Effects
- Abolition of somatosensory evoked potentials and nerve conduction occurs within 30 minutes.
- Application for more than 60 minutes causes tourniquet pain and hypertension.
- Application for more than 2 hours may result in postoperative neuropraxia.
- Evidence of nerve injury may occur at the skin level underlying the edge of the tourniquet.

Muscle Changes
- Cellular hypoxia develops within 2 minutes.
- Cellular creatinine value declines.
- Progressive cellular acidosis occurs.
- Endothelial capillary leak develops after 2 hours.

Systemic Effects of Tourniquet Inflation
- Elevation in arterial and pulmonary artery pressures develops. This is usually slight to moderate if only one limb is occluded. The response is more severe in patients undergoing balanced anesthesia that does not include a potent anesthetic vapor.

Systemic Effects of Tourniquet Release
- Transient fall in core temperature occurs.
- Transient metabolic acidosis occurs.
- Transient fall in central venous oxygen tension occurs, but systemic hypoxemia is unusual.
- Acid metabolites (e.g., thromboxane) are released into the central circulation.
- Transient fall in pulmonary and systemic arterial pressures occurs.
- Transient increase in end-tidal carbon dioxide occurs.

recommendation a year later to between 50 and 75 mmHg more than the patient's systolic pressure.

The ischemic pain associated with tourniquet application is similar to that of thrombotic vascular occlusion and peripheral vascular disease.[16] At about 45 to 60 minutes after tourniquet pressurization, patients report various symptoms associated with dull aching that progress to burning and excruciating pain that may require general anesthesia. Once the pain begins, it is often resistant to analgesics and anesthetic agents, despite the anesthetic technique. Even with a well-controlled general anesthetic at the time of tourniquet inflation, ischemic pain may begin during this same time interval and may cause increasing heart rate and blood pressure that require pharmacologic intervention.[17]

Although specific neural and metabolic factors responsible for tourniquet pain are still unknown, several researchers have identified the nerve fibers responsible for transmission of the impulses. The burning and aching pain corresponds to the activation of the small, slow-conducting, unmyelinated C fibers. The pinprick, tingling, and buzzing sensations that frequently accompany tourniquet application, often even after deflation, correspond to activation of the larger and faster myelinated A-delta fibers.

Myelinated A-delta and unmyelinated C fibers differ in their sensitivity to local anesthetics. As the concentration of local anesthetic decreases, the activation of C fibers increases, but the A-delta fiber activation is still suppressed. This means that C fibers may be more difficult to anesthetize than A-delta fibers, and tourniquet pain therefore seems more consistent with pain sensation carried by C fibers.[16] Other research has shown that certain local anesthetics enhance the effect of the blockade in the presence of increased stimulation of the isolated nerve fiber. For example, the potency of bupivacaine is enhanced by an increase in the rate of nerve stimulation and may offer an advantage by lowering the incidence of tourniquet pain.[18]

Regardless of the sensory level achieved in these patients, they still experience tourniquet pain. It is apparent that a high-quality blockade of the sacral roots is more important than the thoracic sensory level in reducing the incidence of tourniquet pain, because the intensity of pain may be due to ischemia of the entire leg, as well as under the cuff.[19] The addition of opioids, ketorolac, and melatonin to local anesthesia solutions have all shown some efficacy in reducing the incidence of tourniquet pain.[20-22] Sedation with dexmedetomidine is also effective.[23]

Postoperative Tourniquet Paresthesias

Properly placed tourniquets inflated to appropriate pressures rarely cause injury. The use of excessive tourniquet pressure for a prolonged time may cause postoperative paresthesias that are frustrating to treat and very painful for the patient. Excessive tourniquet pressure causes deformation of the underlying nerves—the myelin may be stretched on one side of the node and invaginated on the other. Nerve damage due to rupture of the Schwann cell membranes may also be present. Use of proper padding, appropriate choice of tourniquet size, and adherence to recommendations of appropriate pressure and time minimize the incidence of this complication.

PATIENT POSITIONING

Chapter 21 provides an excellent overview of proper positioning during surgery. It is important to have a thorough understanding of the physiologic changes that occur in various positions. Appropriate patient positioning must allow optimal exposure of the surgical site, allow for appropriate monitoring throughout the procedure, provide good access to the patient's airway, allow for comfort and warmth, minimize or prevent physiologic functioning compromise, protect all body systems, and maintain patient dignity.[24] Positions chosen may include supine, lateral decubitus, prone, and even beach chair/sitting. Neutral alignment and proper padding of exposed neural pathways can help diminish injuries sustained intraoperatively related to positioning. Communication between the entire team (i.e., anesthesia, OR nurse, and surgeon) will yield the best outcomes for the patient.

Over the millennia, human physiology has adapted to being in an upright or erect position for the majority of the wakeful hours. For example, in the upright position there are three zones of ventilation-perfusion within the lungs: (1) areas where alveolar pressure is greater than arterial pressure, (2) areas of complex, variable pressure gradients between alveolar and arterial components, and (3) areas where arterial pressure is greater than alveolar pressure. Figure 40-1 illustrates lung zones 1, 2, and 3. Other examples of physiologic adaptation are the valves found in dependent areas of the venous system, such as the extremities, and the absence of valves in nondependent areas, such as the cranium. Changes from the upright position produce corresponding physiologic changes[24,25] (Figure 40-2).

ARTHROSCOPY

Arthroscopy is a minimally invasive surgical procedure performed to examine and sometimes repair damage of the interior of a joint using an arthroscope.[26] The concept was introduced in the United States in 1926.[27] However, without the availability of practical sources of illumination, arthroscopy languished. The development of fiber-optic light sources in the 1970s brought a resurgence of interest in the use of arthroscopy. Initially, arthroscopy was used to obtain a diagnosis of a patient's orthopedic malady so a definitive, corrective surgical procedure could be performed. As interest in the procedure and technique increased, coupled with development of the necessary smaller surgical instrumentation, previously open surgical procedures on the knee, such as partial or complete meniscectomy, loose-body removal, or ligament repair or reconstruction, were attempted and refined solely via the arthroscope.

Successful performance of arthroscopic procedures on the knee produce several benefits for the patient, including reduced blood loss, less postoperative discomfort, and reduced length of rehabilitation. The success achieved with arthroscopic procedures on the knee led to application of the principles and techniques to other

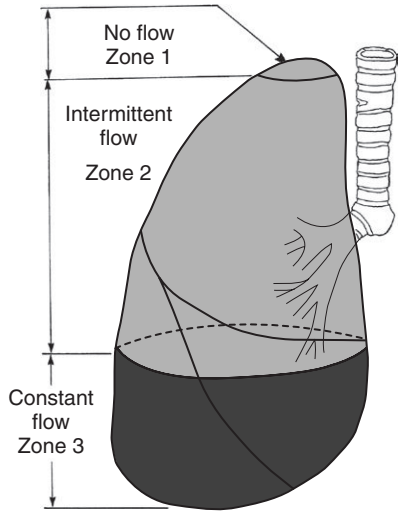

FIGURE **40-1** Lung zones: the effect of gravity on ventilation-perfusion.

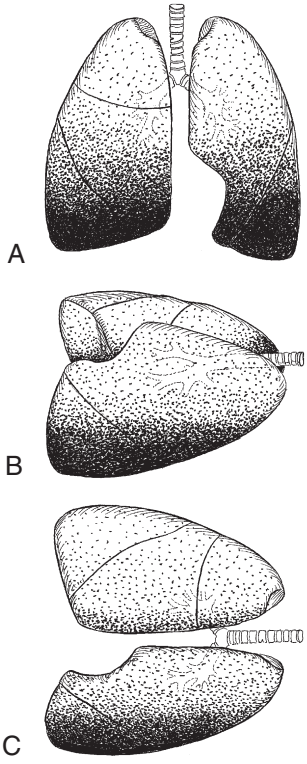

FIGURE **40-2** Gravity dependence of ventilation and perfusion as noted by lungs depicted in the standing **(A)**, supine **(B)**, and lateral **(C),** positions.

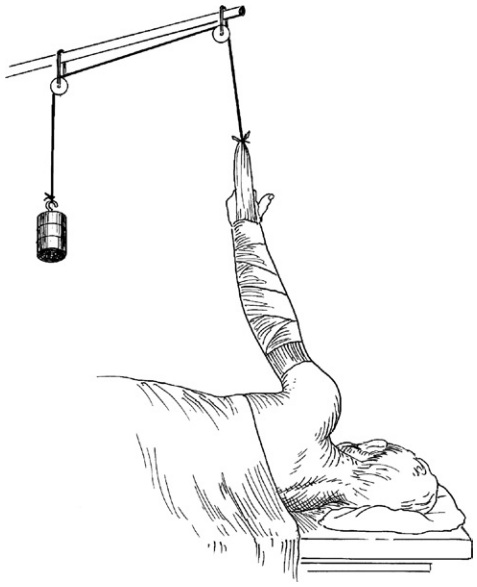

FIGURE **40-3** Shoulder arthroscopy positioning.

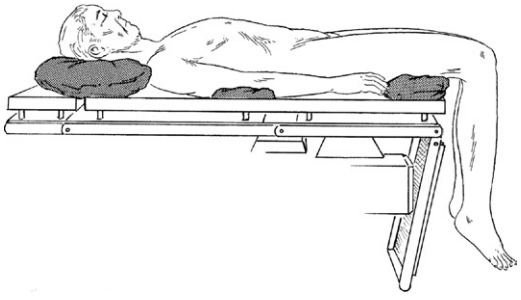

FIGURE **40-4** Positioning for knee procedures.

joints (e.g., the shoulder, elbow, wrist, hip, ankle, and phalangeal joints of the foot).[28,29] Many of these surgeries have become routine outpatient procedures. Through the middle portion of the 1990s, application of arthroscopic procedures focused on the shoulder. Accordingly, shoulder arthroscopy use ranges from simple debridements to more complex rotator cuff repairs.[27] The development and refinement of shoulder arthroscopic procedures mirrors that of knee arthroscopic procedures; that is, as more skill and comfort are obtained with initial procedures, more traditionally open surgical treatments are attempted solely via the arthroscope.

Anesthetic Management

Arthroscopic procedures may be managed by almost any of the available anesthesia techniques (e.g., general anesthesia, regional anesthesia, combined regional and general anesthesia, and local blockade with sedation). Patient selection for a given anesthetic technique is crucial with arthroscopic procedures, as with all operative procedures. As previously mentioned, for some patients there is absolutely no substitute for receiving general anesthesia. Critical factors in the selection and presentation of the available anesthesia techniques appropriate for arthroscopic procedures are the patient positioning necessary to facilitate the proposed arthroscopic procedure and the overall state of health of the patient. For example, shoulder arthroscopy uses one of two positions to accomplish the surgery, either lateral decubitus or modified Fowler's ("beach chair") position.[30] The choice of position is determined in part by the nature and extent of the malady being surgically addressed. For some shoulder arthroscopy procedures, supplemental traction with weights and abduction may be necessary to provide optimum operative visualization (Figure 40-3); for others, the modified Fowler's position may be used with the force of gravity or manual traction providing sufficient operative visibility. Reviewing the patient's chart and more importantly, personally interviewing the patient, along with understanding the physiologic changes associated with various positions, assist in choosing the best care for each patient.

Patient positioning for arthroscopic procedures can encompass virtually the entire gamut of possible operative positions. Most often, arthroscopic procedures for lower extremity joints use the supine position, as do most arthroscopic procedures on the upper extremities. Arthroscopy on the knee requires the supine position with the foot of the OR bed lowered (Figure 40-4). The nonoperative leg should either be wrapped with an elastic bandage or have some form of compression stocking in place to reduce pooling of blood and the potential for thrombus formation. At times, patients undergoing elbow arthroscopy may be placed in the supine, lateral decubitus, or prone position; the position is dictated by operative necessity and surgeon preference (Figures 40-5 and 40-6). The prone position is advantageous primarily because of the better limb stability during the procedure.[31] Shoulder arthroscopy is usually accomplished via either the modified Fowler's position or the lateral decubitus position, based on optimal access to the injury and surgeon preference (see Figure 40-3).[30] Hip arthroscopy is also typically accomplished via the lateral decubitus or the supine position, with the patient on a fracture table (Figure 40-7). The fracture table is used to provide greater stability while traction is applied, using either weights and counterweights (lateral decubitus position) or mechanical traction attached to the leg-holding device of the fracture table (supine position).[32]

Complications from arthroscopic procedures represent a small percentage of the total number of procedures performed.[33-36]

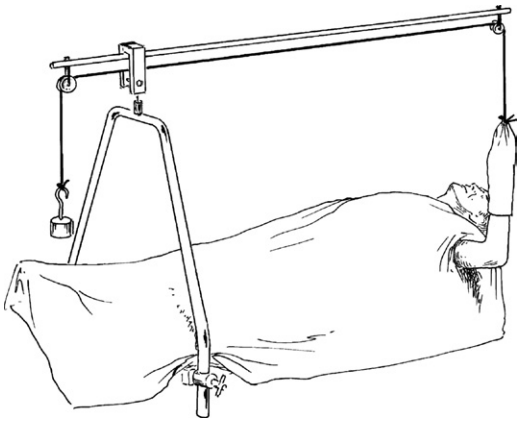

FIGURE **40-5** Supine position for elbow surgery.

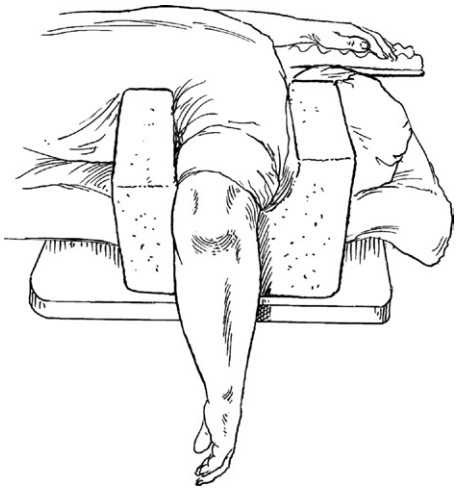

FIGURE **40-6** Prone position for elbow surgery.

Complications that may occur include subcutaneous emphysema, pneumomediastinum, and potentially life-threatening tension pneumothorax. Accordingly, complications resulting from arthroscopic procedures that particularly concern the nurse anesthetist are relatively few. The full range of potential anesthetic complications associated with patient positioning apply (e.g., inadvertent extubation, eye or corneal injury, visual loss from the prone position, and nerve injury from improper patient positioning). Blood loss is not generally a concern, but significant and sustained hypotension warrants immediate and thorough investigation. The pneumatic tourniquet may be used to provide a clear, bloodless surgical field. Trocar insertion sometimes results in inadvertent vessel puncture that may go undetected because of the tourniquet. In cases that are located proximally (i.e., hip or shoulder) and therefore done without a tourniquet, vascular damage is discovered much earlier.

To provide optimal visualization of joint structures during arthroscopic procedures, the irrigating fluid used to distend the operative joint is instilled under pressure. This is achieved through gravity or mechanical pressurization. The typical irrigation setup uses large bags of irrigating solution, 3 to 5 L in volume. The nurse anesthetist should be aware of the fluid being infused in comparison with the outflow. Even small differences can add up to a large volume for the patient, especially in the case of an extended procedure. This absorption could potentially lead to fluid volume overload, congestive heart failure (CHF), pulmonary edema, or even hyponatremia if sterile water is used.[33-36]

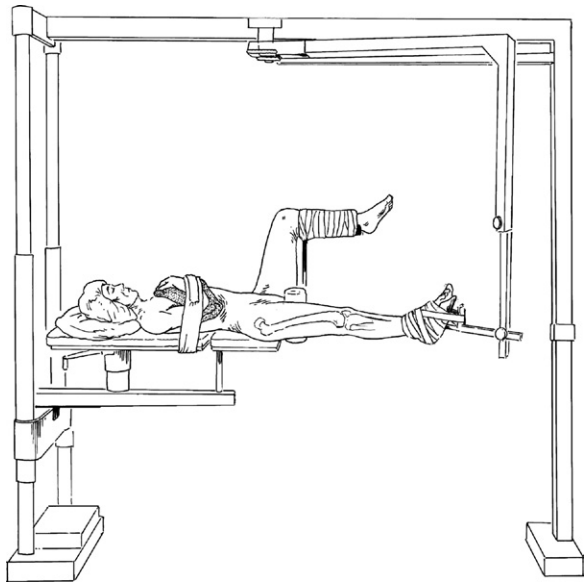

FIGURE **40-7** Fracture table. Allows easy access for x-ray equipment.

BOX **40-3**

Signs and Symptoms of Tension Pneumothorax

- Sudden, inexplicable hypoxemia
- Elevated central venous pressure
- Tachycardia
- Absent breath sounds on the affected side
- Cyanosis
- Diaphoresis
- Decreasing oxygenation
- Tracheal shift
- Agitation (may be observed in patients receiving regional anesthesia)
- Hypotension
- Jugular vein distention
- Increased airway pressure
- Asymmetric chest wall movement
- Percussive hyperresonance over the affected side
- Extreme anxiety (may be observed in patients receiving regional anesthesia)

During subacromial decompression, subcutaneous emphysema, tension pneumothorax, and pneumomediastinum have been reported during shoulder arthroscopy.[35] These complications appear to be associated at least in part with the use of mechanical irrigation pumps and power-saver suction. Careful assessment during this irrigation period is important. Box 40-3 lists the signs and symptoms of tension pneumothorax. Because tension pneumothorax is a potentially life-threatening event, early recognition and treatment are paramount. Ideally, placement of a chest tube is most desirable to relieve the increased intrathoracic pressure. An immediate and very effective treatment is needle decompression with a 14- to 18-gauge intravenous angiocatheter placed into either the second or third intercostal space anteriorly or the fourth or fifth intercostal space laterally. Successful decompression is accompanied by a sudden rush of air, as well as readjustment of physical symptoms and vital signs back toward the patient's normal parameters. After successful decompression, the intravenous catheter stylet should remain in place and be covered or capped to prevent air from being sucked

back into the chest cavity until a chest tube can be properly inserted.[37,38]

ARTHROPLASTY

Arthroplasty is the surgical replacement of all (total arthroplasty) or part (hemiarthroplasty) of a joint to achieve a return of natural motion and function of the joint, as well as restoration of the controlling function of the surrounding soft tissues (i.e., muscles, ligaments, and tendons). The goals of arthroplasty are pain relief, stability of joint motion, and deformity correction. The original hip prosthesis was fabricated from stainless steel. Prostheses currently in use are stronger metal alloys, based on nonferrous metals, generally cobalt or titanium. These alloys demonstrate greater tensile strength and are more resistant to fatigue than the original stainless steel. The search for stronger metals that can withstand greater amounts of abuse is persistent because of the increasing demand for these components to last longer. And in fact, even younger groups of patients are lining up for joint replacements as people have become more active and athletic. The rigors of activities such as running and skiing are leading to the need for increased numbers of joint replacements in patients that are younger than ever before.[39]

Joint Arthroplasty

Hip Surgery

Several hundred thousand patients in the United States undergo some form of hip arthroplasty each year. The majority of patients are over age 65 and more than 75% have at least one comorbidity when they present for surgery.[40] Women are twice as likely as men to require the surgery. Hip arthroplasty is most often indicated for patients experiencing degenerative joint disease or arthritic damage. A report on outcomes noted that, in patients having total joint arthroplasty, younger age and male sex are associated with an increased risk of revision. Older age and male sex are associated with increased risk of mortality and older age is related to worse function, particularly among women. Age and sex do not influence the outcome of pain. Despite these differences, all subgroups derived benefit from total joint arthroplasty.[41]

It is classified as a major surgical undertaking. This procedure requires a large incision, extending from near the iliac crest across the joint to the midthigh level. Several large muscle groups must be incised and dissected through to gain access to the joint, after which the joint is disarticulated. The muscle relaxation provided by a subarachnoid block makes it ideal to facilitate the surgical process. The anesthetic plan for patients undergoing hip surgery frequently involves the use of some sort of regional technique. In the event of patient refusal, or contraindication for spinal anesthetic, general anesthesia may be selected. Nitrous oxide should be avoided due to the risk of air entrapment. The duration of the surgery, level of narcotic required to maintain patient comfort, and required positioning make it less desirable to perform these surgeries utilizing an laryngeal mask airway (LMA).

Once anesthesia induction is complete, the patient is positioned, prepped, and draped for incision. After a final timeout, skin incision is made. The femoral head and neck are excised, leaving the femoral canal open. The femur is highly vascular, as is the acetabulum, and the reaming required to prepare them for receipt of orthopedic components often opens venous sinuses, which can result in significant blood loss. For these patients, intraoperative blood loss ranges from 500 to 1000 mL per case.[42]

The hemoglobin threshold at which red-cell transfusion is warranted is controversial. A recent study compared a liberal strategy of transfusion at a hemoglobin below 10 g/dL after hip fracture with a more restrictive strategy of transfusion at a hemoglobin below 8 g/dL. The liberal and restrictive strategy groups were similar with regard to rates of death, inability to walk independently on 60-day follow-up, and in-hospital morbidity in elderly patients at high cardiovascular risk.[43]

BOX 40-4

Significant Risk Factors for Developing Bone Cement Implantation Syndrome

- Preexisting cardiovascular disease
- Preexisting pulmonary hypertension
- American Society of Anesthesiologists class 3 or higher
- New York Heart Association class 3 or 4
- Canadian Heart Association class 3 or 4
- Surgical technique
- Pathologic fracture
- Intertrochanteric fracture
- Long-stem arthroplasty

Adapted from Donaldson A, et al. Bone cement implantation syndrome. *Br J Anaesth.* 2009;102(1):12-22.

The canal is further cleaned with a sponge to prepare the surface for receipt of adhesive, after which methyl methacrylate (MMA) cement may be instilled into the femoral canal. For some procedures, usually in younger or very physically active patients, MMA is not used to secure the femoral prosthesis, and the prosthesis is referred to as being *press-fit*. The femoral prosthesis is inserted into the canal and forcibly "seated" with a mallet. Physiologic changes are common with the instillation of the MMA. These changes are termed *bone cement implantation syndrome* (BCIS).

BCIS has no agreed-upon definition, although it is characterized by a number of clinical features that may include hypoxia, hypotension, cardiac arrhythmias, increased pulmonary vascular resistance (PVR), unexpected loss of consciousness when regional anesthesia is administered, and cardiac arrest. The etiology of these effects is poorly understood and only suggested. Some theories involve the role of emboli formed during cementing and prosthesis insertion. Several mechanisms such as histamine release, complement activation, and endogenous cannabinoid-mediated vasodilation have been proposed. It is most commonly associated with hip arthroplasty but may also occur during other cemented procedures including knee arthroplasty and vertebroplasty. Although definitive studies are lacking, it is estimated to occur in 2% to 17% of surgeries. It usually occurs at the following stages in the surgical procedure: femoral reaming, acetabular or femoral cement implantation, insertion of the prosthesis or joint reduction, or occasionally after limb tourniquet deflation. Numerous patient-related risk factors have been implicated and are given in Box 40-4.

A fall in end-tidal carbon dioxide concentration may be the first indication of clinically significant BCIS under general anesthesia. Early signs of BCIS in the awake patient undergoing regional anesthesia include dyspnea and altered sensorium. If BCIS is suspected, the inspired oxygen concentration should be increased to 100% and supplementary oxygen should be continued into the postoperative period. It has been suggested that cardiovascular collapse in the context of BCIS be treated as right-sided heart failure. Aggressive fluid resuscitation is recommended and hypotension should be treated with α-agonists.

Communication between the surgical team and the anesthesia team is imperative at the time of cementing. Prior to cementing, the patient's blood pressure should be optimized, the patient

should be placed on 100% Fi_{O_2}, pressure bags should be available for rapid IV fluid administration, and IV fluid bags should be full or near so. It is also important to document the cement time on the anesthesia record. The acetabular component is secured in place with screws and bone grafting.[44]

Positioning. Patients being prepared for hip arthroplasty are generally positioned in the lateral decubitus fashion. Placing the patient in a lateral decubitus position produces physiologic changes similar to those found in the supine patient. Although the majority of organ systems are unaffected, the physiologic alterations of most concern revolve around pulmonary and cardiovascular functioning.[45] Upright positioning contains three zones of ventilation-perfusion distribution. Placing the patient in the lateral decubitus position results in a significantly greater proportion of the uppermost lung being classified as *zone 1*, where ventilation is more abundant than pulmonary blood flow, as well as a large portion of the dependent lung being classified as *zone 3*, where pulmonary blood flow exceeds alveolar ventilation (see Figure 40-2). In addition, the percentage of the *zone 2* areas of the lung fields is reduced and split between the lungs, with the larger amount being in the dependent lung.

The alteration in ventilation-perfusion distribution is accompanied by reductions in vital capacity and tidal volume. On assuming the lateral decubitus position, healthy, conscious individuals experience about a 10% reduction in vital capacity as a result of reduced anterior, as well as lateral, movement of the dependent rib cage along with restriction of the dependent hemidiaphragm. Ventilation-perfusion distribution may be further altered by the shift in the mediastinum toward the dependent side, which rotates the heart on its axis. This cardiac rotation can impede venous return, reducing cardiac output. The reduced cardiac output can produce hypotension, which must be judiciously treated with either fluid challenges or small doses of vasoactive medication. Judicious attention to padding and warming and continuous assessment are required.[45,46]

Thromboprophylaxis. Patients undergoing total hip and total knee arthroplasty as well as other orthopedic patients are at risk for venous thromboembolism. These include deep vein thrombosis and pulmonary embolism. Most deep vein thromboses are asymptomatic, but they can lead to long-term morbidity to the same extent as symptomatic events. Unique coagulation factors may be associated with orthopedic surgery patients that differentiate them from patients undergoing other types of surgery.[47] Many different guidelines exist.[48] The American College of Chest Physicians evidence-based guidelines for preventing thromboembolism in orthopedic surgery have recently been updated. They recommend that patients undergoing major orthopedic surgery receive either low-molecular-weight heparin; fondaparinux; dabigatran, apixaban, and rivaroxaban (total hip or total knee arthroplasty but not hip fracture surgery); low-dose unfractionated heparin; adjusted-dose vitamin K antagonist; aspirin; or an intermittent pneumatic compression device (IPCD) for a minimum of 10 to 14 days. Thromboprophylaxis for up to 35 days is preferred. They recommend the use of low-molecular-weight heparin in preference to the other agents and suggest adding an IPCD during the hospital stay. In patients at increased bleeding risk, the use of an IPCD alone with no pharmacologic prophylaxis is recommended.[49]

Knee Arthroplasty

Total knee arthroplasty is the other frequently performed joint replacement procedure. The pneumatic tourniquet is placed circumferentially over the thigh to decrease blood loss and maintain full view of the joint for the surgeon. Nevertheless, blood loss as a result of total knee arthroplasty can be up to 2 units. During the procedure, the articulating surfaces of the femur and tibia are excised via precise angular cuts, and the patellar articulating surface is shaved, all to conform the bones to surfaces of the prostheses. Both the femoral and tibial surfaces are covered with MMA cement, and the individual prosthesis components are forcibly seated with a mallet. The high-density polyethylene patellar component is cemented and seated with a viselike clamp. The medial and lateral menisci are replaced with a conforming wedge of high-density polyethylene. The same considerations related to MMA as discussed in hip arthroplasty apply here as well.[50]

Ankle Arthroplasty

Ankle arthroplasty is performed for a number of orthopedic problems. The most common intraarticular procedures are osteochondral lesion, ankle or subtalar debridement, subtalar fusion (thirty-three), and partial talectomy. The most common extraarticular procedures are os trigonum excision, tenolysis of the flexor hallucis longus tendon, and endoscopic partial calcanectomy. End-stage osteoarthritis of the ankle is a major cause of pain and disability.[51] **A**rthroscopy is used not only to evaluate and treat intraarticular abnormalities but also for endoscopic and tendoscopic procedures.[52] A tourniquet may be used to facilitate a bloodless field. Deep vein thrombosis (DVT), pulmonary embolism (PE), and fat embolism are all associated with total hip arthroplasty. Thromboprophylaxis is discussed previously.

Anesthetic Management

These procedures can be performed with either a regional or general anesthetic technique. Ankle procedures that require a tourniquet are commonly performed under spinal or epidural anesthesia. A combination of regional techniques such as spinal anesthesia for the surgical procedure with a popliteal, femoral, or a combination of leg blocks for postoperative analgesia.[53,54] Regional anesthesia that combines sciatic and femoral nerve blocks is sufficient for all surgical procedures below the knee that do not require a thigh tourniquet. The femoral nerve innervates the medial leg to the medial malleolus, and the remainder of the leg below the knee, including the foot, is innervated by the common peroneal nerve and tibial nerve, both branches of the sciatic nerve. The sciatic nerve is usually blocked high in the popliteal fossa to ensure anesthesia to the tibial and peroneal nerves.[55]

Upper Extremity Arthroplasty

The number of shoulder arthroplasties, particularly total shoulder arthroplasties, performed is rapidly increasing. The use of reverse total arthroplasty, which was approved by the Food and Drug Administration in 2003, may be part of the reason for this increase.[56]

The goals of shoulder arthroplasty include pain reduction and increasing range of motion. Indications for shoulder arthroplasty include posttraumatic brachial plexus injuries, paralysis of the deltoid muscle and rotator cuff, chronic infection, failed revision arthroplasty, severe refractory instability, and bone deficiency after resection of a tumor in the proximal aspect of the humerus.[57] Shoulder arthroplasty is performed with the patient in either the lateral decubitus or modified Fowler ("beach chair") position (see Figure 40-3). Because a pneumatic tourniquet cannot be used, shoulder arthroplasty is associated with higher amounts of blood loss.

Elbow arthroplasty is performed with less frequency than shoulder arthroplasty. The goals for elbow arthroplasty are much the same as for shoulder arthroplasty: pain relief and improvement

in joint function. The indications for elbow arthroplasty include rheumatoid arthritis, traumatic arthritis, and ankylosis of the joint.

Anesthetic Management

Patients undergoing total shoulder arthroplasty can be managed by general anesthesia, interscalene blockade, or supraclavicular blockade. Combined regional and general anesthesia is also a choice. It is important to be mindful of the ongoing potential for inadvertent extubation. This is a result of the surgical manipulations and desired patient positioning necessary while in close proximity to the patient's head and neck. The patient's neck may be subjected to excessive stretch during the surgical manipulations, and if the patient's head becomes dislodged from the supportive device used, there is the potential for cervical spine injury. Special attention to the head supports avoids pressure on the patient's eyes.

For the patient undergoing shoulder arthroscopy, pulmonary function will more closely resemble "normal" function as a result of being in the modified Fowler's position. The potential for venous air embolism is somewhat increased in this position. The risk of fat or bone marrow embolism and thromboembolism is incumbent with the required reaming of the shaft of one of the body's long bones. The potential cardiovascular effects of MMA cement also must be considered if the humeral component is cemented in place. The sitting position may result in detrimental cerebral damage to patients experiencing hypotension.[58] Complications during shoulder arthroscopy in the beach chair and lateral decubitus positions are compared in Table 40-1. Prevention of position-related complications during shoulder arthroscopy are shown in Table 40-2.

Visual loss may be especially problematic in patients having arthroscopic procedures using deliberate hypotensive techniques. When intraoperative hypotensive techniques are used, cerebral perfusion and blood supply to the cranial nerves, including the optic nerve, is diminished. Intraoperative cerebral ischemia has been reported, resulting from hypoperfusion. The decreased cerebral perfusion is likely due to several factors, including the decrease in blood pressure associated with anesthesia and upright position. Other factors include failure to correct for cerebral pressure being lower than the point of blood pressure measurement, and vascular compromise related to malpositioning of the head and neck, probably through changes in cerebral blood flow from a combination of postural hypotension and excessive head and neck manipulation. Pressure measurements must be assessed at the level of the brain because autoregulation occurs in the intracranial arterioles and capillaries. When the patient is seated upright, there is a significant hydrostatic gradient between the brain and the site of blood pressure measurement. The magnitude of the gradient is approximately 2 mmHg per inch of height differential. When the cuff is on the upper arm, this difference can easily be 25 mmHg. Failure to properly measure the blood pressure may lead to inaccurate assessment of the patient's true cerebral perfusion.[59]

Hypotensive bradycardic episodes (HBEs) are a relatively common adverse effect of shoulder arthroscopy and may lead to potentially devastating complications. HBEs have been defined as a decrease in heart rate of at least 30 beats/min within a 5-minute interval, any heart rate less than 50 beats/min, and/or a decrease in systolic blood pressure of more than 30 mmHg within a 5-minute interval or any systolic pressure below 90 mmHg. These transient but profound hypotensive and/or bradycardic events have been reported in patients undergoing shoulder surgery in a semiupright position under an isolated interscalene block anesthetic with a reported incidence approaching 30%. The etiology of these HBEs is unknown, but the most common proposed mechanism is activation of the Bezold-Jarisch reflex.

TABLE 40-1 Position-Related Complications During Shoulder Arthroscopy

Beach Chair	Lateral Decubitus
Hypotensive bradycardic events with interscalene block (4%-29%)	Temporary paresthesia (10%)
Cervical neurapraxia (rare)	Permanent neurapraxia (2.5%)
Air embolism/pneumothorax	Risk of musculotendinous nerve injury (5-o'clock portal) (rare)
Cerebral hypoperfusion event	Fluid-related obstructive airway compromise

Adapted from Rains DD, et al. Pathomechanisms and complications related to patient positioning and anesthesia during shoulder arthroscopy. *Arthroscopy*. 2011;27(4):543-541.

TABLE 40-2 Prevention of Position-Related Complications During Shoulder Arthroscopy

Beach Chair	Lateral Decubitus
Reference systolic pressures at level of brain	Use of safe shoulder positions when arm is placed in traction
	45 degrees of forward flexion with 90 degrees of abduction
	45 degrees of forward flexion with 0 degrees of abduction
Attentive care to intraoperative head positioning	Placement of anterior inferior portal out of traction
Consider use of HBE prophylactic measures when using interscalene block	Consider use of general anesthesia for longer cases

From Rains DD, et al. Pathomechanisms and complications related to patient positioning and anesthesia during shoulder arthroscopy. *Arthroscopy*. 2011;27(4):543-541.
HBE, Hypotensive bradycardic episodes.

The Bezold-Jarisch reflex is an inhibitory reflex mediated through cardiac sensory receptors with a vagal efferent limb. In the case of surgical positioning with the patient in the beach-chair position, enhanced venous pooling occurs due to dependent extremities, leading to a subsequent increase in sympathetic tone and ultimately a low-volume, hypercontractile ventricle. Cardiac hypercontractions lead to activation of the Bezold-Jarisch reflex with an abrupt autonomic withdrawal of sympathetic response and activation of increased vagal tone. The combination of venous pooling and paradoxical increased vagal tone results in sudden, profound bradycardia and hypotension that can be difficult to rapidly reverse.

The first descriptions of HBE, historically, were in patients receiving spinal anesthesia for a variety of surgeries. The mechanism clearly involves sympathetic blockade; however, decreased sympathetic tone to the heart with decreased cardiac filling is an important contributor. It has been proposed that epinephrine used with the local anesthetics for interscalene block may actually contribute to HBE by increasing cardiac hypercontractility, as well as exacerbating the position-related hypovolemic state.

It is possible that when administered in a regional block, epinephrine is absorbed slowly and may be physiologically equivalent

to a low-dose intravenous administration. At such concentrations, epinephrine could predispose to HBE by increasing cardiac contractility, resulting in ventricular emptying, increasing heart rate (which reduces cardiac filling), and peripheral vasodilation and pooling (decreased afterload); these factors ultimately create ventricular hypovolemia with hypercontractions.

Prophylaxis to prevent HBE includes aggressive treatment of fluid deficits and blood loss. Minimize venous pooling in the upright position with support stockings. Avoid the use of local anesthetics containing epinephrine and consider the use of intraoperative β-blockade in select patients.[59]

Elbow arthroplasty can be performed in any of three positions: supine, lateral decubitus, or prone. The deciding factors on which position to use for this procedure are surgeon preference and the health of the patient. Elbow arthroplasty can be managed by general anesthesia or supraclavicular, intraclavicular, interscalene, or brachial plexus blockade. During elbow arthroplasty, the pneumatic tourniquet is generally used to minimize blood loss and provide a clear surgical field. It is necessary to be prepared to treat the patient's tourniquet pain whenever regional anesthesia is used. Any time a pneumatic tourniquet is used, the risk of thromboembolism exists. This risk is increased in those patients with a history of venous thromboembolism (VTE).[60]

SPINAL SURGERY

Minimally invasive techniques are being used for noncomplex spinal procedures. Percutaneous endoscopic lumbar discectomy (PELD) is the technique of choice for minimally invasive spine surgery (MISS).[61] Other procedures that may be treated with minimally invasive techniques include vertebroplasty and kyphoplasty, cervical discectomy and foraminectomy, and intradiscal electrothermal therapy. The procedures are performed in an interventional radiology suite and usually require local anesthesia with intravenous sedation. General anesthesia is occasionally used for difficult procedures, and low-dose propofol, remifentanil, or dexmedetomidine infusions have all been used successfully. The greatest anesthetic challenge may be positioning because these patients often have severe osteoporosis and other spinal deformities. They are often elderly and have significant comorbidities, so a thorough preoperative workup and preparation is essential.[62] Attention to postoperative analgesia improves recovery.[63]

Back injuries account for a large percentage of work-related injuries and are a leading cause of work absences. Occupational factors suspected of accelerating spinal degeneration include accident-related trauma; heavy physical loading, lifting, bending, and twisting; prolonged sitting; and sustained nonneutral work postures and long periods of sitting while driving.

Complex spinal surgery presents several anesthetic challenges including airway control, positioning, fluid and blood transfusion management, hemodynamic control, and postoperative analgesia. The majority of spine patients will be placed in the prone position for surgery.

Patients in this position for prolonged periods present significant challenges. It is important to maintain adequate venous return to maintain the hemodynamics of the patient.[64] If the increased intraabdominal or intrathoracic pressures resulting from being prone reduce venous return, it will reduce cardiac output. In addition, placing a patient in the prone position produces significant increases in both systemic and pulmonary vascular resistance. These increases lead to significant decreases in stroke volume and cardiac index.[65]

Respiratory dynamics are greatly affected by placing the patient in the prone position. The three-zone model discussed earlier is rearranged. The proportion of zone 2 reduces, whereas that of zone 3 increases.[66] Care is taken to prevent barotraumas through appropriate changes in ventilatory settings to maintain oxygenation and positive pressures within acceptable limits.

Finally, the prone position can alter central nervous system (CNS) dynamics more than the supine position, which is of particular concern if head injury or closed head pathology is present or suspected. The anterior neck is particularly supple and lacks considerably bony structural and protective support. With the unconscious patient or one under general anesthesia, head rotation during positioning must be done with great care. If the patient's head is rotated 60 degrees, compression of the contralateral vertebral artery begins to constrain blood flow; if rotated 80 degrees, the contralateral vertebral artery becomes completely occluded.[67] The carotid artery and jugular vein on the upper side of the neck can become compressed by extreme degrees of head rotation, and those on the down side of the neck may become compressed by inappropriate head support.[64]

Under general anesthesia or with a patient whose level of consciousness is already altered, the alteration in arterial blood supply to the brain may not be easily recognized. Therefore, patients in whom any aberration in carotid blood flow is suspected or who have head injury should probably have the head maintained in a neutral anatomic alignment while in the prone position. In addition, even if no arterial or venous compression occurs, if the patient's head rests below the level of the heart, he or she is at an increased risk for postoperative visual loss, which is discussed below. Whether the head is rotated to the side or placed in a neutral sagittal position, careful attention must be directed to the avoidance of pressure on the orbit. This can be accomplished with soft surgical pillows or one of several commercially available foam supports. Mayfield tongs provide an additional level of stability and eliminate pressure on the face or the eyes.[65]

In the past, laminectomies required large incisions to afford the surgeon optimal visualization of the affected area of the spinal column. Currently less invasive techniques that make use of the microscope afford the surgeon better visualization while eliminating the need for the large incisions that were commonplace in the recent past, even for straightforward, "simple" lumbar laminectomies. In addition, the smaller incision results in reduced blood loss, faster wound healing, less trauma to surrounding soft tissues, shorter recovery, shorter length of hospitalization, and quicker return to a preinjury level of activity.

The most common reasons for spinal surgery are intervertebral disc herniation and spinal stenosis. These maladies can occur anywhere along the spinal column from C2 to C3 through the L5 to S1 vertebrae. Surgical intervention via the posterior approach consists of a midline incision and tissue dissection to expose the disc herniation or stenotic areas. Surgery is undertaken to relieve the pressure on the nerve root that is causing the pain. Certain conditions require the fusion of two or more vertebrae together. This fusion can provide increased stability.

Several agents can be used to accomplish this fusion, whether via bone grafting, plates and screws, or with the use of cage devices. The goal is to prevent further degeneration and loss of the surgical correction achieved. Interbody cage devices facilitate fusion of the specific vertebral joint.[68] Interbody cage procedures, done by experienced surgeons, are more quickly accomplished than the previously standard bone-grafting procedure, are less costly, provide greater stability, and afford faster recovery and rehabilitation times.[69]

In contrast to interbody cage devices and procedures, total disc replacement procedures are accomplished most commonly via an

anterior approach. Anterior approaches to spinal surgery often require the assistance of a general surgeon to aid in displacement of organs and vasculature.[70-73] A double-lumen tube may be used for lung isolation to facilitate surgical exposure. Fusion within the cervical spine is most often accomplished by initial discectomy followed by a wedge of bone graft, often cadaveric, or by fusion of the joint with a plate and screws.

Scoliosis is lateral curvature of the spinal column. The majority (75% to 80%) of scoliosis cases are idiopathic. The remaining 20% to 25% can be identified as resulting from such conditions as congenital skeletal abnormalities, neuromuscular disease, neurofibromatosis, trauma, or irritative phenomena resulting from spinal cord compression from a tumor. Untreated, scoliosis can lead to complex deformity in two planes (sagittal and coronal), chronic pain, neurologic and cardiopulmonary compromise, and cosmetic concerns.[74] Treatment pathways are determined by the severity and cause of the deformity and may be nonsurgical or surgical.

Surgical intervention consists primarily of fusion of multiple joint spaces, with or without anterior release, and may include extensive instrumentation (e.g., Harrington rods or other instrumentation). Scoliosis repair may require anterior or posterior approaches for repair. Either approach is a major surgical intervention, but the anterior approach is more technically involved. The anterior approach to the thoracic spine requires performing a thoracotomy.

In conjunction with the development of "cage" technology, the principles of laparoscopy/endoscopy are being adapted and applied to spinal surgery. The first use of laparoscope for lumbar discectomy was documented by Obenchain[75] in 1991. Laparoscopic techniques were first used by Mack et al.[76] for thoracic spinal surgery in 1993. Application of laparoscopic principles and techniques offers numerous advantages to anterior vertebral joint fusion (Box 40-5), the most important being better respiratory functioning, diminished blood loss, and shorter length of stay, resulting in decreased medical costs. The major disadvantage of using laparoscopic techniques in spinal surgery is the time it takes for the user to become proficient at the technique to avoid prolonged time in the operating room.

Not all patients are good candidates for the laparoscopic approach. It is contraindicated for lumbar repair in patients with abdominal adhesions from inflammatory processes, laparotomy, or abdominal trauma patients. In addition, those patients with marked cardiac or pulmonary disease processes may not be able to tolerate the hypercarbia that can result from abdominal insufflation of carbon dioxide. For thoracic spinal surgery candidates, laparoscopy is currently contraindicated for patients unable to tolerate one-lung ventilation and those with severe or acute respiratory insufficiency, high positive airway pressures, and pleural symphysis. Patients who have required previous thoracotomy or chest-tube placement must be more extensively evaluated preoperatively to determine whether thoracoscopic spinal surgery should be used. Also, at present, patients in need of internal fixation with extensive instrumentation of the anterior spine are not considered candidates for thorascopic spinal surgery.[77]

BOX 40-5

Advantages of Laparoscopy for Anterior Spinal Surgery

- Enhanced visualization
- Decreased potential for infection
- Reduced trauma to surrounding soft tissues
- Shorter hospitalization
- Shorter rehabilitation period
- Decreased blood loss
- Improved intraoperative and postoperative ventilation
- Reduced intensive care unit time
- Better cosmetic appearance
- Reduced overall costs

Anesthetic Management

General anesthesia provides the safest approach for spinal surgery. Not only is the airway secure, but muscle relaxants can be used, preventing movement at critical times during surgery. Aspirin, antiplatelet drugs, and anticoagulants should be appropriately managed and discontinued as possible. Preoperative testing should include a complete blood count, platelet count, and coagulation studies. A preoperative chest x-ray, pulmonary function tests, electrocardiogram (ECG), and echocardiogram should be obtained as appropriate. Evoked potentials will likely be monitored along with other neurologic testing as indicated (see Chapters 18 and 28).

A major anesthesia concern during spinal surgery centers on patient positioning. For spinal surgery involving the posterior approach, to facilitate the surgery, the patient will almost always be placed prone. While turning the patient, special attention must be given to the head and the endotracheal tube. Foam, gel pads, or head supports should be in place prior to the turning. Once turned, the first goal is to reconnect the breathing circuit and recheck the breath sounds to ascertain whether the tube is still in the correct place and has not migrated into the bronchus. The potential for eye or corneal injury is high in the prone position. Care must be taken to pad the extremities and to prevent neural injury.

When positioned prone, the patient's abdomen should not be compressed, because compression of the abdominal cavity will displace the organs, and therefore the diaphragm, in the cephalad direction, producing reduced functional residual capacity, reduced tidal volume, and increased airway pressures. Abdominal compression also contributes to engorgement of the epidural venous network and can be a contributing factor to greater blood loss during the surgical procedure. To avoid abdominal compression, the abdomen must be elevated from the surface of the OR bed.

Numerous methods and devices can be used to greatly reduce or eliminate abdominal compression. The simplest method is the use of bilateral "prone or chest rolls," which are firm but compressible pads that extend from the shoulder to the iliac crest (Figure 40-8). Other devices include the Wilson frame (Figure 40-9), the Relton adjustable pedestal frame (Figure 40-10), and the Andrews frame, or spinal-surgery table (Figure 40-11). Each of these positioning devices is designed to allow the abdomen to "hang" freely and reduce the possibility of compressing major vascular structures.

The Andrews spinal-surgery table is the most complex of the positioning devices. With the Andrews table, as with the other positioning devices, the patient is induced and intubated on the transport stretcher, after which he or she is lifted onto the table.

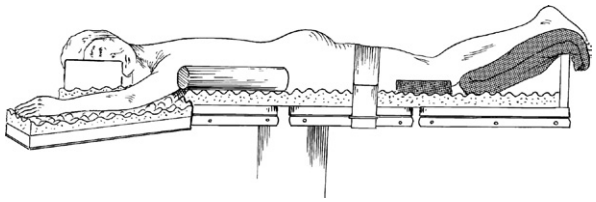

FIGURE **40-8** Prone position using chest rolls.

On initial positioning on the Andrews table, the patient lies flat with the legs resting perpendicular to the plane of the table. A buttock support is securely attached to the framework of the table and the bony prominences of the hips and, particularly, the knees are adequately padded. The leg portion of the table is then lowered until the weight of the lower body rests on the knees, resulting in the patient's hips and knees being flexed at 90 degrees. This table produces a modified knee-chest position, allows the abdomen to "hang" freely, and greatly reduces the potential for compression of the major vascular structures of the lower abdomen and pelvic region (femoral arteries and veins). This position also maximizes the surgeon's visualization of the surgical site. Blood loss is decreased by using the Andrews spinal-surgery table.[78] However, hypotension occurs frequently when using this table as a result of blood pooling in the dependent lower extremities. Antiembolic stockings may help counteract the tendency for blood to pool in the lower extremities, and any hypotensive event must be treated.

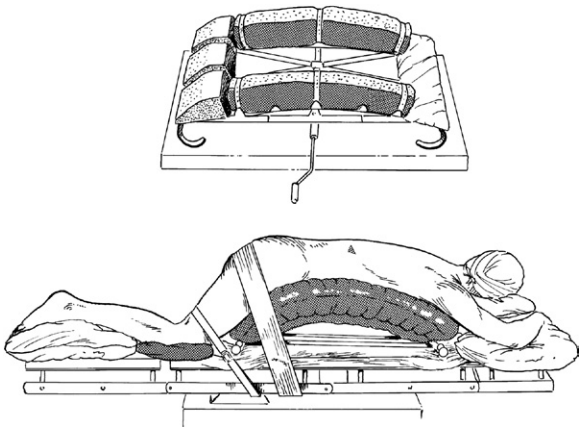

FIGURE **40-9** Spinal operations using a convex saddle frame (Wilson frame).

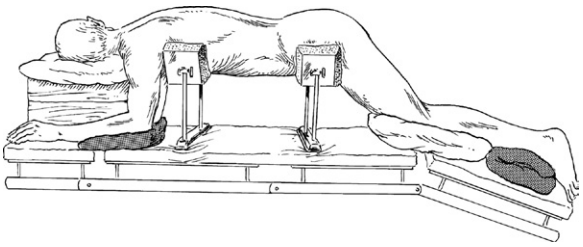

FIGURE **40-10** The Relton adjustable pedestal frame.

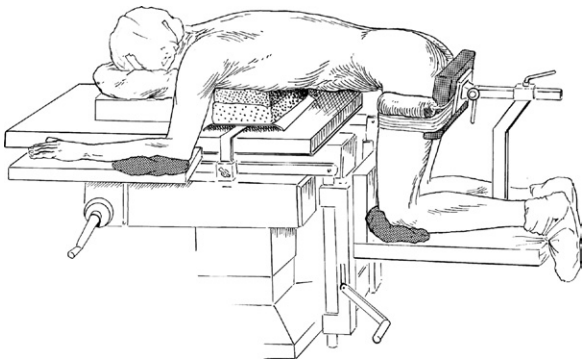

FIGURE **40-11** The Andrews frame.

Scoliosis correction with large-scale instrumentation (e.g., Harrington instrumentation) is a major surgical intervention. The surgeon may choose a posterior, anterior, or thoracoabdominal approach to accomplish the procedure, depending on the location and severity of the defect. The posterior approach requires the patient to be in the prone position. Scoliosis of the lower thoracic to upper lumbar spine may necessitate a thoracoabdominal incision and require the patient to be placed in a semilateral position. Scoliosis exclusively of the thoracic spine requires the patient to be placed in the lateral decubitus position.

Entry into the thoracic cavity necessitates placement of a double-lumen endobronchial tube so the ipsilateral lung can be deflated to facilitate visualization of the thoracic spine. Intubation may be difficult at best if the patient has a severe deformity For surgical correction of scoliosis by spinal fusion with anterior release, the patient is placed in the lateral decubitus position for the thoracotomy incision and requires endobronchial intubation. Depending on the direction of curvature of the thoracic spine, the heart may necessarily be manipulated, which may produce cardiac dysrhythmias. In patients who are myelopathic or have cervical spine instability, a fiberoptic or other assisted device intubation, either awake or after the induction of general anesthesia, may be indicated. This also may be necessary in patients who have undergone previous spinal fusion with limitation of neck extension. In the anesthetized patient, evoked potentials can be measured before and after intubation as well as before, during, and after positioning.[65]

With the large incision and complex dissection required for the multilevel spinal fusions and instrumentation needed to surgically correct the scoliosis, significant blood loss may occur. Blood transfusion is virtually ensured during the course of the procedure. Procedures more likely to be associated with major blood loss are those involving the thoracic spine, particularly for malignancy or trauma. Autologous blood donation, the use of cell salvage devices, and serial hemoglobin and hematocrit determinations and urine output are all used to manage fluid and transfusion therapy. The choice of anesthetic drugs is standard with consideration for evoked potential monitoring and postoperative analgesia as part of the plan.

As described, laparoscopic principles and techniques are beginning to be applied more frequently to spinal-fusion surgery. Spinal fusion via laparoscopy provides the surgeon with enhanced visualization of the surgical site, reduces operative time once the surgeon and staff have acquired and are comfortable with the necessary skills, results in greatly reduced trauma to the surrounding soft tissues, produces dramatically less blood loss, reduces recovery and rehabilitation time, greatly reduces medical costs, contributes to an earlier return to preinjury level of activity, and is aesthetically more pleasing to the patient. It is important to compensate for any hypercarbia that may accompany insufflation of carbon dioxide, particularly during long procedures.

Sudden, dramatic, unanticipated, sustained hypotension requires rapid intervention and assessment of cause. The surgeon should be informed, and together a plan to rapidly determine the cause and initiate appropriate effective treatment measures may be instituted. Because of the close proximity to the spinal column, injury to the aorta can occur during surgery on the thoracic or lumbar spine. In addition to aortic injury, the inferior vena cava, iliac vessels, and common femoral vessels may be damaged as a result of traction during laparoscopic spinal procedures.[77] Injury to these vascular structures can be a truly emergent situation. If the patient is in the prone position, rapid closure of the surgical wound is imperative so the patient can be repositioned to facilitate repair

BOX **40-6**

Recommendations of the ASA Task Force on Perioperative Blindness

- The consensus of the Task Force is that a high-risk patient's vision should be assessed when the patient becomes alert (e.g., in the recovery room, intensive care unit, or nursing floor). If there is concern regarding potential visual loss, an urgent ophthalmologic consultation should be obtained to determine its cause. Additional management may include optimizing hemoglobin or hematocrit levels, hemodynamic status, and arterial oxygenation. To rule out intracranial causes of visual loss, consider magnetic resonance imaging. The Task Force believes that there is no role for antiplatelet agents, steroids, or intraocular pressure–lowering agents in the treatment of perioperative ischemic optic neuropathy.
- There is a subset of patients who undergo spinal procedures while they are positioned prone and receiving general anesthesia who have an increased risk for the development of perioperative visual loss. This subset includes patients who are anticipated before operation to undergo procedures that are prolonged, have substantial blood loss, or both (high-risk patients).
- Consider informing high-risk patients that there is a small, unpredictable risk of perioperative visual loss.
- The use of deliberate hypotensive techniques during spinal surgery has not been shown to be associated with the development of perioperative visual loss.
- Colloids should be used along with crystalloids to maintain intravascular volume in patients who have substantial blood loss.
- At this time, there is no apparent transfusion threshold that would eliminate the risk of perioperative visual loss related to anemia.
- High-risk patients should be positioned with the head level with or higher than the heart when possible. In addition, the head should be maintained in a neutral forward position (e.g., without significant neck flexion, extension, lateral flexion, or rotation) when possible.
- Consideration should be given to the use of staged spinal procedures in high-risk patients.

Adapted from Lee LA, et al. The American Society of Anesthesiologists Postoperative Visual Loss Registry: analysis of 93 spine surgery cases with postoperative visual loss. *Anesthesiology*. 2006;105(4):652-659; Lee LA, et al. Postoperative Visual Loss Study Group. Risk factors associated with ischemic optic neuropathy after spinal fusion surgery. *Anesthesiology*. 2012;116(1):15-24. ASA, American Society of Anesthesiologists.

to the damaged vessel. Volume resuscitation may be required in the event of an injury to a blood vessel. For this reason, it is imperative to have two large-bore IV access sites in addition to verifying the availability of blood. Venous air embolism can occur in certain procedures, and appropriate monitoring and vigilance is required (see Chapter 28).

Postoperative Visual Loss

Postoperative vision loss (POVL) associated with general anesthesia and prone positioning in spinal surgery have been increasing in incidence over the past several decades. The American Society of Anesthesiologists (ASA) developed a Postoperative Visual Loss Registry in an effort to better understand and evaluate this devastating operative complication. Over 93 incidents have been reported between 1999 and 2005.[79] The main causes of visual loss after nonocular surgery are retinal vascular occlusion and ischemic optic neuropathy. Direct pressure to the periorbital region of the eye can cause increased intraocular pressure and blindness as the result of central retinal artery occlusion. The cause of ischemic optic neuropathy (ION) is still unclear. Although it can strike patients of any age, there is an increased incidence in patients less than 18 and more than 65 years of age. The Postoperative Visual Loss Study Group has reported that obese and male patients have an increased risk of developing ION after major spinal surgery in the prone position. Increased intraabdominal, intrathoracic, and intraocular pressure in the prone position may lead to venous congestion and therefore contribute to the problem. Obesity, male sex, Wilson frame use, longer anesthetic duration, greater estimated blood loss, and decreased percent colloid administration were significantly and independently associated with ION after spinal fusion surgery.[80,81] Other researchers have also noted that significant risk factors include male sex, anemia from blood loss greater than 1 liter, surgery lasting over 5 hours, and intraoperative hypotension. Unlike corneal abrasion, the most common eye injury, which is usually self-limiting, the prognosis for visual recovery from POVL is poor.[82]

Most cases of POVL occurring after spinal surgery are bilateral. Visual loss was typically within the first 24 to 48 hours postoperatively. There is usually painless visual loss, an afferent pupil defect or nonreactive pupil, and no light perception, or visual field deficit. Color vision is decreased or absent. Elevated intraocular pressures greater than 40 mmHg from prolonged prone positioning and fluids may be a factor. It is advisable to position a patient's head level with or above the heart, where possible, and in a neutral position.

A foam headrest should be used. Placing the head in pins is also used but is more invasive. For most procedures in which the patient is prone, it is reasonable to use any of the commercially available square foam headrests. It is not advisable to cover the eyes with goggles when the head is positioned prone in a square foam headrest. With a transparent surgical table headpiece, a mirror can enable indirect viewing of the eyes. A foam headrest with a mirror attachment allows eyes to be viewed easily during surgery. Ensure that the eyes are properly positioned and checked intermittently by palpation and visualization. Document eye checks at least every 20 minutes. A horseshoe headrest should not be used because of the greater risk of head movement caused by the surgeon, along with the resulting compression of the eye.[83-87] The ASA Task Force recommendations for the prevention of visual loss are given in Box 40-6.[79,87] A complete discussion of postoperative visual loss can be found in Chapter 21.

FOOT AND ANKLE SURGERY

Each of us is acutely aware of any problems with our ankles or feet. They carry the weight of our bodies around, and we can feel any compromise in their integrity almost immediately. Patients may seek the care of an orthopedic surgeon for problems with their feet, or they may see a doctor of podiatric medicine (DPM). Both of these specialists are highly skilled in the surgical correction of the multitude of problems that occur with the feet and ankles.

The most commonly performed procedures on the ankle involve surgical repair of ankle fractures and fusion of the ankle joint. The Achilles tendon is also a frequent focus of surgery, particularly on more physically active individuals. The most widely known surgical procedures on the feet are bunionectomy

(with or without fusion), correction of hammertoe deformities (with or without fusion), and plantar fasciotomy (either open or endoscopic).

Open repair of ankle fractures is usually accomplished using plates and screws to hold the bone fragment in proper alignment until the fragments grow back together. Ankle fusion (arthrodesis) is performed for a multitude of medical reasons and may involve two or three bones being fused together to provide pain relief and greater joint stability. Incisions are usually made on both the medial and lateral aspects of the ankle joint to allow for optimal surgical access to the involved bones. The fracture is reduced, after which a plate is placed across the fracture site or sites. Holes are drilled with the plate acting as the template, and screws are placed into these holes. For ankle fusions, incisions are typically made across the medial and lateral aspects of the joint, and wires or screws are used to fuse the appropriate bones in place. The incisions are closed, and some type of inflexible stabilizing device is applied (e.g., cast or plaster splints or ambulatory boot) while the patient is under anesthesia. Pneumatic tourniquets are almost always used to keep blood loss at a minimum and provide a clear surgical field.

Bunion deformity usually involves the first, or great, toe. Incision is made along the anterior surface from about midtoe across the metatarsophalangeal joint. The bony deformity is excised. Depending on the variation of the bunionectomy procedure chosen, excision of the bony deformity may be the totality of the procedure, or the angular deformity may be corrected with a screw or wire fusion.

Hammertoe deformity correction involves incision of the anterior surface of the malformed toe or toes. The incision crosses the joint containing the bony deformity. The surgeon dissects down to the joint and excises the bony deformity. Depending on the severity of the deformity, the interphalangeal joint may be fused by inserting a wire.

Plantar fasciotomy is indicated for severe foot pain during or after ambulating or on arising after sleep. Pain results from chronic plantar fasciitis that has not responded to conservative therapy. Open fasciotomy is accomplished via a small incision along the posterior surface of the calcaneus. The plantar fascia is incised to relieve the tension across the plantar arch. Endoscopic plantar fasciotomy is accomplished via two "miniature" incisions, one medial and one lateral, at the beginning of the plantar arch. A small trocar is inserted through these incisions. The sheath of the trocar is slotted to allow visualization of the plantar fascia with the endoscope. The full thickness of the plantar fascia is incised, and the skin incisions are closed.

Anesthetic Management

Patients scheduled for foot or ankle surgery are excellent candidates for regional anesthesia. Most surgical procedures on the foot or ankle can be accomplished within a 2-hour timeframe, often on an outpatient basis. Spinal anesthesia provides sufficient surgical anesthesia to allow completion of most procedures. However, the postanesthesia recovery phase may be unacceptably long and require an overnight stay in the hospital or outpatient facility, which may be unacceptable to the patient.

Nerve blocks are especially effective for surgical procedures on the foot or ankle. Intravenous sedation by either continuous infusion or intermittent bolus can provide amnesia and minimize or eliminate any anxiety the patient may have. The surgeon can inject the surgical site with long-acting local anesthetic (e.g., bupivacaine) to maintain the patient's comfort immediately and for several hours postoperatively.

FOREARM AND HAND SURGERY

Surgical procedures on the hand or forearm may be precipitated by trauma resulting in complex or dislocated fractures to the bones of the forearm, hand, or fingers, or may be performed to alleviate numbness of the hand resulting from compression of the nerves of the forearm or wrist, as in carpal tunnel syndrome. Procedures on the fingers and hand are often relatively quick, requiring 1 hour or less to complete, whereas surgical correction of complex or dislocated fractures of the forearm may require considerable instrumentation and time to complete. For virtually all surgical procedures of the hand and forearm, the pneumatic tourniquet is used.

Anesthetic Management

Patients scheduled for surgical procedures on the forearm or hand are well-suited candidates for regional anesthesia. Ultrasound-guided brachial plexus blockade or an intravenous regional block provide excellent surgical anesthesia for most surgical procedures of the forearm and hand anticipated to require 1 hour or less to accomplish.

For procedures that may require considerable amounts of time to accomplish—those precipitated by traumatic injury, such as complex, comminuted fractures or reconstruction of the vascular and nerve structures of the hand or forearm, for example—the better anesthetic choice may be general anesthesia. Tourniquet pain becomes an issue with longer procedures if regional anesthesia is chosen. Also, for the patient requiring surgery as the result of traumatic injury, the issue of the patient's nothing-by-mouth (NPO) status becomes important. Frequently, trauma patients have eaten or ingested liquids close to the time of the injury. Alcohol ingestion may be involved as well. For these reasons, rapid-sequence induction of general anesthesia may be a more appropriate anesthetic course.

ARTHRITIC SYNDROMES

Of the many arthritic syndromes, two are especially disconcerting: rheumatoid arthritis (RA) and ankylosing spondylitis (AS). Both of these arthritic conditions extend beyond the primary affliction to the skeletal system and orthopedic medicine. They are both also associated with specific concerns related to the airway and should be indicators for a thorough airway assessment in the preoperative period.

In 2010 the American College of Rheumatology and the European League Against Rheumatism revised the classification criteria for RA. It is listed in Box 40-7.[88]

Of particular concern are the effects of RA on the cervical spine, temporomandibular joint, larynx, and pulmonary system. Deposition of rheumatoid nodules causes inflammation of the intervertebral discs and dura, which is expressed as atlantoaxial joint subluxation. The synovium of the temporomandibular joint is also affected by RA and can result in severe limitation of joint range of motion. The cricoarytenoid joints are common sites for rheumatoid nodule deposition. The resultant chronic synovitis may cause fixation of the vocal cords in adduction and airway obstruction. Finally, RA is associated with several forms of pulmonary disease, including pleural effusion, interstitial lung disease, obliterative bronchiolitis, and vasculitis (Box 40-8).

Ankylosing spondylitis is also a chronic inflammatory process. The primary target is the spinal column and surrounding soft tissues. The progressive nature of AS means the spine can be injured by seemingly inconsequential trauma. Patients with AS also may experience cardiac valvular dysfunction, conduction delays, bundle branch blocks, and restrictive lung disease.

BOX **40-7**

The 2010 American College of Rheumatology/ European League Against Rheumatism Classification Criteria for Rheumatoid Arthritis

Who should be tested? The target population includes patients who:
1) Have at least one joint with definite clinical synovitis (swelling)
2) Have synovitis that is not better explained by another disease

Classification Criteria for RA

Add score of categories A-D below. A score of ≥ 6 to 10 is needed for classification of a patient as having definite RA.

	Score
A. Joint involvement	
1 large joint	0
2 to 10 large joints	1
1 to 3 small joints (with or without involvement of large joints)	2
4 to 10 small joints (with or without involvement of large joints)	3
More than 10 joints (at least 1 small joint)	5
B. Serology (at least one test result is needed for classification)	
Negative RF and negative ACPA	0
Low-positive RF or low-positive ACPA	2
High-positive RF or high-positive ACPA	3
C. Acute-phase reactants (at least one test result is needed for classification)	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
D. Duration of symptoms	
Less than 6 weeks	0
6 weeks or more	1

From Aletaha D, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum*. 2010; 62(9):2569-2581; Neogi T, et al. The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis: phase 2 methodological report. *Arthritis Rheum*. 2010;62(9):2582-2591; Aletaha D, Deogi T: 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis*. 2010;69(9):1580-1588.

ACPA, Anticitrullinated protein antibody; *CRP*, C-reactive protein; *ESR*, erythrocyte sedimentation rate; *RA*, rheumatoid arthritis; *RF*, rheumatoid factor.

Anesthetic Management

The primary concern when caring for a patient with either RA or AS is the patient's airway. The mobility of the patient's cervical spine must be meticulously evaluated during the preoperative interview. Any neurologic symptoms that occur during movement of the cervical spine must be thoroughly documented at that time. As a result of RA or AS, cervical mobility may be severely restricted; therefore, the patient may prove to be extremely difficult to intubate. Because of the high risk to these patients from cervical-spine manipulation during direct laryngoscopy for tracheal intubation, awake fiberoptic or other intubation techniques may be the safer course of action. The prudent anesthetic course also may include positioning the patient such that neurologic symptoms remain absent before induction of general anesthesia. The cervical spine must be neutrally positioned throughout any surgical procedure, during emergence, and during transfer to the postanesthesia care unit. Regional anesthesia is a safe approach to extremity surgery in these patients.[71,72]

BOX **40-8**

Types of Pulmonary Diseases Commonly Found in Rheumatoid Arthritis Patients

- Pleural effusion
- Intrapulmonary nodules
- Rheumatoid pneumoconiosis (Caplan syndrome)
- Interstitial lung disease
- Vasculitis
- Obliterative bronchiolitis
- Upper lobe fibrosis
- Pulmonary infections
- Bronchogenic carcinoma

SUMMARY

Orthopedic surgical procedures are varied and require a wide variety of anesthetic plans. The patient's health history and acceptability of various anesthetic techniques, the proposed surgery and its duration, the patient's intraoperative position, and the need for postoperative pain management are important considerations in the planning and preparation for a safe and comfortable outcome. In addition, many of these procedures carry high risk for blood loss, so preoperative type and screen are indicated in nearly all of these cases. The anesthetic plan must adapt to the needs of the patient and the proposed surgery rather than expect the patient to adapt to one anesthetic technique.

Growth in orthopedics over the last few decades has increased not only options and techniques but also a linear increase in patient outcomes. The invention of the arthroscope has diminished some of the severity of certain repairs and has provided a diagnostic tool for surgeons. Coupled with this is a decreased length of stay and fewer side effects from anesthesia. Trauma and high-profile surgeries corresponding to the increasing geriatric population are challenging and require techniques that reduce complications and provide postoperative pain management.

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The Immune System and Anesthesia

CHAPTER 41

◆ *Michael P. O'Donnell*

The field of immunology addresses the body's defense mechanisms against pathogens, such as bacteria and viruses that have the potential to trigger tissue injury and disease. Protection from infection and disease depends on the functions of particular leukocytes, the phagocytes and lymphocytes, with the assistance of auxiliary cells such as mast cells, basophils, and platelets (Table 41-1).[1-3] Immune responses involve not only these various cell types, but also soluble mediator molecules secreted by the cells. These soluble mediators include *cytokines*, a superfamily of peptide molecules that regulate the actions of immune system cells (Box 41-1).

Two components of immunity provide defense against invading pathogens: the innate immune system and the adaptive (acquired) immune system. This chapter highlights immune system physiology and pathology, including the effects of human immunodeficiency virus (HIV) on the immune system, with particular consideration of the effects of anesthesia on immune function.

THE IMMUNE SYSTEM

Innate Immune System

Innate immunity is nonspecific, that is, it provides defense against a very large number of pathogens, rather than being directed at one specific microorganism or type of microorganism. Components of innate immunity include physical barriers such as the skin and lung alveoli, the pathogen-hostile environment of the gastrointestinal tract, leukocytes whose primary function is phagocytosis and destruction of invading pathogens, and soluble molecules such as interferons and the complement system.[1-3]

Phagocytes

Polymorphonuclear neutrophils (PMNs) and macrophages are the primary phagocytes of the immune system. Polymorphonuclear neutrophils and monocytes, the cellular precursors of tissue macrophages, are generated from pluripotent hematopoietic stem cells in the bone marrow (Figure 41-1). Both cell types are continually released to the blood, and many are stored in the marrow until mobilized for defense. Chemical substances known as *colony-stimulating factors* that enter the circulation from an area of infection are transported to the marrow to stimulate production and release of PMNs and monocytes. Colony-stimulating factors are members of the cytokine superfamily (see Box 41-1).

After release from bone marrow, PMNs and monocytes circulate for a short time (less than 24 hours) in the blood before moving either directly across, or through pores between, venule endothelial cells to enter tissues. This process is known as *diapedesis*. Transendothelial movement of PMNs and monocytes and their subsequent movement within tissue to a site of inflammation are not random events, but rather are orchestrated by numerous chemotactic substances that include chemokines produced by endothelial cells, bacterial and viral components, and products C3a and C5a of the blood complement system (Figure 41-2). Production of endothelial-cell chemokines and adhesion molecules, which permit leukocytes to "stick" to the endothelium prior to diapedesis, is stimulated by proinflammatory cytokines, in particular, tumor necrosis factor-alpha (TNF-α) produced by activated macrophages (Figure 41-3).

The primary function of PMNs and macrophages is phagocytosis of pathogens such as bacteria and viruses. In this process, the phagocyte engulfs and destroys the foreign agent. Of critical importance is the ability of the phagocyte to distinguish between what is foreign and what is self. To this end, phagocytes have receptors that recognize carbohydrate and lipid moieties, known as *pathogen-associated molecular patterns* (PAMPs), present on cell surfaces of many pathogens but typically not on cells of the host. An example of a microbial PAMP is lipopolysaccharide in the cell walls of gram-negative bacteria. Phagocyte recognition of PAMPs permits the phagocyte to bind directly to the pathogen.

Phagocyte selectivity also can be provided by the process of opsonization, in which serum components bind to the pathogen and permit indirect recognition by phagocytes. Antibodies directed against a pathogen (and produced as part of acquired immunity) act as opsonins by binding to the pathogen and subsequently to antibody receptors on the phagocyte cell membrane (Figure 41-4). Alternatively, the complement product C3b may act as an opsonin, with subsequent binding of C3b to its receptors on phagocyte cell membranes. Phagocyte binding to a pathogen is followed by endocytosis of the pathogen and its intracellular destruction by lysosomal enzymes and products of the phagocyte respiratory burst, which include superoxide ion, hydrogen peroxide, and nitric oxide (Figure 41-5).

Although some macrophages are mobile and migrate through tissues in response to chemotactic signals, many are fixed within tissues for long periods of time (resident macrophages) as part of the mononuclear phagocyte system (also called the *reticuloendothelial system;* Figure 41-6). This system includes the network of monocytes, mobile macrophages, and fixed macrophages that provides phagocytic function in body tissues. The resident macrophages are particularly important in those tissues potentially exposed to large amounts of pathogens, that is, skin, lymph nodes, lung alveoli, liver sinusoids, and the spleen. When these macrophages encounter a pathogen, a number of responses are rapidly set into play: (1) phagocytosis of the pathogen, which provides a first line of defense against infection, (2) secretion of chemotactic mediators that promote infiltration of leukocytes to the site of infection, (3) secretion of colony-stimulating factors that mobilize PMNs and monocytes from the bone marrow, and (4) secretion of proinflammatory cytokines such as TNF-α and interleukin-1 (IL-1). Neutrophil infiltration provides a rapid second line of defense against the pathogen, while a delayed but potent third line of defense occurs as infiltrating monocytes mature into macrophages, and lymphocytes migrate to the area of infection.

TABLE 41-1 Cellular Components of Immunity

Components	Functions
Phagocytes	
Polymorphonuclear neutrophils (PMNs)	Phagocytosis and destruction of microorganisms; contain bactericidal substances and produce bactericidal reactive oxygen molecules
Monocytes	Circulating cells of the mononuclear phagocyte system; after entering tissues, monocytes mature into macrophages
Macrophages	Mobile and fixed tissue cells of the mononuclear phagocyte system; perform phagocytosis and destruction of microorganisms, present antigen to helper T (T_H) cells and secrete cytokines
Eosinophils	Provide defense against parasitic infections and perform phagocytosis of allergen-antibody complexes formed in an allergic response
Lymphocytes	
Natural killer (NK) cells (also called *large granular lymphocytes* [LGLs])	Destruction of virus-infected "self" cells and tumor cells; secrete cytokines
B lymphocytes	Differentiate into plasma cells that secrete antibodies; present antigen to T_H cells
Helper T lymphocytes (T_H cells)	Secrete cytokines that stimulate T_H cell proliferation and activation of B lymphocytes, cytotoxic T lymphocytes, and macrophages
Cytotoxic T lymphocytes (CTLs)	Engage antigen and secrete pore-forming proteins known as *perforins* into foreign cell membrane; secrete granzymes that destroy the targeted cell
Auxiliary Cells	
Mast cells and basophils	Release histamine and other proinflammatory mediators responsible for hyperemia, increased vascular permeability, and pain
Dendritic cells	Present antigen to T_H cells
Platelets	Participate in coagulation and "walling off" areas of inflammation; secrete proinflammatory mediators

BOX 41-1

Cytokines

- Cytokines are peptide molecules that regulate the actions of immune system cells.
- The cytokine superfamily includes interferons (IFNs), interleukins (ILs), tumor necrosis factor-alpha (TNF-α), colony-stimulating factors (CSFs), and chemokines (chemotactic cytokines).
- IFNs have antiviral activity and act to suppress spread of viral infection; IFN-α and IFN-β are produced by cells already infected by virus, and IFN-γ is produced by activated NK cells and T_H1 lymphocytes.
- IL-1 and IL-6 are produced by several cell types, including lymphocytes and macrophages.
- IL-2 is produced by T_H1 lymphocytes and promotes proliferation and function of T lymphocytes, B lymphocytes, and natural killer (NK) cells.
- IL-4 and IL-10 are produced by T_H2 lymphocytes; IL-4 activates B lymphocytes.
- IL-6 stimulates hepatocytes to release acute phase proteins such as C-reactive protein (CRP).
- IL-12 is produced by antigen-presenting cells (APCs) and promotes differentiation of T_H0 lymphocytes into T_H1 lymphocytes.
- TNF-α is released from activated macrophages and T_H1 lymphocytes.
- IFN-γ, IL-1, IL-6, IL-12, and TNF-α are important proinflammatory cytokines.
- IL-4 and IL-10 are important antiinflammatory cytokines.
- Granulocyte, monocyte, and granulocyte-monocyte CSFs are released from activated macrophages and vascular endothelial cells and stimulate bone marrow to release PMNs and monocytes into the circulation.
- Chemokines are produced by venule endothelial cells and activated macrophages and act to attract leukocytes to an area of infection.

Adapted from Rang HP, et al. *Rang and Dale's Pharmacology*. 7th ed. Edinburgh: Churchill Livingstone; 2012.

Phagocytosis and breakdown of pathogens also permits macrophages to present chemical components (e.g., peptide fragments) of pathogens to cells of the acquired immune system. In this way, macrophages behave as "antigen-presenting cells" to recruit the acquired immune system and greatly augment the body's defense responses to pathogens.

Natural Killer Cells

Another cellular component of the innate immune system is the natural killer (NK) cell. These cells have some morphologic resemblance to lymphocytes, and hence are also referred to as *large granular lymphocytes* (see Table 41-1). NK cells develop in the bone marrow (see Figure 41-1), though the exact mechanism of their differentiation from precursor cells is not well understood. NK cells are potent killers of virus-infected "self" cells. Although leukocytes known as *cytotoxic T lymphocytes* (CTLs; discussed later) destroy many virus-infected cells, some viruses (e.g., herpes simplex virus [HSV]) evade detection by these lymphocytes. Fortunately, NK cells can recognize and kill HSV-infected cells. The mechanism by which NK cells kill virus-infected cells is the same as that by which CTLs destroy infected self-cells and foreign cells. The NK cell binds to the infected cell, secretes a pore-producing protein known as *perforin* into the infected cell membrane, and then releases cytotoxic proteolytic enzymes into the infected cell.

Natural killer cells have other key functions. They are the main immune cells of the pregnant uterus, where they act to protect the uterus and the fetus from viral infections during pregnancy. NK cells are very important in the surveillance of tumor cells (i.e., transformed self-cells) and can destroy some tumor cells. They also release cytokines that influence the immune response to pathogens. One key cytokine released by NK cells is interferon-gamma (IFN-γ).

Interferons

As noted in Box 41-1, the interferons (IFNs) are cytokines with antiviral activity. Indeed, the name *interferon* derives from the ability of these substances to "interfere" with viral replication. There are two main IFN families: type I and type II. Type I IFNs include IFN-α and IFN-β, which are released from many cell types within hours after initiation of viral infection. These cytokines act on neighboring

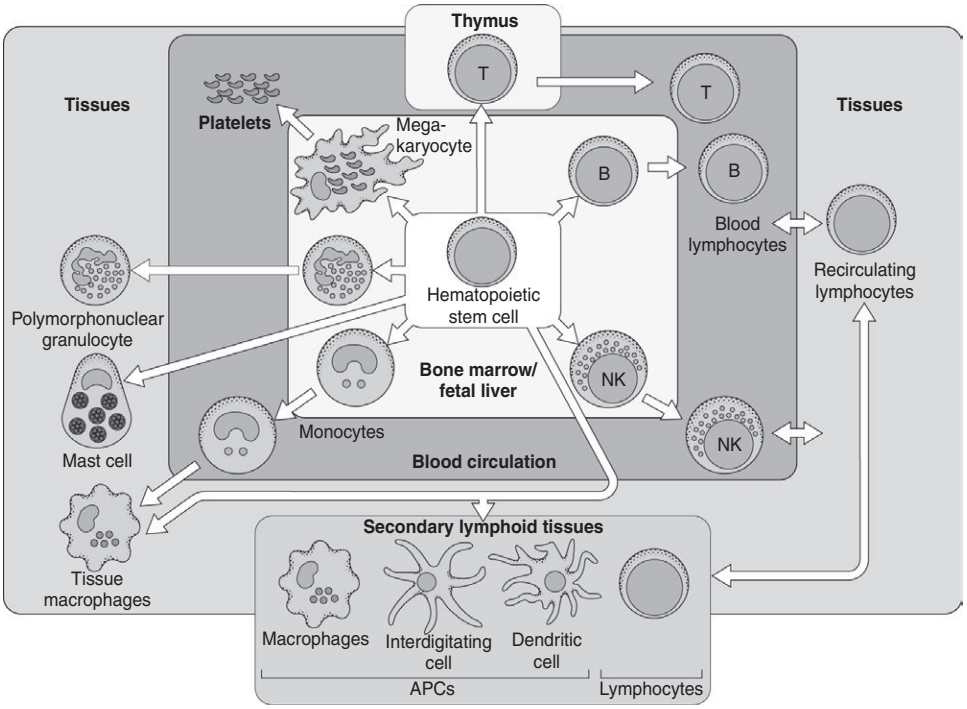


FIGURE **41-1** All immune cells originate from hematopoietic stem cells. Polymorphonuclear cells and monocytes are released from bone marrow to the circulation and then pass into tissues. B cells mature in the fetal liver and postnatal bone marrow, and T cells mature in the thymus gland. These lymphocytes are released into the circulation and pass into tissues. Other cells that originate from hematopoietic stem cells include mast cells, platelets, antigen-presenting cells (APCs), and natural killer (NK) cells. (From Male D, et al. *Immunology*. 8th ed. Philadelphia: Saunders; 2013:18.)

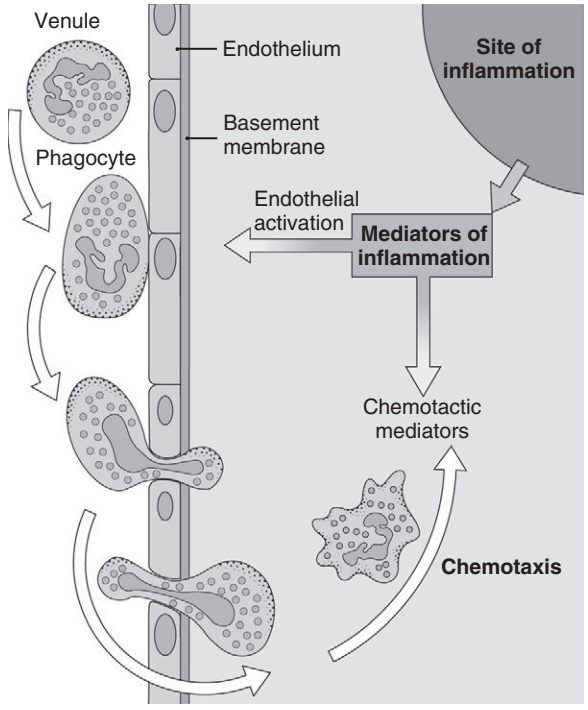


FIGURE **41-2** Infection or tissue injury causes inflammation and release of inflammatory mediators, some of which stimulate chemotaxis of phagocytes to the site of inflammation. Chemokines stimulate phagocytes to stick to the venular endothelium and undergo migration across the vessel wall (diapedesis). Phagocytes then move to the site of inflammation in response to a concentration gradient of chemotactic molecules such as complement product C5a. (From Male D, et al. *Immunology*. 8th ed. Philadelphia: Saunders; 2013:14.)

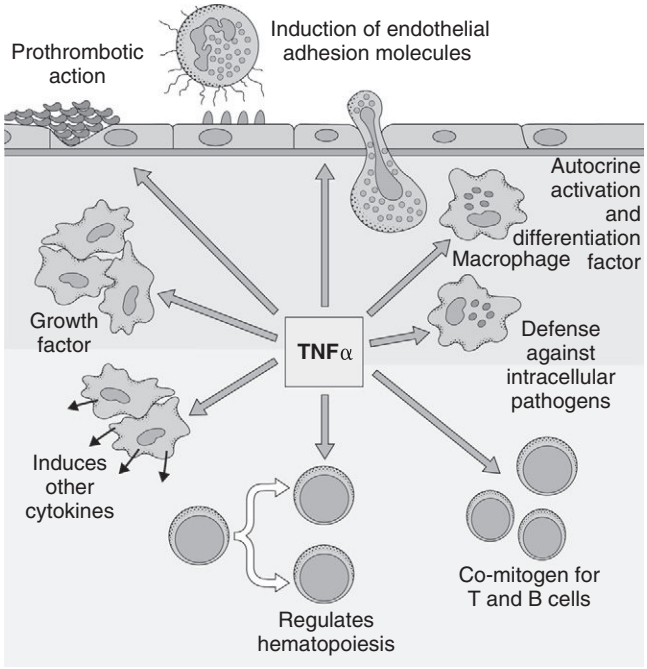


FIGURE **41-3** The cytokine TNF-α plays a central role in inflammation. Among its proinflammatory actions, it promotes clotting, leukocyte adhesion and diapedesis, macrophage activation, and cytokine production by other cells. (From Male D, et al. *Immunology*. 8th ed. Philadelphia: Saunders; 2013:112.)

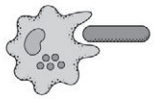
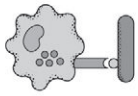
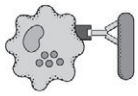
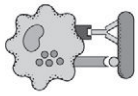
Phagocyte	Opsonin	Binding
1 	–	±
2 	Complement C3b	++
3 	Antibody	++
4 	Antibody and complement C3b	++++

FIGURE **41-4** Phagocytes have some intrinsic ability to bind and phagocytize pathogens *(1)*. Phagocytosis is enhanced if the pathogen has been opsonized by complement product C3b *(2)* or antibody *(3)*. Phagocytes have C3b and Fc receptors that bind opsonized pathogens. Phagocytosis is greatly enhanced if both C3b and antibody opsonize the pathogen *(4)*. (From Male D, et al. *Immunology*. 8th ed. Philadelphia: Saunders; 2013:10.)

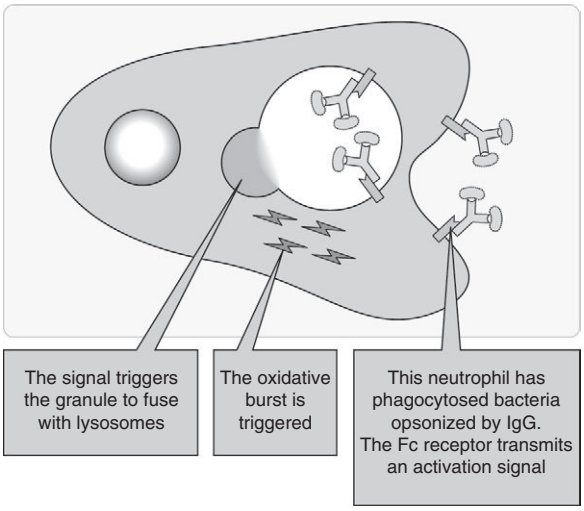


FIGURE **41-5** Mechanism of phagocyte killing of pathogen. Opsonized pathogen undergoes phagocytosis, triggering the respiratory (oxidative) burst and fusion of the phagocytic granule with intracellular lysosomes, which digest the pathogen. (From Nairn R, Helbert M. *Immunology for Medical Students*. 2nd ed. Philadelphia: Mosby; 2007.)

noninfected cells in a paracrine fashion to prevent spread of the viral infection. In addition, type I IFNs promote proliferation and activation of NK cells, which can bind to and destroy virus-infected cells. Synthetic IFN-α produced by recombinant technology is used to treat hepatitis B infection and some neoplasms. Recombinant IFN-β has been used successfully to reduce nervous system inflammation in some patients with multiple sclerosis.

Type II IFN is IFN-γ released from activated NK and T lymphocytes. Like the type I IFNs, IFN-γ can exert protective antiviral activity in noninfected cells, but more importantly it serves to activate macrophages, promote further NK-cell activity, and stimulate differentiation of T lymphocytes. Synthetic IFN-γ is used for treatment of chronic granulomatous disease (discussed later).

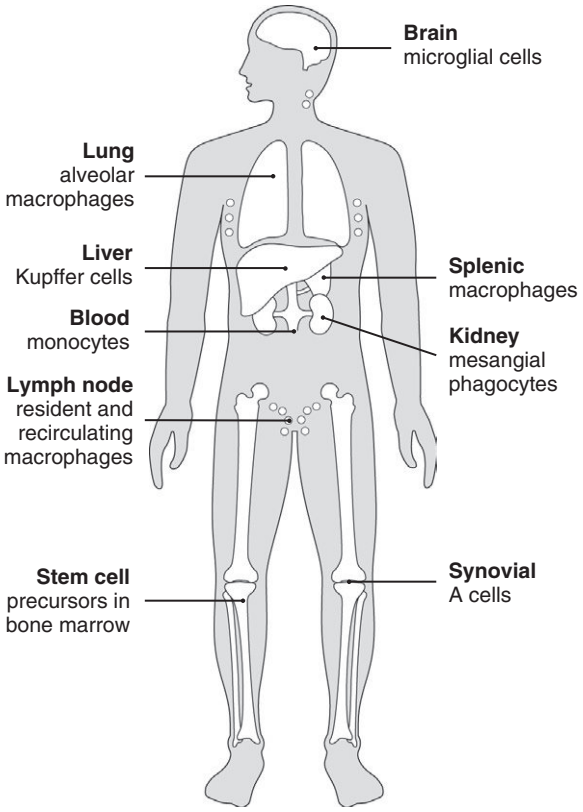


FIGURE **41-6** Cells of the mononuclear phagocyte system are located in many tissues and organs. These cells all derive from blood monocytes that originate from hematopoietic stem cells in the bone marrow. (From Male D, et al. *Immunology*. 8th ed. Philadelphia: Saunders; 2013:5.)

Complement

The complement system is a collection of plasma proteins produced mainly by the liver; it plays a key role in both innate and acquired immunity. When the complement system is activated, a cascade of reactions occurs in which a particular complement component catalyzes the production of the next component in the cascade and so on until the final product is produced. The main proteins of the complement system are labeled C1 through C9. The complement cascade can be triggered by an antigen-antibody reaction that activates C1 (the classical pathway) or by direct microorganism interaction with C3 (the alternative and lectin pathways). In either case, activation of the complement cascade generates products that cause opsonization, chemotaxis, and activation of mast cells and basophils. The final product of the cascade is a complex of five complement factors—C5b6789—that acts as a membrane attack complex by inserting cytolytic pores into pathogen cell membranes (Figure 41-7).

Acquired Immune System

Acquired, or adaptive, immunity is specific, that is, the immune responses are directed against a particular antigen, which is usually a component of a microorganism or foreign tissue.[1-3] In some cases, though, a "self" antigen may generate an autoimmune response that results in tissue injury. By one definition, an antigen is a chemical substance with a molecular weight greater than or equal to 8000 Da, and thus antigens are typically polypeptides or large polysaccharides.[3] Acquired immunity directed against a particular antigen is usually directed at one or more small regions, known as *epitopes*, within the antigen structure.[1-3]

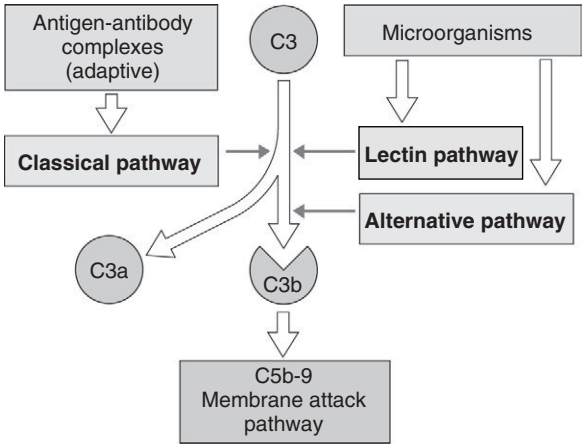


FIGURE **41-7** Three pathways can serve to activate the complement cascade. Antigen-antibody reaction typically activates the classical pathway. The alternative and lectin pathways do not require antibody and are directly activated by chemical groups on the pathogen surface. Thus the alternative and lectin pathways serve innate immunity, whereas the classical pathway is linked to the adaptive immune system. All three pathways convert C3 to C3b as the central event of the complement cascade. C3b can then promote the formation of the membrane attack complex. (From Male D, et al. *Immunology*. 8th ed. Philadelphia: Saunders; 2013:72.)

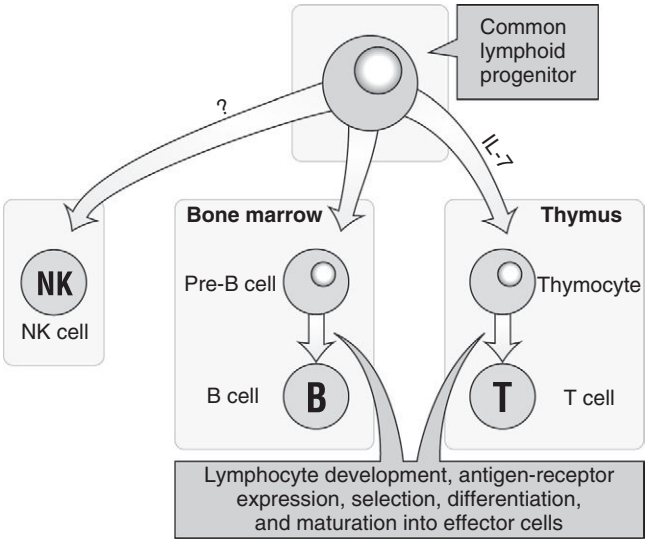


FIGURE **41-8** Development of B cells, T cells, and natural killer (NK) cells from a common lymphoid progenitor. B cells begin maturation in the bone marrow, and T cells mature in the thymus gland. NK cells develop in the bone marrow, although the mechanism of their differentiation is unclear. (From Nairn R, Helbert M. *Immunology for Medical Students*. 2nd ed. Philadelphia: Mosby; 2007.)

Acquired immunity depends fundamentally on lymphocytes, which comprise approximately 30% of circulating leukocytes. There are two main families of lymphocytes: B lymphocytes (B cells) and T lymphocytes (T cells). B lymphocytes are responsible for humoral immunity, which is provided by soluble antibodies directed against a particular antigen. T lymphocytes are responsible for cell-mediated immunity directed against a particular antigen.

Maturation of lymphocytes occurs in primary lymphoid tissues: the thymus gland, fetal liver, and bone marrow. Initially, some pluripotent hematopoietic stem cells differentiate to become lymphoid progenitor cells, which in turn differentiate to become either pre-T cells (thymocytes) or pre-B cells (Figures 41-1 and 41-8). Pre-T cells migrate from the marrow to the thymus gland, where they are processed to become mature T cells directed against specific antigens. T-cell maturation is characterized in part by the appearance of T-cell receptors (TCRs) on the cell membranes. Specificity of a particular T cell for an antigen reflects the specificity of its TCRs to recognize and bind that antigen. As a critical part of thymic processing, T cells that recognize and bind self-antigens undergo programmed cell death, known as *apoptosis*, whereas T cells that recognize foreign antigens expand and migrate to secondary lymphoid tissues—lymph nodes, adenoids, and tonsils; submucosal lymph tissue; and the spleen. Literally thousands of different T-cell clones develop in the thymus gland, each clone having TCRs directed against a particular antigen.

Distinct populations of T cells are produced during thymic maturation. The two main populations are $CD4^+$ T cells, also known as *helper T (Th) cells*, and $CD8^+$ T cells, also known as *cytotoxic T lymphocytes* (CTLs). (The abbreviation *CD* refers to "cluster of differentiation" and indicates a particular cell-membrane marker molecule that can be used to identify the hematopoietic cell type.) Naive helper T cells (Th0 cells) have not been exposed to antigen and can differentiate into several subsets, including Th1 and Th2 cells, based on the nature of an ongoing immune response and cytokines present in the local environment (Figure 41-9).

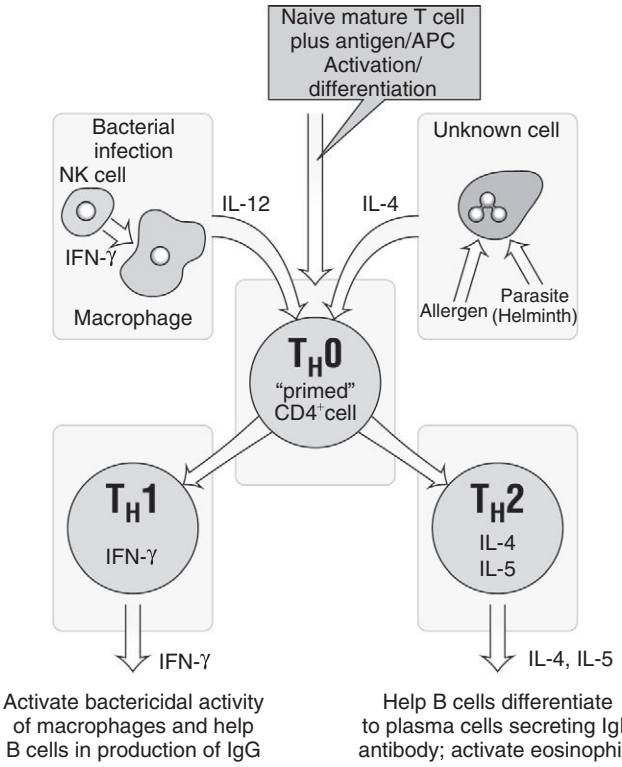


FIGURE **41-9** Differentiation of T helper subsets. When a naive, mature T helper cell is presented antigen by an antigen-presenting cell (APC), it becomes "primed" to differentiate into either a Th1 or Th2 cell. Preference of differentiation is driven by the nature of the infection and the local cytokine environment. After differentiation, Th1 cells secrete interferon-gamma (IFN-γ) and promote cellular immunity, and Th2 cells secrete interleukin (IL)-4 and -5 and promote humoral immunity. Th1 = T_H1 and Th2 = T_H2. (From Nairn R, Helbert M. *Immunology for Medical Students*. 2nd ed. Philadelphia: Mosby; 2007.)

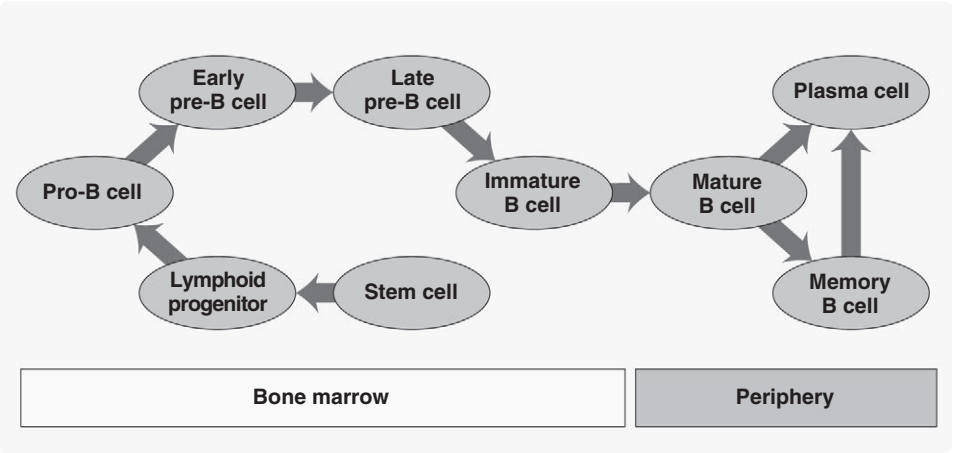


FIGURE **41-10** Stages of B-cell development. After B-cell release from the bone marrow, maturation is completed in the periphery. When activated by exposure to antigen, mature B cells differentiate into antibody-secreting plasma cells and proliferate to form memory B cells that provide for clonal expansion. (From Nairn R, Helbert M. *Immunology for Medical Students*. 2nd ed. Philadelphia: Mosby; 2007.)

Th1 cells promote the function of the mononuclear phagocytes, whereas Th2 cells promote the function of B lymphocytes.

Development of B cells begins in the fetal and postnatal bone marrow and is completed in secondary lymphoid tissues such as the spleen and lymph nodes (Figure 41-10). As maturation proceeds, B cells that recognize self-antigens undergo apoptosis and are not released into the blood. Those B cells that do leave the bone marrow and migrate to secondary lymphoid tissue acquire two types of immunoglobulin (Ig) molecules on the cell surface, IgM and IgD. These surface-bound Ig molecules are functionally analogous to the TCRs on surfaces of mature T cells, that is, they recognize and bind specific antigens. Other Ig molecules that may be expressed on B-cell surfaces include IgA, IgG, and IgE. Similar to the situation for T cells, thousands of different B-cell clones are produced, each clone having surface Ig molecules directed against a particular antigen.

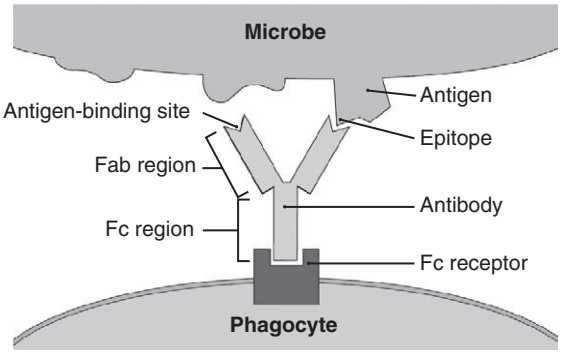


FIGURE **41-11** The Fab region of an antibody binds to a small portion (epitope) of an antigen on the pathogen surface. The "stem" of the antibody is its Fc region, which binds to phagocyte Fc receptors to promote phagocytosis. (From Male D, et al. *Immunology*, 8th ed. Philadelphia: Saunders; 2013:10.)

Humoral Response to Antigen

When a mature B cell encounters and binds antigen, it proliferates and differentiates into plasma cells that secrete soluble antibodies directed against the antigen. In addition, memory B cells are produced that expand the clone of B cells directed against that antigen. The secreted antibodies are Ig molecules and are members of the gamma globulin fraction of serum proteins. Five main classes of Ig molecules exist, which differ substantially in molecular size and charge: IgA, IgD, IgE, IgG, and IgM. Immunoglobulin G comprises approximately 70% of serum immunoglobulins, whereas IgA and IgM comprise approximately 20% and 10%, respectively. Normally, serum levels of IgD and IgE are very low. Rather, IgD is located primarily on B-cell surfaces, where it serves to bind antigen, whereas IgE is found primarily on the surfaces of tissue mast cells and circulating basophils and plays a role in hypersensitivity reactions.

An Ig molecule consists of two or more pairs of light chain–heavy chain polypeptide combinations. The variable, or Fab, regions of an Ig molecule are regions in which the amino acid sequence permits specific, high-affinity binding to antigen (hence, the variable regions "vary" in amino acid sequence among antibody molecules). The constant, or Fc, portion of Ig molecules has a relatively "constant" amino acid sequence that can bind to Fc receptors on phagocyte cell membranes (Figure 41-11).

Antibodies promote antigen removal by different mechanisms, including activation of the classical complement pathway, opsonization of a pathogen for phagocytosis, and binding to a pathogen to permit recognition by NK cells. Recently, monoclonal antibodies (mAbs) (i.e., antibodies with very high specificity for antigen) have been developed by recombinant technology for treatment of diseases such as rheumatoid arthritis, Crohn's disease, and breast cancer, as well as for other applications (Box 41-2). Adalimumab and infliximab are mAbs directed against the proinflammatory mediator TNF-α.

Antibodies can provide effective defense against toxins or pathogens in the extracellular compartment. However, many pathogens exist within cells of the host, and defense against these pathogens requires a second component of the adaptive immune response—cell-mediated immunity provided by T lymphocytes.

T-Lymphocyte Response to Antigen

Cell-mediated immunity requires "presentation" of antigen to T lymphocytes by infected cells or antigen-presenting cells (APCs) such as dendritic cells, macrophages, and B lymphocytes. What is actually presented to the T cell is a small portion of the parent antigen that has been processed, or degraded, by the presenting cell. The antigen fragment is presented bound to a major histocompatibility (MHC) molecule on the presenting cell surface. T-cell receptors on T cells directed against the antigen then recognize and bind the antigen-MHC complex (Figure 41-12).

BOX **41-2**

Monoclonal Antibodies

The monoclonal antibodies (mAbs) are genetically engineered immunoglobulins (IgGs) that react with specific molecular targets. They may be part mouse/part human (termed *chimeric* or *humanized*, depending on the degree of mouse Ig sequences) or fully human. In chimeric and humanized mAbs, antigen-recognizing portions of mouse antibodies are joined to the framework of a human IgG molecule.

- **Abciximab:** Chimeric mAb against the clotting receptor GpIIb-IIIa on platelets; used to prevent clotting in patients undergoing coronary angioplasty.
- **Adalimumab:** Humanized mAb against the cytokine TNF-α; used for rheumatoid arthritis.
- **Alemtuzumab:** Humanized mAb against an antigen on T and B lymphocytes; used to treat B-cell leukemia.
- **Basiliximab:** Chimeric mAb against the receptor for the cytokine interleukin-2 on activated T cells; used in acute rejection of kidney transplants.
- **Daclizumab:** Humanized mAb against the receptor for the cytokine interleukin-2 on activated T cells; used in acute rejection of kidney transplants.
- **Etanercept:** Fusion protein for the tumor necrosis factor used in therapy for rheumatoid arthritis.
- **Infliximab:** Chimeric mAb against the cytokine TNF-α; used for rheumatoid arthritis and Crohn's disease.
- **Omalizumab:** Humanized mAb against the binding of IgE to the high-affinity IgE receptor on the surface of mast cells and basophils; used for the treatment of asthma.
- **Palivizumab:** Humanized mAb against a protein of respiratory syncytial virus (RSV); used to treat RSV infection in children.
- **Rituximab:** Humanized mAb against the cytokine CD20 receptor on B cells; used in non-Hodgkin lymphoma.
- **Trastuzumab:** mAb against HER2; used for breast cancer treatment.

Adapted from Rang HP, et al. *Rang and Dale's Pharmacology*. 7th ed. Edinburgh: Churchill Livingstone; 2012.

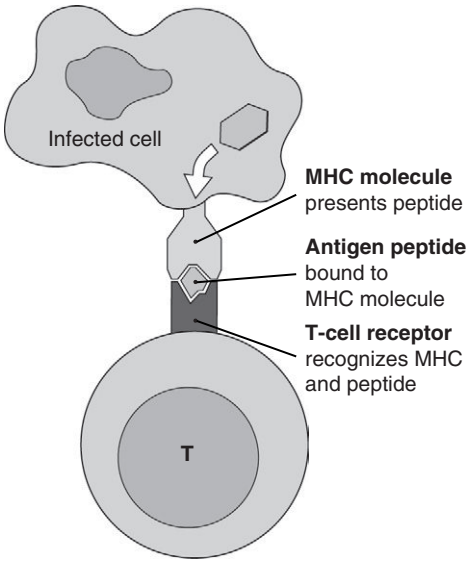


FIGURE **41-12** General mechanism of antigen presentation to T cells. A surface major histocompatibility complex (MHC) molecule presents a peptide portion of pathogen in an infected cell. The T-cell receptor recognizes and binds the MHC molecule/peptide combination. (From Male D, et al. *Immunology*. 8th ed. Philadelphia: Saunders; 2013:10.)

The MHC is a collection of genes that serve immune recognition in all mammals. There are two types of MHC molecules that function in immune recognition. Class I molecules are present on the surfaces of all nucleated cells, and class II molecules are present on the surfaces of APCs. In humans, the MHC is known as the *human leukocyte antigen* (HLA). Three regions, or loci, on the HLA encode for MHC class I molecules found on nucleated cell surfaces. Collectively, these three regions comprise more than 100 genes and are known as *HLA-A*, *HLA-B*, and *HLA-C*. A separate region on the HLA, known as *HLA-D*, encodes for MHC class II molecules found on APCs. Within this region are three loci, known as *HLA-DP*, *HLA-DQ*, and *HLA-DR*. A key characteristic of the HLA is the high degree of polymorphism of the MHC molecules for which it encodes. An individual's HLA type (haplotype) is determined by the MHC molecules expressed on that person's cell membranes. Genetic variability in HLA type influences susceptibility to infection and autoimmune disease and rejection of transplanted tissue. Tissue typing prior to organ transplantation involves characterization of the HLA types of donor and recipient to determine whether an acceptable "match" is present.

MHC class I molecules present antigen derived from an intracellular pathogen, such as a virus, that has infected the cell. The antigen-MHC class I complex is presented to CTLs, which bind the complex and destroy the infected cell. MHC class II molecules present antigen derived from pathogens that have undergone phagocytosis and subsequent processing. The antigen-class II complex is presented to Th0 cells, which can then differentiate into several subsets of Th cells, two of which are Th1 and Th2 cells (see Figure 41-9). The Th1/Th2 ratio is determined by the nature of the immune response and the local cytokine environment. Interleukin-12 produced by APCs favors Th1 differentiation. Th1 cells secrete IFN-γ, which activates mononuclear phagocytes. Th2 cells secrete IL-4 and IL-5, which promote conversion of B lymphocytes to antibody-secreting plasma cells and stimulate mast cells to release inflammatory mediators. Activation of T cells in response to antigen also promotes T-cell production of IL-2, which acts locally to promote T-cell proliferation and augment the immune response to the antigen.

Vaccination

A key characteristic of the immune response to antigen is clonal expansion of specific B and T lymphocytes directed at the antigen. Clonal expansion allows a more rapid and vigorous immune response on subsequent exposure to the antigen. Vaccination is a process that produces acquired immunity against specific diseases by deliberate exposure of an individual to particular antigens. Vaccination against diseases such as typhoid, cholera, pertussis, and influenza is accomplished by administration of dead organisms that have retained their chemical antigens (epitopes), yet cannot cause an actual disease state. Toxoid vaccines are chemical modifications of toxins produced by pathogens such as tetanus and diphtheria. Attenuated microorganisms are mutated pathogens that themselves do not readily produce disease, but may be used to produce immunity against diseases such as poliomyelitis, measles, rubella, and smallpox.

Passive immunity is produced by administering preformed antibody to provide protection against an invasive pathogen or toxin,

often as a lifesaving maneuver. For example, passive immunity may be a maneuver used to treat botulism, diphtheria, or snakebite. Preformed antibodies are obtained from human or animal blood after immunization against a particular antigen.

Inflammation

Inflammation is the collective response to tissue injury, which can be caused by invasion of infectious microorganisms, toxins, or trauma. The inflammatory response consists of several components: localized vasodilation and increased blood flow; increased capillary permeability and extravasation of plasma proteins, including complement and coagulation factors; and chemotactic movement of leukocytes to the site of injury. The clinical manifestations of inflammation include erythema, localized edema, and pain.[1,2]

Both the innate and acquired immune systems participate in the production of inflammation. Communication between the two immune systems is provided by a network of peptide mediators known as cytokines (see Box 41-1). Normally these substances act locally to regulate the immune response and may exert synergistic or inhibitory interactions in the regulation of immune cell activity. If produced in high amounts during an exuberant inflammatory response, though, some cytokines may demonstrate measurable blood levels and exert adverse systemic effects.

When resident macrophages encounter a pathogen, they become activated to phagocytize the pathogen and secrete proinflammatory cytokines such as TNF-α, IL-1, IL-6, and IL-12. Among its various actions, TNF-α stimulates the production of endothelial-cell adhesion molecules and chemokines, which are necessary for leukocyte infiltration to the site of infection (see Figure 41-3). Overproduction of TNF-α can have deleterious local and systemic effects. Indeed, high circulating levels of TNF-α are characteristic of chronic major illness and systemic inflammatory response syndrome.

Like TNF-α, IL-1 stimulates endothelial-cell adhesion molecule production. It also has other actions, one of which is to alter the hypothalamic core temperature set-point and produce fever. One important consequence of increased body temperature is more rapid lymphocyte proliferation to combat infectious microorganisms. IL-1 also activates T lymphocytes, thereby recruiting those cell types against the infection. IL-12 promotes preferential differentiation of Th0 cells to the Th1 subtype and activates NK cells. Both Th1 cells and NK cells release IFN-γ, which enhances NK-cell activity and inhibits Th2 cell function. IL-6 stimulates B lymphocytes and may play a role in wound healing. In addition, a recent study in mice has provided evidence that IL-6 can directly stimulate adrenocortical secretion of glucocorticoids, providing a unique mechanism by which the inflammatory response can provoke stress hormone secretion.[4]

TNF-α, IL-1, and IL-6 stimulate production of acute-phase proteins.[1,2] These serum proteins are produced by hepatocytes, and their serum levels increase rapidly with the onset of infection. One acute-phase protein of particular importance is C-reactive protein (CRP), which derives its name from its affinity for the C protein of pneumococci. Indeed, CRP serves to opsonize pneumococci and promote their phagocytosis by macrophages. The serum CRP level is often used as a clinical measure of inflammation and may have particular prognostic significance. A number of large, prospective studies have demonstrated the serum CRP level to be an independent predictor of cardiovascular risk.[5,6] It has also been suggested that elevated serum CRP levels might be predictive of perioperative morbidity. One recent study found an association between elevated CRP level and increased length of hospital stay in patients with medium cardiovascular risk undergoing orthopedic procedures.[7]

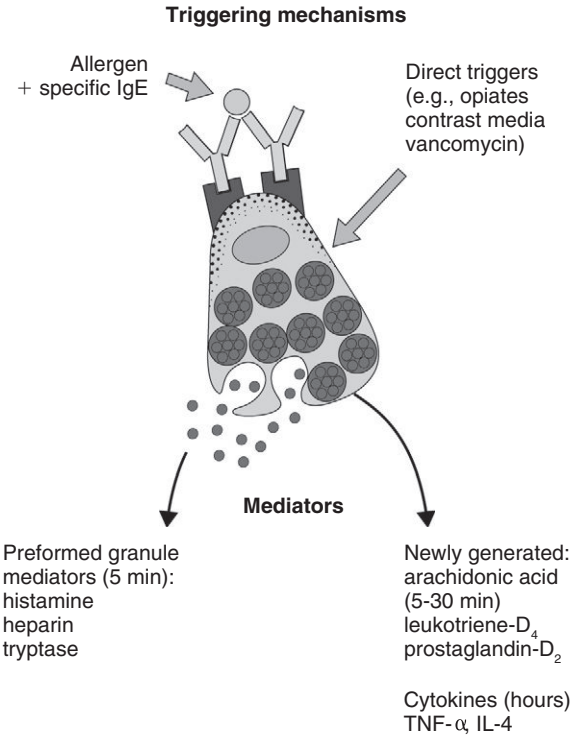


FIGURE **41-13** Release of proinflammatory mediators after binding of antigen to IgE molecules on mast cell membranes. Preformed mediators such as histamine are rapidly released, whereas de novo synthesis delays release of other mediators such as leukotrienes and cytokines. Mast cells can also be directly activated by agents such as opioids, vancomycin, radiocontrast media, and complement products C3a and C5a. Similar events occur in response to activation of circulating basophils. (From Male D, et al. *Immunology*. 8th ed. Philadelphia: Saunders; 2013:381.)

If the immune response is successful in clearing the pathogen and allowing recovery of tissue function, the inflammatory response is termed *acute inflammation*.[1,2] In some situations, though, the initial immune response does not completely remove the pathogen, and infection persists, causing chronic inflammation to develop. Chronic inflammation is characterized by greater numbers of macrophages and CTLs, compared with the leukocyte population seen with acute inflammation. One concern with chronic inflammation is that it can cause significant injury to host tissues. Chronic bacterial infection, such as occurs with tuberculosis, can lead to the formation of granulomas. These structures are composed of a central core of macrophages and epithelioid cells (produced from activated macrophages) surrounded by infiltrating T lymphocytes. TNF-α is a key cytokine responsible for granuloma formation. Chronic viral infections can also cause tissue injury, such as occurs with chronic hepatitis B virus infection.

Auxiliary cells, such as tissue mast cells, circulating basophils, and platelets, play a key role in inflammation and mobilization of immune responses (see Table 41-1). Mast cells and basophils can be activated by allergens that cross-link antibody molecules bound to the cell surface (to be discussed), by complement products C3a and C5a, by particular drugs such as codeine, morphine, and vancomycin, and by radiocontrast media. Once activated, mast cells and basophils undergo rapid release of proinflammatory substances such as histamine and serotonin and slower de novo production and release of leukotriene D_4 (a powerful bronchoconstrictor) and cytokines TNF-α and IL-4 (Figure 41-13).

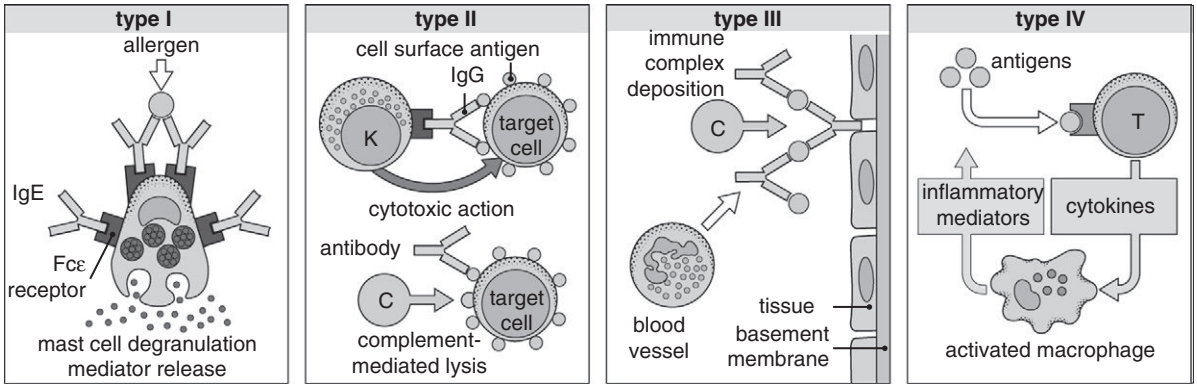


FIGURE **41-14** The Coombs and Gell classifications of the four types of hypersensitivity reactions. Type I reactions are immediate hypersensitivity reactions, and type IV reactions are delayed-type hypersensitivity reactions. See discussion in text for characteristics of each type of reaction. (From Male D, et al. *Immunology*. 8th ed. Philadelphia: Saunders; 2013:372.)

Blood platelets can be activated in several ways, including contact with damaged endothelial cells, by IgG immune complexes, and by platelet-activating factor released from activated macrophages. Activated platelets can aggregate and help to "wall off" an area of inflammation. In addition, activated platelets release serotonin, which acts to increase capillary permeability.

IMMUNE SYSTEM PATHOLOGY

Hypersensitivity and Allergic Reactions

In some cases, the immune response to antigen is greatly exaggerated, a situation referred to as *hypersensitivity*.[1,2] In 1963, Coombs and Gell classified hypersensitivity reactions into types I, II, III, and IV (Figure 41-14). Recently, however, it has been recognized that this classification system is somewhat artificial, as there are overlapping mechanisms of action in types I, II, and III.

Type I Hypersensitivity

Type I hypersensitivity is a rapidly developing reaction that results from antigen-antibody interaction in an individual who has been previously exposed and sensitized to the antigen. The responsible antigen, referred to as an *allergen*, reacts with specific IgE antibodies on tissue mast cells and circulating basophils to trigger mediator release (see Figure 41-13) and an allergic response. A key mediator of allergic symptoms is histamine (Box 41-3). Chemically, allergens are usually proteins, and a multitude of environmental factors, including grass, pollen, dust, mites, molds, and animal dander, can generate type I hypersensitivity reactions.

Allergic reactions present with symptoms such as rhinitis, conjunctivitis, urticaria, pruritus, and possibly anaphylaxis. The term *anaphylaxis* refers to a severe, generalized, immediate hypersensitivity reaction that includes pruritus, urticaria, angioedema (especially laryngeal edema), hypotension, wheezing and bronchospasm, and direct cardiac effects, including arrhythmias. A shocklike state can develop from hypotension secondary to systemic vasodilation and extravasation of protein and fluid. Clinical manifestations of an allergic reaction can present in various combinations and usually occur within minutes of exposure to the precipitating antigen(s). In some cases, though, the onset of signs and symptoms may be delayed for an hour or longer. Signs and symptoms can be protracted and variably responsive to treatment. Biphasic anaphylaxis also can occur, in which early signs and symptoms clear, either spontaneously or after acute therapy, and then symptoms recur several or many hours later. Generally, the severity of an anaphylactic event relates to the suddenness of its onset and to the magnitude of the challenge, that is, the bigger the provocative stimulus, the more severe the reaction. However, anaphylaxis can occur after exposure to minute amounts of allergen in highly sensitive individuals.

BOX 41-3

Histamine

- Histamine is a basic amine stored in granules within mast cells and basophils and secreted when allergen interacts with membrane-bound IgE or when complement components C3a and C5a interact with specific membrane receptors.
- Histamine produces symptoms of allergic reactions by acting on H_1 or H_2 receptors on target cells.
- The main actions of histamine in humans (via the receptors involved) are:
  - Vasodilation (H_1)
  - Increased vascular permeability (H_1)
  - Contraction of most smooth muscle other than that of blood vessels (H_1)
  - Cardiac stimulation (H_2)
  - Stimulation of gastric secretion (H_2)
- Intradermal injection of histamine causes the cutaneous "triple response": erythema from local vasodilation, wheal from increased vascular permeability and protein and fluid extravasation, and flare from an "axon" reflex in sensory nerves that releases a peptide mediator.
- The pathophysiologic effects of histamine can be blocked by H_1-receptor antagonists (diphenhydramine, hydroxyzine, cyclizine, loratadine) and H_2-receptor antagonists (cimetidine, ranitidine, famotidine)

Adapted from Rang HP, et al. *Rang and Dale's Pharmacology*. 7th ed. Edinburgh: Churchill Livingstone; 2012.

Anaphylactoid reactions are caused by mediator release from basophils and mast cells in response to a non–IgE-mediated triggering event. Such reactions present with similar clinical manifestations as those with anaphylaxis, though symptoms may be less severe than those associated with IgE-mediated reactions.[8]

Tryptase is a marker for mechanistic delineation of an allergic response. It is an enzyme released from mast cells, along with histamine and other inflammatory mediators, during an allergic response. Tryptase has a half-life of several hours and is stable at room temperature. It demonstrates a positive predictive value of 92.6% and a negative predictive value of 54.6% as an indicator of

an immunologically mediated event. Thus a significantly elevated tryptase level (greater than 25 mcg/L) strongly suggests an allergic mechanism. The presence of a normal tryptase level, however, does not exclude an immunologic reaction because elevated tryptase levels are not found in almost one third of anaphylactic cases. Although diagnosis of anaphylaxis should not rely on a single test, the high positive predictive value of tryptase makes it useful medicolegally and for subsequent patient management.[8,9]

Type II Hypersensitivity

Type II hypersensitivity reactions result from IgG and IgM antibodies binding to antigens on cell surfaces or extracellular tissue components such as basement membrane (see Figure 41-14).[1,2] The antigen-antibody reaction activates the complement cascade, causing production of C3a and C5a, which attract PMNs and macrophages, and production of the C5b5789 membrane attack complex that inserts into target cell membranes. Examples of type II hypersensitivity reactions include transfusion reactions, autoimmune hemolytic anemia, myasthenia gravis, and Goodpasture syndrome.

Type III Hypersensitivity

Type III hypersensitivity represents immune complex disease, in which antigen-antibody complexes deposit in tissues and cause injury (see Figure 41-14). Normally, immune complexes are cleared by the mononuclear phagocyte system shortly after their formation. In some situations, however, immune complexes persist and deposit in tissues. Protracted infections or autoimmune processes can lead to type III reactions. The mechanism of tissue injury is similar to that in type II reactions, involving activation of complement and recruitment of phagocytes. Systemic lupus erythematosus, rheumatoid arthritis, and glomerulonephritis are examples of immune complex diseases.

Type IV Hypersensitivity

Type IV hypersensitivity is also referred to as *delayed-type hypersensitivity* (see Figure 41-14). By the strict Coombs and Gell definition, type IV reactions require at least 12 hours after contact with antigen. Migration of antigen-specific $CD4^+$ lymphocytes to the reaction site is followed by cytokine release and a local inflammatory response. Contact hypersensitivity is one form of type IV reaction and occurs where skin has come into contact with antigen. Contact dermatitis and the response to poison ivy are examples of contact hypersensitivity. Another form of type IV hypersensitivity is granulomatous hypersensitivity, in which chronic infection leads to the formation of granulomas in tissues. Granulomatous diseases include tuberculosis, sarcoidosis, and Crohn's disease.

Drug Reactions

Predicting who will react adversely to a drug or combination of drugs is difficult. Fortunately, life-threatening adverse reactions to drugs and products used during anesthesia and surgery are very uncommon, with the overall incidence estimated to be 1 in every 5000 to 10,000 anesthetics.[8] Much of the information regarding the epidemiology of adverse reactions to anesthetic agents derives from a series of European studies, and there may be limitations in extrapolating the results of such studies to anesthesia in the United States. Indeed, there appears to be geographic differences in the relative risk of allergic drug reactions.[10]

Dong and Mertes et al.[8] have reported that immune-mediated reactions account for approximately 63% of all perioperative hypersensitivity events. Of the perioperative agents that triggered anaphylactic reactions, neuromuscular blocking agents (NMBAs) did so most often, followed by latex and antibiotics (Table 41-2). Moreover, of the NMBAs that caused allergic reactions, succinylcholine was most frequently cited, followed by atracurium, cisatracurium, vecuronium, and rocuronium and in that order. Anaphylactoid (nonimmune-mediated) reactions may account for as much as 37% of adverse reactions to NMBAs.

TABLE 41-2 Agents Responsible for Perioperative Allergic Reactions in France: 2005-2007

Causal Agent	Percentage
Neuromuscular blocking agents	47.4
Latex	20
Antibiotics	18.1
Hypnotics	1.1
Opioids	2.2
Colloids	2.3
Other agents (contrast media, protamine, others)	8.8
Local anesthetics	0.6

From Dong SW. Hypersensitivity reactions during anesthesia: Results from the ninth French survey (2005-2007). *Minerva Anestesiol.* 2012;78(8):868-78.

Although anaphylactic reactions to local anesthetics are rare, ester local anesthetics are more likely than amide agents to elicit an allergic response.[8,11] Ester local anesthetic metabolites, such as para-aminobenzoic acid, have been identified to be responsible for this higher incidence of allergic response. Local anesthetic solutions containing methylparaben and propylparaben as preservatives may induce allergic responses in susceptible individuals. Thus administration of preservative-free local anesthetic solutions may reduce the likelihood of an allergic response. Recent theories suggest that allergies to various antioxidants and certain sulfite components may be responsible for some degree of allergic reactions to local anesthetic preparations. Adverse reactions to local anesthetics are much more likely to result from accidental intravascular injection of the local anesthetic or absorption of epinephrine coadministered with the anesthetic.

Persons who have an increased allergic tendency are termed *atopic* and exhibit a genetic predisposition to such events. Atopic patients frequently present with some history of hay fever, rhinitis, asthma, or food or drug allergy. There has been long-standing concern as to whether such patients are at increased risk for an anaphylactic or anaphylactoid reaction during anesthesia. Such a relationship does appear to exist for latex allergy, in which a history of generalized atopy or specific allergy to certain fruits, such as kiwi, avocado, or figs, is recognized as a significant risk factor for latex reactions.[8,9] By contrast, a generalized history of allergy does not necessarily predispose a patient to anaphylactic or anaphylactoid reactions to anesthetic drugs. However, if a patient has a history of sensitivity to a particular anesthetic drug, such as a muscle relaxant, that individual may well be at increased risk for allergic responses to other agents in that class. Indeed, Mertes et al.[8] found cross-sensitization in 60% to 70% of patients allergic to NMBAs.

Avoiding known causal agents (particularly those that induce histamine release), combined with careful selection and application of additional drugs, can reduce risk of adverse reactions. A thorough history and discussion with the patient or the patient's guardian can usually reveal the potential for untoward drug effects and alert the anesthesia provider to avoid suspicious agents. Patients frequently mistake drug sensitivity or an unpleasant

response for an allergy. This is especially true with local anesthetic solutions containing epinephrine or administered with opioids. Careful investigation and cautious interviewing techniques are usually beneficial in clarifying these questionable areas. Reviewing past procedural notes and anesthesia records, and possible consultation with an allergist when appropriate, can further help in determining situational specifics and facilitate appropriate planning. The administration of H_1- and H_2-receptor antagonists preemptively may prevent allergic reactions in many cases when a known or suspected sensitivity is present.

Treatment of Intraoperative Allergic Reactions

There is considerable variability in the severity of hypersensitivity reactions as well as in patient responses to treatment. Unfortunately there are no randomized controlled trials of anaphylaxis treatment regimens in patients. Thus the clinician must formulate a treatment scheme based on the clinical presentation and the availability of treatment options. Fortunately during anesthesia, the patient is monitored and intravenous access is usually available, both of which facilitate successful treatment. If possible, all drugs and surgery should be interrupted. Airway patency must be maintained, and 100% oxygen should be administered. Intravenous epinephrine and fluid administration are key interventions. The rate and amount of epinephrine administration are dictated by the severity of symptoms, which can be stratified as grades 1 to 4 (Box 41-4).

Antihistamines also may be useful in the treatment of anaphylaxis, particularly for symptoms of urticaria and angioedema (see Box 41-4). An H_1-receptor antagonist, alone or in combination with an H_2-receptor antagonist, may be useful in reversing hypotension refractory to epinephrine and intravascular fluid replacement. Glucocorticoids, such as intravenous hydrocortisone, may reduce the risk of recurring or protracted anaphylaxis (see Box 41-4).

BOX 41-4

Treatment of Intraoperative Allergic Reactions

Epinephrine

Titrate dose according to severity of symptoms[1] and patient response; repeat dose every 1 to 2 min as necessary; use IV infusion for larger doses.

Adults

- Grade 2: 10-20 mcg
- Grade 3: 100-200 mcg
- Grade 4: 1 mg
- IV infusion starting dose: 0.05-0.1 mcg/min

Children

- Grade 2-3: 1-5 mcg/kg
- Grade 4: 10 mcg/kg

Fluid Therapy

- Normal saline: 10-25 mL/kg for 20 min (repeat if necessary), *or* Colloid: 10 mL/kg

Anaphylaxis Refractory to Epinephrine

- Vasopressin: IV doses of 2-10 international units until response
- Norepinephrine: Initial dose of 0.05-0.1 mg/kg/min

Antihistamines

- H_1-receptor antagonist (e.g., diphenhydramine): 0.5-1.0 mg/kg IV
- H_2-receptor antagonist (e.g., ranitidine): 50 mg IV

Corticosteroids

Hydrocortisone

- Adults: 250 mg IV
- Children: 50-100 mg IV

Classifications of Immediate Hypersensitivity Reactions According to Grade of Severity

- Grade 1: Erythema, urticaria, with or without angioedema; epinephrine is not administered
- Grade 2: Moderate severity; cutaneous signs, hypotension and tachycardia; cough, difficult to ventilate
- Grade 3: Life-threatening severity; cardiovascular collapse, tachycardia or bradycardia, dysrhythmias, bronchospasm
- Grade 4: Cardiac and/or respiratory arrest

From Mertes PM, et al. Perioperative anaphylaxis. *Med Clin North Am*. 2010;94(4):761-789.

Transfusion Reactions

Because of advances in technologic capabilities and quality-control practices, blood transfusion reactions are fortunately not a common occurrence. The relative risk of an allergic transfusion reaction of mild severity (i.e., urticaria and pruritus) is approximately 1:500, whereas a fatal hemolytic reaction occurs in approximately 1 in 250,000 to 600,000 transfusions administered nationally. The mechanism responsible for most transfusion reactions involves ABO incompatibility. Transfusion of incompatible blood type causes recipient antibodies to react with donor red blood cells, causing their destruction and the potential for significant consequences. Disseminated intravascular coagulation, renal failure, and death are not uncommon after this type of reaction. Because the most common cause for a major hemolytic transfusion reaction is human error, it should never be assumed that another person is solely responsible for checking blood that one is preparing to administer to a patient.

Transfusion reactions are frequently masked, or at least delayed appreciably, during anesthesia. Hallmark symptoms of cardiovascular instability such as hypotension, as well as fever, hemoglobinuria, and bleeding diathesis, are indicative of a transfusion incompatibility and should be immediately treated.[12]

Latex Allergy

It has been estimated that approximately 1% to 2% of the general population has allergy to latex.[13] Allergies to latex-containing products continue to be a source of significant problems for specific populations. Health-care workers who experience frequent exposure to devices and products that contain latex are at increased risk of developing latex allergy.[13] Certain patients, particularly those with congenital neural tube deficits and those who have undergone multiple surgical procedures, have an increased rate of latex sensitivity. Moreover, individuals with particular food allergies (Box 41-5) are at increased risk for latex allergy.

The most frequent clinical manifestations of latex reactions include some form of contact dermatitis, type I hypersensitivity reaction with the potential for anaphylaxis, or type IV hypersensitivity reaction. Dong et al.[8] found latex reactions to be the second most common cause of anaphylactic reactions during anesthesia and surgery. Box 41-6 lists clinical manifestations of latex reactions in both awake and anesthetized patients.

Preventive procedures and recommended protocols have been established for the management of latex allergies that can have significant anaphylactic consequences. The incidence of latex allergies increased proportionately with the 10-fold increase in

BOX 41-5

Food Allergies That Increase Risk of Latex Allergy

- Avocado
- Banana
- Figs
- Cherimoya
- Chestnut
- Eggplant
- Kiwi
- Mango
- Melon
- Papaya
- Passion Fruit
- Pineapple
- Potato
- Tomato
- Wheat

BOX 41-6

Latex Reactions

Awake Patient	Anesthetized Patient
Itchy eyes	Tachycardia
Generalized pruritus	Hypertension
Shortness of breath	Wheezing
Feeling of faintness	Bronchospasm
Feeling of impending doom	Cardiorespiratory arrest
Nausea	Flushing
Vomiting	Facial edema
Abdominal cramping	Laryngeal edema
Diarrhea	Urticaria
Wheezing	

BOX 41-7

Immunosuppressant Drugs

Most immunosuppressant drugs act in the induction phase of the immunologic response to reduce lymphocyte proliferation; some also inhibit components of the effector phase. The drugs used for immunosuppression can be roughly divided into agents that:

- Inhibit cytokine gene expression, e.g., glucocorticoids
- Inhibit purine or pyrimidine synthesis, e.g., azathioprine, mycophenolate mofetil
- Inhibit IL-2 production or action, e.g., cyclosporine, tacrolimus, rapamycin
- Block T-cell IL-2 receptors, e.g., basiliximab, daclizumab

Immunosuppressant drugs are used to:

- Suppress rejection of transplanted organs
- Suppress graft-versus-host disease in bone marrow transplants
- Treat autoimmune diseases, including idiopathic thrombocytopenic purpura and some types of hemolytic anemia, glomerulonephritis, and myasthenia gravis
- Treat arthritic diseases such as rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis
- Treat severe inflammatory bowel disease such as ulcerative colitis and Crohn's disease

Adapted from Rang HP, et al. *Rang and Dale's Pharmacology*. 7th ed. Edinburgh: Churchill Livingstone; 2012.

medical glove usage to accommodate universal precautions and barrier protection during anesthesia, surgery, and obstetric care. Using gloves that do not contain latex (e.g., gloves processed from polyvinyl or neoprene) can prevent this source of latex exposure. Although skin prick, patch testing, and radioallergosorbent tests for latex allergy are available, all present various challenges in qualifying a conclusive diagnosis. The American Latex Allergy Association provides protocols and detailed plans for avoiding and treating latex allergic responses.[14]

DISEASES OF THE IMMUNE SYSTEM

Autoimmune Disease

In the process of lymphocyte maturation, there normally occurs negative selection (apoptosis) of most cells that react against self-antigens.[1,2] Despite the efficiency of this self-tolerance mechanism, however, individuals normally display detectable levels of autoreactive B cells and T cells, which are usually not activated, owing to inadequate presentation of self-antigen or other factors that prevent autoreactivity. Impairment in the mechanisms that act to prevent autoreactivity can lead to production of excess amounts of autoreactive antibodies and T cells and autoimmune disease. Examples of such diseases are Hashimoto thyroiditis, insulin-dependent diabetes mellitus (IDDM), myasthenia gravis, rheumatoid arthritis, and systemic lupus erythematosus (SLE).

There is much evidence that certain HLA haplotypes predispose a patient to autoimmune disease. Rheumatoid arthritis, for example, associates with certain HLA-DR haplotypes, and the risk of IDDM is greatly increased in persons with certain HLA-DQ haplotypes. The majority of autoimmune diseases affect women more often than men; in particular, they affect women of childbearing and working age. Moreover, it is not uncommon for an individual to have more than one autoimmune disease.

In some cases, autoimmune disease may result secondarily from an infection in which microbial antigens contain epitopes that are shared with self-antigens. Presentation of microbial antigen to Th cells as part of the normal response to infection then triggers activation and proliferation of lymphocytes directed against not only the microbe but also self-antigens in tissues. This process of microbial cross-reactivity is the basis of rheumatic heart disease that develops in some individuals after a streptococcal infection. In this case, antibodies produced against streptococcal antigens cross-react with certain heart valve antigens. Microbial cross-reactivity also may play a role in the development of rheumatoid arthritis and ankylosing spondylitis.

Treatment of autoimmune disease depends in part on whether the disease is organ-specific (e.g., hypothyroidism, myasthenia gravis, IDDM) or systemic (e.g., rheumatoid arthritis, SLE). Organ-specific disease may be treated with discrete strategies, for example, cholinesterase inhibitors used to treat myasthenia gravis and exogenous insulin used to treat IDDM. Systemic disease may be treated with antiinflammatory and/or immunosuppressive regimens. Antiinflammatory agents that may be used include cyclooxygenase inhibitors, corticosteroids (see Box 41-4), and more recently monoclonal antibodies directed against the inflammatory mediator TNF-α (see Box 41-2). Treatment with immunosuppressant drugs (Box 41-7) may reduce the immune response but carries significant risk of opportunistic infections.

Immunodeficiency

Primary immunodeficiency is caused by deficient function of lymphocytes, the complement system, or phagocytes.[1,2] Deficient B-cell and antibody function can predispose to pyogenic infections, in which bacterial infection causes pus accumulation. IgA deficiency is a primary disorder and is the most common immunodeficiency syndrome. It occurs almost exclusively in Caucasians, with a prevalence of 1 in 700, and affected individuals are prone to develop type III hypersensitivity reactions. Approximately one

fifth of patients with IgA deficiency also have deficient production of two IgG subclasses, IgG2 and IgG4, which makes them susceptible to pyogenic infections. Individuals with deficient antibody responses are prone to recurring respiratory infections with encapsulated bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae*. Such recurrent infections can result in bronchiectasis and chronic obstructive pulmonary disease.

Individuals who lack T cells or who have deficient T-cell function are prone to opportunistic infections by environmental pathogens such as yeast and chickenpox, microorganisms to which normal individuals develop prompt immunity. Because T cells support (in part) B-cell function, T-cell defects also may be accompanied by deficient humoral immunity. Individuals born with severe combined immunodeficiency (SCID) have low levels of circulating lymphocytes, lymphoid tissue that is virtually devoid of lymphocytes, and an immature thymus gland. A number of genetic mutations, including X-linked and autosomal recessive genes, can cause SCID. Affected infants are prone to develop diarrhea and pneumonia and usually do not survive more than 2 years unless treated with a bone-marrow transplant. T-cell deficiency also accompanies the DiGeorge syndrome, which results from abnormal development of the thymus and parathyroid glands, structures that originate from the same embryonic tissue. The syndrome is characterized by an "elfin-like appearance," with eyes set widely apart and a shortened infranasal depression. Structural micrognathia is frequently associated with this syndrome and can hinder laryngoscopy and airway management efforts. Congenital cardiac abnormalities and tetany secondary to deficient parathyroid gland function are also characteristic of DiGeorge syndrome.

Genetic abnormalities in complement proteins may cause primary immunodeficiency syndromes. Hereditary angioneurotic edema (HAE) is caused by absent or defective C1 inhibitor, a protein that normally acts to control complement activation and coagulation mechanisms. Deficient C1 inhibitor activity can lead to kinin accumulation, angioedema, and upper airway obstruction. Exogenous C1 inhibitor can be administered to treat acute angioedema.

Deficiencies in PMNs or the mononuclear phagocyte system can result in severe, life-threatening infections. Neutropenia represents a variable reduction in PMNs, which can predispose the affected individual to severe bacterial infections. Chronic granulomatous disease (CGD) results when defective PMNs are unable to generate a bactericidal respiratory burst after bacterial phagocytosis. Ingested pathogens that survive within the phagocytes trigger a cell-mediated immune response against the phagocytes and formation of granulomas. Symptoms of CGD in pediatric patients include pneumonia and abscesses in various tissues.

Secondary immunodeficiency can result as an adverse effect of immunosuppressive drugs administered to prevent graft rejection or to treat autoimmune disease (see Box 41-7). Glucocorticoids have potent immunosuppressive effects. These steroid agents markedly reduce circulating levels of lymphocytes and monocytes, inhibit immune cell cytokine production, and inhibit T-cell activation. Lymphocytopenia and monocytopenia result within hours after a single dose of glucocorticoid and resolve within 24 hours. Azathioprine is a cytostatic immunosuppressive agent that is effective only on dividing lymphocytes, reducing levels of both B and T lymphocytes. Mycophenolate mofetil inhibits lymphocyte proliferation by blocking the last step of purine synthesis necessary for DNA replication. Cyclosporine, tacrolimus (formerly known as *FK-506*), and rapamycin bind to cytoplasmic proteins known as *immunophilins*, causing blockade of signal transduction pathways from the cell membrane and inhibition of T-cell proliferation.

BOX 41-8

Routes of HIV Transmission

Absolute
- Blood
- Body fluids containing blood

Possible
- Cerebrospinal fluid
- Pericardial fluids
- Amniotic fluids
- Semen, vaginal secretions
- Synovial fluid
- Pleural fluid

Remote
- Feces
- Saliva
- Sputum
- Sweat
- Tears
- Urine
- Wound drainage
- Nasal secretions

Not Implicated in Health-Care Settings
- Human breast milk

Human Immunodeficiency Virus

Secondary immunosuppression also can result from infection that causes depletion of immune cells. In this regard, infection with HIV is the most significant etiology. The virus exists as two main types, HIV-1 and HIV-2. Of the two, HIV-1 is more prevalent and more pathogenic. The primary targets of HIV infection are $CD4^+$ lymphocytes. A glycoprotein on the viral envelope binds to the CD4 antigen to allow the virus to enter the T cell. HIV is a retrovirus, that is, its genome contains two strands of single-stranded RNA. After the virus enters the host cell, its RNA undergoes reverse transcription to produce complementary DNA that is incorporated into the host-cell DNA. Synthesis of new viral RNA then occurs in the host cell, followed by formation of new virus particles and their release to infect other $CD4^+$ cells. Infection with HIV alters T-cell function and causes cytotoxicity, leading to the characteristic decline in $CD4^+$ cells. Exactly how HIV infection kills T cells, though, is not known and may involve several mechanisms. Ultimately, with a sufficient fall in $CD4^+$ cells, individuals become susceptible to life-threatening opportunistic infections.

Epidemiology

The epidemiologic basis for HIV infection begins with transmission of the virus through certain body fluids. Box 41-8 lists the potential sources of transmission of HIV, which can enter the body through blood contact, sexual transmission, and perinatal exposure. In 2009 the Centers for Disease Control and Prevention estimated that approximately 1.7 million individuals 13 years of age and older in the United States were living with HIV/AIDS. Moreover, the annual incidence of HIV infection in the United States was estimated to be nearly 50,000.[15] Infection with HIV can progress to acquired immune deficiency syndrome (AIDS) and fatal disease. Although there is no cure for HIV infection, early diagnosis and pharmacologic intervention have become very successful in controlling HIV infection in many individuals while preserving immune system integrity.

Acute infection with HIV is characterized by a mononucleosis-like illness, in which release of inflammatory mediators, including IL-1 and TNF-α, causes symptoms such as malaise, fever, myalgias, and rash. At the same time, a transient decline in circulating $CD4^+$ cells occurs. Over several weeks after the primary infection, antibodies directed against virus envelope proteins are produced, and CTLs begin to kill infected T cells that display HIV peptides. These immune responses permit resolution of the symptoms of acute infection; however, anti-HIV antibodies and CTLs become

overwhelmed by viral replication and mutation, and progression of HIV infection occurs.

Spontaneous resolution of the acute symptoms of HIV infection is followed by a variable period of asymptomatic infection. If the infection is not treated, a gradual, progressive fall in $CD4^+$ cells occurs in conjunction with a gradual increase in the plasma viral load. Progression to AIDS in untreated individuals occurs in an average time of 10 years, although in some individuals progression may occur much more rapidly or perhaps not at all. With respect to the latter possibility, there are reports of individuals who have not developed AIDS despite multiple exposures to HIV, suggesting that the adaptive immune system in some individuals may provide chronic protection by an as yet undefined mechanism. Clinically, AIDS is defined as a $CD4^+$ cell count less than 200 cells/μL or by the presence of an AIDS-indicator condition (discussed later).

Treatment Modalities

Antiretroviral agents from several classes of drugs are currently available to treat HIV infection. These drug classes include the nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), entry inhibitors, and integrase inhibitors. Most current therapies involve a "cocktail" of antiretroviral agents. A combination of three or four agents, known as *combined antiretroviral therapy,* is now the usual therapeutic approach.

Nucleoside/Nucleotide Reverse Transcriptase Inhibitors. The NRTIs bind to and inhibit the viral reverse transcriptase enzyme responsible for production of HIV RNA. The prototype agent in this class is zidovudine, also known as *ZDV,* which was the first antiretroviral drug to be approved by the U.S. Food and Drug Administration for treatment of HIV infection. Resistance to zidovudine may occur with certain HIV strains, and the most significant side effect of AZT therapy is bone-marrow suppression, which causes anemia and neutropenia. Other NRTIs include abacavir, didanosine, lamivudine (3TC), and stavudine (d4T).

Nonnucleoside Reverse Transcriptase Inhibitors. Like the NRTIs, the NNRTIs bind to and inhibit the viral reverse transcriptase enzyme but at a different molecular site. Resistance to NNRTI monotherapy can readily occur, and adverse effects include skin rash and (uncommonly) Stevens-Johnson syndrome. NNRTIs are metabolized by hepatic CYP3A4, and agents can either induce or inhibit this cytochrome P-450 isoform. Thus the practitioner should be prepared for possible interactions with other drugs, including some anesthetic agents that are metabolized by CYP3A4. The prototype NNRTI is nevirapine; other NNRTIS include delavirdine and efavirenz.

Protease Inhibitors. The viral enzyme protease catalyzes production of viral core structural proteins from immature polypeptide precursors. By inhibiting this enzyme, the PIs cause production of altered, noninfectious virions. Drugs in this class include amprenavir, indinavir, ritonavir, saquinavir, and tipranavir. Adverse effects of the PIs include Cushing-like signs and symptoms (e.g., central obesity, buffalo hump, glucose intolerance). Like the NNRTIs, the PIs can either induce or inhibit CYP3A4, and drug interactions should be anticipated. Of note, ritonavir can reduce fentanyl clearance and increase its plasma half-life.[16]

Entry Inhibitors. Entry inhibitors prevent viral adherence to and entry into the host cell. Enfuvirtide is an entry inhibitor that binds to the gp41protein on the virus surface, thereby interfering with virus attachment to the $CD4^+$ cell. It is injected subcutaneously, and clearance does not involve cytochrome P-450 enzymes. Another agent, maraviroc, binds to the CCR5 receptor on the $CD4^+$ cell to prevent virus entry.

Integrase Inhibitors. Integrase inhibitors, agents in this newest class of antiretroviral agents, inhibit HIV DNA integrase, which is the enzyme responsible for splicing HIV DNA into the host cell genome. The only integrase inhibitor currently available is ratelgravir.[17]

Therapeutic modalities may fail owing to patient nonadherence, inadequate potency of antiretroviral agents, or viral resistance. Ongoing research continues to address resistance and investigate multiple strains of the virus that may not respond to current therapeutic approaches. Ultimately, of course, the goal is to develop a cure for HIV. In this regard, numerous clinical trials of HIV vaccines have been conducted over the past decade in locations around the world and have produced mixed results. The STEP study, an international HIV vaccine clinical trial conducted in part by the National Institute of Allergy and Infectious Diseases, included 3000 participants in nine countries including the United States. Unfortunately, the study was discontinued after an independent monitoring board determined that the vaccine did not prevent HIV infection or affect the course of the disease in those who became infected with HIV. Numerous organizations, including the National Institute of Allergy and Infectious Diseases Center for HIV/AIDS Vaccine Immunology (http://www.niaid.nih.gov/topics/hivaids/Pages), The Collaboration for AIDS Vaccine Discovery (http://www.cavd.org), The Global HIV Vaccine Enterprise (http://www.hivvaccineenterprise.org), and the International AIDS Vaccine Initiative (http://www.iavi.org) are currently pursuing trials of potential HIV vaccines.

Anesthesia Management

The perioperative care of HIV patients should take into account several underlying conditions. Frequent complications include: espiratory impairment and alteration in neuronal functions related to viral factors, host response, and environmental factors such as alcohol, drug addiction, and hepatitis C co-infections. Cognitive dysfunction or a peripheral neuropathy are common. Lipodystrophy, dyslipidemia, and insulin resistance are the main metabolic-related side effects of combined antiretroviral therapy. Atherosclerosis, coronary artery disease, and major nutritional impairment are also common.[18] Patients with HIV infection may require a variety of surgical interventions. Although several studies have evaluated the effects of surgery and anesthesia in patients with HIV infection, to date there is no conclusive evidence to support any particular set of recommendations. The protease inhibitors decrease the metabolic pathways of opioids, nonsteroidal antiinflammatory drugs (NSAIDs), and benzodiazepines, increasing the risk of overdose.[18] Midazolam's effects may be enhanced when administered to patients taking certain protease inhibitors that inhibit cytochrome dependant drug metabolism. This enzyme inhibition prevents the breakdown of midazolam. Careful titration of reduced doses should be adapted until individual patient responses can be gauged. Most alterations caused by various anesthetic agents and techniques are transient and have not been shown to contribute to any adverse outcome. Many clinicians avoid regional anesthesia to reduce needle-induced spread of infectious materials.

Preoperative evaluation should consider the patient's medical management and adherence to antiretroviral therapy and other treatments. Consultation with and participation of the patient's primary care provider in the planning process may be beneficial. Other factors that may be important in the preoperative risk stratification include the patient's CD4 count and viral load.

When anesthesia care is planned, attention should focus on possible end-organ and systemic dysfunction. Clinically significant alterations occur in many organ systems, particularly in the advanced disease stages of HIV infection, when vigilant

monitoring and at times intensive intervention may be necessary. The patient (or his or her legal representative or caregiver) should be included in the planning and evaluation of potential care options. Informed consent may be the responsibility of a legal guardian or durable power of attorney designee for the patient who may be mentally incompetent.

The immunocompromised patient may have combined deficiencies that predispose to significant or fatal outcomes. It is important to remember that microorganisms that are not routinely pathogenic can cause the demise of these patients. Meticulous implementation of infection control measures throughout the perioperative period should be a primary focus in the care of these vulnerable patients. Respiratory isolation should be used when it is either known or suspected that airborne pathogens may be transmitted. Examples of such pathogens include the causative agents of tuberculosis and varicella. The immune-system compromise resulting from HIV infection markedly increases the susceptibility to tuberculosis, and recurrent or newly acquired tuberculosis is frequently the cause of death for persons infected with HIV. A striking clinical feature of tuberculosis in patients with HIV infection is a high incidence of extrapulmonary involvement, usually with concomitant pulmonary presentation.[18-20]

Although equipment preparedness is important for every patient to whom anesthesia is administered, it is of particular significance with the immunocompromised patient. Meticulous attention to behaviors and adherence to strict aseptic technique in providing care to these most vulnerable patients is paramount to safe practice and quality patient care. The anesthesia machine and its multitude of components should be adequately maintained, cleaned, and disinfected. It is advisable to use a new disposable circuit, including a new carbon dioxide sampling port and a 22-micron heat and moisture exchanger (HME) filter, on all patients.

A multitude of clinical presentations have the potential to affect anesthesia management in the patient infected with HIV. Oxygenation and metabolic functions are often impaired during progressive HIV infection. Pulmonary infections can alter both gas exchange and lung perfusion and create ventilation-perfusion mismatch. Dehydration and hypovolemia secondary to gastrointestinal disturbances can further complicate the patient's clinical course. Patients with HIV infection also may present with pain-related syndromes,[21] neuropathies, and muscle weakness.[22] A thorough preoperative assessment, including current physical examination, laboratory results, and radiographic examination, combined with other studies as indicated by patient presentation and current disease state, is critical prior to anesthesia.

Complications from HIV

Wasting syndrome may be seen in patients with HIV infection and results from disturbances in food absorption and metabolism. This syndrome is defined as profound, involuntary weight loss greater than 10% of baseline body weight. Chronic diarrhea frequently contributes to this scenario. Parenteral nutrition and appetite stimulation are usually required when this syndrome is persistent. Preoperative assessment should include evaluation of volume status and related physiologic studies to plan appropriate management.

Neurologic evaluation is essential for patients with HIV infection. Both the central and peripheral nervous systems can be impaired due to direct disease effects, concomitant opportunistic infections, or adverse effects of therapeutic agents used to combat viral insult. Peripheral neuropathies may result in considerable discomfort or physical limitations, and autonomic neuropathy may result in some degree of cardiovascular instability requiring immediate or continuous intervention. AIDS-related dementia can influence both motor and cognitive states, particularly in advanced disease states.

Non-Hodgkin lymphoma, manifesting as a space-occupying lesion within the central nervous system, may require surgical or chemotherapeutic intervention. Kaposi sarcoma, a cancer that invades endothelial tissues, can attack both skin and internal organs. Women infected with HIV may develop cervical dysplasia and cancers.

As HIV infection progresses to AIDS, advanced disease combinations emerge that would otherwise be resisted in the immunocompetent host. These opportunistic disease processes increase in both manifestation and severity as the immune system fails. Both acute and chronic bacterial infections tend to plague HIV-infected individuals. *Mycobacterium avium-intracellulare* (MAI) infection is characterized by intractable diarrhea and resultant wasting states. Splenic and pulmonary infections with MAI lead to severe thrombocytopenia and tuberculosis. MAI attacks the immunosuppressed host easily and is transmissible.

Several viral infections can occur or recur from previously dormant states as HIV disease progresses. Herpes simplex and varicella infections can invade oral and esophageal tissues and the central nervous system. Cytomegalovirus can affect the gastrointestinal and pulmonary systems, resulting in colitis and pneumonia. Retinal invasion may lead to marked visual disturbances and blindness. Ganciclovir is used to treat cytomegalovirus infection.

Opportunistic protozoal infections can develop in persons with advanced HIV infection. *Pneumocystis jiroveci* pneumonia is responsible for the majority of deaths secondary to opportunistic infection in persons with HIV infection. Fever and impaired gas exchange frequently result in hypoxemia, and pneumothorax is not uncommon. Toxoplasmosis encephalitis can affect both central nervous system function and the sensorium. Cryptosporidiosis can trigger considerable diarrhea, resulting in significant dehydration and related electrolyte imbalance. Volume status must be judiciously evaluated and monitored.

Fungal infection is responsible for histoplasmosis and aspergillosis pneumonia in the patients with HIV infection. Such insults can result in significant febrile and hypoxic states, with impairment of gas exchange and overall sensorium. Disseminated candidiasis infections are responsible for oropharyngeal and esophageal pathology that includes stomatitis, dysphagia, and esophagitis. Patients with cryptococcal meningitis can experience increased intracranial pressure.

Childbearing women constitute a significant portion of reported cases of HIV and AIDS. This observation is of considerable significance in that perinatal transmission accounts for greater than 80% of all pediatric AIDS cases that have been reported in the United States. The Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission recommends antepartum combination therapy in pregnant women to reduce the risk of perinatal transmission. If the parturient with HIV infection has not received antepartum antiretroviral therapy, then antiretroviral drugs should be administered intrapartum along with antiretroviral prophylaxis in the neonate to reduce the risk of transmission. A 6-week treatment with zidovudine is recommended for all neonates of women with HIV infection.[23] Moreover, neonates of women who did not receive antepartum antiretroviral drugs should receive a combination drug regimen, such as zidovudine, for 6 weeks combined with three doses of nevirapine in the first week after birth.

The pregnant patient with HIV presents unique challenges for health maintenance. Anemia can be particularly significant in advanced states of HIV infection, frequently necessitating transfusion therapy. Elective cesarean section in the HIV-positive parturient appears to reduce the risk of HIV transmission from mother to neonate.[24] However, complications of cesarean section, including blood loss and wound infection, may be exaggerated in parturients with HIV infection as a result of immunosuppression.[25] Avidan et al.[26] reported no increase in intra- or postoperative complications associated with spinal anesthesia and cesarean section in parturients with HIV infection who were receiving effective antiretroviral therapy and who received preoperative broad-spectrum antibiotics. Such an approach may be effective in reducing risk of perinatal HIV transmission in parturients in whom antiretroviral therapy is effective and spinal anesthesia is not contraindicated.

Perioperative pain management can be a particular challenge in patients with advanced HIV infection. Indeed, patients with HIV infection frequently present with pain-related syndromes and thus may be taking prescription or over-the-counter analgesic medications and are frequently opioid dependent.[21] Both routine analgesic modalities and analgesic agents combined with the use of various chemotherapies, nerve blocks, and complementary therapies have been beneficial in treating acute postoperative and obstetric pain in patients with HIV infection.[27]

Managing HIV Infection

Occupational Safety. The primary emphasis in managing HIV infection during anesthesia and other aspects of patient care is an effective prevention program. Because the routes of HIV transmission are well known, an appropriate infection control program, with consistent application of proven blood and body substance precautions, can prevent disease transmission. Universal precautions were developed after known modes of transmission of both HIV and hepatitis B virus (both blood-borne pathogens) were clarified. More recent efforts to apply this practice throughout all patient care areas have resulted in the consistent application of standard precautions during patient care. The basic premise on which these guidelines are based is the prevention of parenteral, mucous membrane, and nonintact skin exposure to blood and certain body fluids from all patients. Guidelines include the following:

- Gloves must be worn when contact with body substances is suspected or possible.
- A plastic gown or apron must be worn when soiling with body substances is likely.
- Protective masks and eyewear must be worn in the presence of airborne disease or for preventing splash or aerosolization of body substances to eyes or mucous membranes.
- Hands must be thoroughly washed before and after body substances or articles possibly covered with body substances have been handled and after gloves have been removed at the completion of each task or procedure.
- Uncapped needles and syringes must be discarded in puncture-resistant receptacles placed as close to their point of use as is practical.
- Trash and linens must be discarded in impervious, sealed plastic bags that are labeled as infectious and transported according to standard precautions.

Self-protection against HIV and all other infectious blood-borne pathogens such as hepatitis B and C viruses is an essential element of safe practice. The Occupational Safety and Health Administration (OSHA) Act, which became effective in 1992, mandates that employers minimize occupational exposure to all blood-borne pathogens in workplaces where a potential for such exposures exists. Known or suspected exposure to blood-borne pathogens should be responded to immediately with appropriate action, as recommended by OSHA and institutional infection control standards. The AANA infection control guide details recommended practices for managing blood-borne pathogens during anesthesia care.[28] Current HIV/AIDS treatment guidelines and protocols may be obtained from the National HIV/AIDS Clinicians' Consultation website at http://www.nccc.ucsf.edu/.

HIV Postexposure Prophylaxis. As of December 2001, the Centers for Disease Control and Prevention (CDC) had received voluntary reports of 57 documented cases of HIV seroconversion temporally associated with occupational exposure to HIV among U.S. healthcare personnel. Because there is no cure or effective vaccine for HIV, optimal postexposure care, including the administration of antiretroviral drugs, remains a high priority for protecting healthcare personnel.[29,30]

Percutaneous injury with a hollow-bore needle is the most common mechanism of occupational HIV transmission. Pooled data from several prospective studies of healthcare personnel suggest that the average risk of HIV transmission is approximately 0.3% after a percutaneous exposure to HIV-infected blood and approximately 0.09% after a mucous membrane exposure.[29] The average risk associated with exposure of nonintact skin and exposure to HIV-infected fluids and tissues other than blood or bloody fluids is too low to be estimated in prospective studies.

In a retrospective study, the CDC found that the risk of HIV transmission to healthcare workers was increased when the device causing the injury was visibly contaminated with blood or was used for insertion into a vein or artery, when a deep injury occurred, or when the source patient died within 2 months after the exposure.[29] A low-plasma HIV RNA titer does not exclude the possibility of transmission, especially because this measurement does not account for cell-associated HIV. Transmission from source patients with undetectable HIV RNA has been documented.

Suture needles have not been implicated as a source of infection in prospective studies, but occupational HIV infection has been reported among surgical personnel, and suture needles are one potential source of such infection. Exposure of intact skin to contaminated blood has not been identified as a risk for HIV transmission.

Evidence suggests that postexposure prophylaxis (PEP) with antiretroviral drugs soon after occupational exposure to HIV decreases risk of infection. The CDC recommends that PEP be initiated within hours of exposure and that the regimen be administered for 4 weeks. In most cases, individuals exposed to HIV will receive a two-drug regimen (basic regimen). A third, and even a fourth, drug (expanded regimen) may be considered for individuals at increased risk for infection, although there are no data that demonstrate increased efficacy of a three- or four-drug regimen. Indeed, it is clear that protection afforded by PEP is not absolute. Of six healthcare workers known to have acquired HIV infection despite PEP, three individuals received three drugs and one received four drugs.[29]

ANESTHESIA AND THE IMMUNE SYSTEM

The effects of anesthesia on the immune system have been investigated for more than 30 years. For two reasons, however, no clear picture regarding how anesthetic agents alter immune function has emerged. First, anesthesia is administered in the context of surgery, which itself has significant effects on immune function. Second, many in vitro studies have been performed to examine the effects of anesthetic agents on immune components in controlled, experimental situations. Results of these in vitro studies,

although possibly yielding mechanistic insights, do not always agree with in vivo observations. The focus of this final section of the chapter is to describe the relationship between stress and the immune system and to summarize the results of in vitro and in vivo studies of the effects of individual anesthetic agents on the principal components of the immune system, that is, phagocytes, lymphocytes, and soluble mediators.

Effects of Surgery on the Immune System

The immune response to surgery is variable and involves both the innate and the adaptive immune systems. Tissue injury caused by surgery induces an immediate, localized response by cells, particularly macrophages, of the innate immune system.[31,32] Cytokines such as IL-1 and TNF-α are released from resident macrophages and promote a local inflammatory response in the injured tissue. Among their effects, IL-1 and TNF-α stimulate production of IL-6, which in turn acts on hepatocytes to stimulate the synthesis and release of acute-phase proteins such as CRP. The magnitude of the inflammatory response and the perioperative plasma IL-6 levels appear to correlate with the severity of the surgical procedure.[33] In this regard, higher IL-6 levels have been found in patients undergoing open cholecystectomy than in patients undergoing laparoscopic cholecystectomy.[34] Of potential clinical importance, the plasma IL-6 level may predict the likelihood of postoperative morbidity and mortality.[32] Moreover, as previously discussed, plasma CRP levels may be predictive of perioperative morbidity.[7]

In addition to the inflammatory response at the site of surgical tissue injury, surgery strongly stimulates the body's neurohumoral stress response, which in turn can produce immunosuppression by several mechanisms.[32,35,36] First, a variety of stressors associated with surgery, including hypotension, hypothermia, activation of pain pathways, and proinflammatory cytokines (e.g., IL-1, IL-6, and TNF-α) released from the site of surgical injury, can stimulate the hypothalamic-pituitary-adrenal (HPA) axis and cause release of the glucocorticoid cortisol from the adrenal cortex. Glucocorticoids such as cortisol have potent antiinflammatory and immunomodulatory effects. Among its effects, cortisol shifts the Th1/Th2 cell balance, suppressing APC production of IL-12 and Th1-mediated cellular immunity and stimulating Th2 cell production of antiinflammatory cytokines such as IL-4 and IL-10. Although this cortisol-mediated effect functions to prevent exaggerated inflammation at the surgical site, diminished Th1 cell activity and increased production of Th2 cytokines effectively produces immunosuppression characterized by depressed cell-mediated immunity (via phagocytes, CTLs, and NK cells) and susceptibility to infectious pathogens and metastasis of tumor cells.

In addition to stimulating the HPA axis, surgical stress strongly activates the sympathetic nervous system activation, increasing secretion of catecholamines from the adrenal medulla.[32,35,36] Catecholamines may promote immunosuppression through activation of β-adrenergic receptors on immune cells. In this regard, activation of β-adrenergic receptors has been found to suppress in vitro monocyte production of TNF-α and IL-1 and PMN production of reactive oxygen molecules.[37,38] Moreover, like cortisol, catecholamines may facilitate a stress-induced shift in the Th1/Th2 cell balance. Elenkov et al.[39] treated whole blood with bacterial lipopolysaccharide (endotoxin) to stimulate monocyte cytokine production.[39] Dexamethasone, used to mimic the in vivo effects of cortisol, inhibited monocyte IL-12 production. The catecholamines epinephrine and norepinephrine also inhibited IL-12 production and increased IL-10 production. The effects of the catecholamines were blocked by the β-adrenergic antagonist propranolol. As discussed, IL-12 induces Th0 cell differentiation to Th1 cells and promotes cellular immunity. By contrast, IL-10 inhibits Th1 cell function and promotes Th2 cell responses and humoral immunity. The authors suggested that stress hormones, that is, glucocorticoids and catecholamines, can shift the Th1/Th2 cytokine balance to a pattern that predisposes to infections by pathogens that would normally be intercepted by cellular immunity.

Evidence from animal and human studies indicates that the extent of surgery-induced immunosuppression correlates with the invasiveness of the surgical procedure. Anesthetized animals that underwent experimental laparoscopy had preserved postoperative cellular immunity compared with animals that underwent more invasive laparotomy.[40,41] Similarly, in humans, laparoscopic cholecystectomy caused less postoperative suppression of T-cell proliferation than did open cholecystectomy,[42] and minimally invasive thoracic surgery caused less postoperative suppression of circulating lymphocytes than did conventional thoracotomy.[43]

Anesthesia may attenuate the stress response to surgically induced tissue injury, and thus influence the perioperative immune response to surgery. Moreover, attenuation of the stress response may be of greater significance with regional versus general anesthesia. However, anesthetic agents themselves may have immunomodulatory activity, which must be considered in formulating an overall picture of how anesthesia affects perioperative immune function.

Effects of Anesthesia and Anesthetic Agents on Immune Function

Lymphocyte Number and Function

Several studies have found that anesthesia and surgery together can alter the levels of circulating lymphocytes. In patients undergoing elective abdominal surgery with isoflurane general anesthesia, arterial blood lymphocytes were increased at 5 minutes after induction of anesthesia, 5 minutes after skin incision, and 5 minutes after peritoneal incision.[44] Unfortunately, the authors did not measure lymphocyte levels later in the surgical procedure or in the postoperative period.

An early rise in circulating lymphocytes might be transient. Indeed, several studies indicate that perioperative lymphopenia can occur in patients undergoing inhalational anesthesia and surgery.[45] Rem et al.[46] reported decreased blood lymphocytes at 6 and 9 hours after skin incision in women undergoing hysterectomy with halothane anesthesia. Similarly, Corsi et al.[47] found reduced number of T lymphocytes at 10 minutes after the initiation of hysterectomy surgery in patients anesthetized with isoflurane. In these studies, the lymphopenia resolved by 48 hours after surgery. In patients undergoing craniotomy, the postoperative Th1/Th2 cell ratio was reduced in patients anesthetized with isoflurane.[48] A trend toward reductions in both the Th1 cell count and the postoperative Th1/Th2 cell ratio was observed in patients undergoing isoflurane general anesthesia for transurethral resection of the prostate (TURP), although the reductions did not achieve statistical significance.[49]

Perioperative lymphopenia in patients undergoing surgery with isoflurane anesthesia is consistent with data showing reduced plasma levels of IL-2, a key cytokine responsible for T-cell proliferation, in patients undergoing isoflurane anesthesia.[50] Plasma IL-2 was reduced at the end of surgery and had returned to the preinduction level at 24 hours postoperatively. Moreover, because IL-2 promotes T-cell differentiation to Th1 cells, a perioperative reduction in the Th1/Th2 cell ratio is consistent with isoflurane anesthesia suppression of IL-2 production.

One or more circulating factors associated with general anesthesia and surgery may contribute to perioperative lymphopenia.

Such factors might include cortisol and catecholamines released as components of the stress response to surgery, as discussed earlier, as well as intravenous and inhalation anesthetic agents themselves. Indeed, there is evidence that induction agents may suppress lymphocyte proliferation. Devlin et al.[51] treated blood obtained from healthy volunteers with phytohemagglutinin (PHA), an agent commonly used to provoke in vitro T-cell proliferation. Intravenous induction agents such as etomidate inhibit T-cell proliferation at concentrations representative of those achieved in the blood during anesthesia. By contrast, propofol did not impair in vitro T-cell proliferation. In a follow-up study by the same group, blood was collected from healthy volunteers who received intravenous injections of either thiopental or etomidate but did not undergo surgery.[52] In contrast to results of the in vitro studies, the authors found no alteration of PHA-stimulated in vitro T-cell proliferation, although they did find depression of delayed-type hypersensitivity (DTH) reactions to allergens, suggesting that in vivo T-cell *function* was impaired by administration of the induction agents. These latter results are of potential clinical significance because there has been reported an association between depressed DTH reactions and increased postoperative mortality.[53]

In vitro studies suggest that inhalational agents might contribute to perioperative lymphopenia by suppressing lymphocyte proliferation[54] and production of IL-1 and TNF-α[55] and by inducing lymphocyte apoptosis.[56] However, PHA-induced proliferation of lymphocytes obtained from volunteers administered inhalation anesthesia with enflurane or halothane, but who did not undergo surgery, was not impaired.[57]

Studies of B-cell function, although limited, suggest that postoperative reduction of B-cell numbers[45] and suppression of B-cell function[58] can occur in surgical patients. Such responses, however, may result primarily from the stress response to the surgical procedure. In anesthetized patients, B-cell function was not altered until after the surgical procedure was initiated. Recently investigators reported on immune suppression that happens from the effects of anesthesia. Neurosurgical patients were anesthetized using a propofol, sevoflurane, and vecuronium technique. Immune cell numbers of neutrophils, monocytes, lymphocytes, and lymphocyte subsets including T cells, inducer and helper T cells, suppressor and cytotoxic T cells, NK cells, and B cells were measured. Thirty minutes after induction neutrophils, monocytes, and lymphocytes decreased compared with their levels before anesthesia. At extubation the neutrophils returned to the base level. Natural killer cells decreased significantly during anesthesia. The concentration of cytokines in peripheral blood did not change significantly. They concluded that a transient but significant alteration in the distribution of white blood cell populations and lymphocyte subsets was induced by anesthesia.[59] Procopio et al. reported no change in antibody responses to antigen in healthy volunteers who received either isoflurane anesthesia or lumbar epidural anesthesia (lidocaine) but did not undergo surgery.[60]

Anesthesia and surgery may suppress NK-cell number and function and predispose cancer patients to tumor cell metastases.[36,61,62] Activation of the neuroendocrine stress response may be responsible, at least in part, for suppression of NK-cell activity in surgical patients. The intrinsic function to fight cancer cells is competent immune cells, particularly $CD4^+$ T helper 1-type cells, $CD8^+$ cytotoxic T cells, and natural killer cells. However, surgical inflammation, some anesthetics, and inadvertent anesthesia management suppress these effector cells and induce suppressive immune cells, which render cancer patients susceptible to tumor recurrence and metastasis after surgery. Accumulated basic and clinical data suggest that total intravenous anesthesia with propofol, cyclooxygenase antagonists, and regional anesthesia can decrease negative consequences associated with perioperative immunosuppression. Volatile anesthesia, systemic morphine administration, unnecessary blood transfusions, intraoperative hypoxia, hypotension, hypothermia, and hyperglycemia should be avoided.[61] In this regard, NK-cell activity was reduced after hysterectomy[63,64] or upper abdominal surgery.[65] However, Procopio et al.[60] reported *increased* NK-cell cytotoxicity in healthy volunteers who received either isoflurane anesthesia or lumbar epidural anesthesia (lidocaine) but did not undergo surgery. Catecholamine release may be particularly important in surgery-induced NK-cell suppression, because β-adrenergic blockade has been shown to attenuate stress-induced NK-cell suppression in humans.[65]

Some agents used for anesthesia and analgesia may cause suppression of NK cells. In vitro studies have shown inhalational agents to cause dose-dependent suppression of NK-cell activity.[66] Moreover, Melamed et al.[67] demonstrated that administration of halothane, ketamine, or thiopental for 1 hour suppressed NK-cell activity and promoted tumor metastases in a nonsurgical rat model of breast cancer metastasis. By contrast, propofol did not affect NK-cell function nor did it promote tumor metastasis.

Opioids may have effects on NK cells, which express μ and δ opioid receptors. Morphine can decrease the effectiveness of several functions of both natural and adaptive immunity, and significantly reduce cellular immunity.[68] By contrast, intravenous fentanyl administered at clinically relevant doses *augmented* NK-cell cytotoxicity in healthy volunteers who did not undergo surgery.[69] The relevance of this latter finding to surgical patients, though, is unclear. Indeed, patients who received either low- or high-dose fentanyl during surgery demonstrated postoperative suppression of NK-cell cytotoxic activity, the duration of which was greater in those patients who received high-dose fentanyl.[70] Tramadol, a weak opioid agonist that also inhibits norepinephrine and serotonin reuptake, has been found to provide postoperative analgesia comparable to that of morphine without suppressing NK-cell activity.[71]

Of agents used for anesthesia, propofol may have the least effect on lymphocyte function. PHA-stimulated proliferation of T cells isolated from healthy volunteers was not altered by propofol,[51] and propofol increased the in vitro Th1/Th2 cell ratio.[72] In patients undergoing craniotomy, the postoperative Th1/Th2 cell ratio was reduced in patients anesthetized with isoflurane but not in patients anesthetized with propofol.[48] Propofol anesthesia might therefore be beneficial in patients with depressed immune function in whom a decrease in the Th1/Th2 cell ratio could exaggerate the condition.[36]

Phagocyte Function

Numerous studies indicate that anesthesia and surgery can impair phagocyte function and that this effect may result in part from a direct effect of anesthetic agents on PMNs and monocytes/macrophages. Inhalational agents may have suppressive effects on PMN function. Halothane, isoflurane, and sevoflurane were found to inhibit in vitro adhesion of PMNs to endothelial cells,[73] and halothane and isoflurane inhibited in vitro PMN superoxide ion production, that is, the "respiratory burst" important for killing pathogens.[74,75] Heine et al.[76] studied PMNs isolated from surgical patients and found in vitro phagocytosis and respiratory burst to be suppressed after 4 hours of isoflurane anesthesia. Inhalational agents also impair in vitro monocyte chemotaxis,[45] and Kotani et al.[77] found decreased phagocytic activity of alveolar macrophages isolated from patients undergoing orthopedic surgery with isoflurane anesthesia.

Intravenous agents used in anesthesia may alter PMN function. Propofol, etomidate, ketamine, and thiopental were found to suppress in vitro PMN phagocytosis and superoxide production.[78-81] Neutrophils isolated from surgical patients displayed reduced in vitro phagocytosis and respiratory burst after 4 hours of propofol anesthesia.[76] The effects of propofol on PMN function might depend on its lipid carrier. Propofol dissolved in long-chain triglycerides (LCTs) suppressed in vitro PMN superoxide formation and phagocytosis. By contrast, propofol dissolved in a mixture of LCTs and medium-chain triglycerides (MCTs) enhanced PMN production of reactive oxygen molecules.[79] Similarly, etomidate dissolved in a LCT/MCT mixture enhanced PMN function, whereas etomidate dissolved in conventional propylene glycol solvent modestly suppressed PMN function. Interestingly, and of potential clinical significance, the α_2-agonist sedative agents clonidine and dexmedetomidine do not suppress in vitro PMN phagocytosis or superoxide ion formation, despite the fact that PMNs do display α_2 adrenoceptors.[82]

Intravenous anesthetic agents may also impair monocyte/macrophage function. Ketamine and midazolam reduced in vitro monocyte chemotaxis and proliferation, and thiopental, etomidate, and propofol inhibited proliferation of cultured monocytes.[83,84] Kotani et al.[77] found decreased phagocytic activity of alveolar macrophages isolated from patients undergoing orthopedic surgery with propofol anesthesia.

Among the opioids commonly used in anesthesia and surgery, morphine may be the only agent that suppresses phagocyte function. Welters et al.[85] demonstrated dose-dependent reduction of PMN phagocytosis and respiratory burst in vitro by morphine action on μ-3 opioid receptors on PMN cell membranes. The inhibitory effects of morphine were linked to nitric oxide production and were blocked by the μ-receptor antagonist naloxone. By contrast, alfentanil, fentanyl, and remifentanil had no effect on PMN respiratory burst or phagocytosis.[80,86] These latter results are consistent with reports that fentanyl does not bind to the μ-3 receptor.[87] Morphine also inhibits macrophage phagocytosis[88] and release of IL-10 and IL-12.[89]

Regional Anesthesia and Analgesia

It is generally agreed that the stress response to surgery is less with neuraxial anesthesia than with general anesthesia. Neuraxial anesthesia can be very effective in attenuating postoperative pain, which is a potent activator of the stress response and probable contributor to postoperative immunosuppression. Not unexpectedly, a number of studies have shown that neuraxial anesthesia can prevent, or reduce the degree of, perioperative immune dysfunction.

In a study of women undergoing elective hysterectomy, Rem et al.[46] demonstrated that epidural anesthesia prevented postoperative lymphopenia that occurred in patients who underwent general anesthesia. In another study of patients undergoing hysterectomy, epidural anesthesia prevented lymphopenia and reduced NK-cell activity that occurred in patients undergoing neuroleptanesthesia. In addition, epidural anesthesia attenuated the perioperative increase in cortisol level.[63]

Hole and Unsgaard[90] isolated lymphocytes from patients undergoing total hip replacement under either general or epidural anesthesia. Lymphocytes were then treated with PHA to provoke in vitro T-cell proliferation. PHA-induced T-cell proliferation was depressed during and after surgery in patients receiving general anesthesia but not in patients receiving epidural anesthesia. In a separate study by Hole[91], serum obtained from patients undergoing general anesthesia, but not that from patients undergoing epidural anesthesia, showed suppressed proliferation of T cells when compared with cells obtained from healthy, nonsurgical volunteers. In a recent meta-analysis, researchers compared the effect of central neuraxial (spinal or epidural) anesthesia with general anesthesia on postoperative NK-T lymphocyte function. Anesthetic technique did not appear to significantly affect postoperative NK-T lymphocyte function. [92]

In patients undergoing TURP, significant reductions in lymphocyte number and in vitro response to mitogens were observed in patients who received general anesthesia, but not in patients who received spinal anesthesia.[93] Le Cras et al.[49] found the postoperative Th1/Th2 cell ratio to be increased in TURP patients who received spinal anesthesia, compared with a trend for reduced Th1/Th2 cell ratio in patients who received isoflurane general anesthesia. The combination of spinal block with sevoflurane general anesthesia preserved the Th1/Th2 cell ratio and attenuated tumor cell metastases after experimental laparotomy in mice.

SUMMARY

Two components of immunity provide defense against invading pathogens: the innate immune system and the adaptive immune system. Innate immunity is nonspecific, and adaptive, or acquired, immunity is specifically directed against a particular antigen.

Both the innate and acquired immune systems participate in the production of inflammation, which is the collective response to tissue injury caused by infectious microorganisms, toxins, or trauma. In some cases, the immune response can be greatly exaggerated, a situation referred to as *hypersensitivity*. Anaphylaxis is a severe and potentially life-threatening type I hypersensitivity reaction.

Immune system dysfunction can manifest as autoimmune disease or immunosuppression. Impairment in mechanisms that normally act to prevent autoreactivity of the immune system can lead to autoimmune disease. Primary immunodeficiency is caused by deficient function of lymphocytes, the complement system, or phagocytes.

Secondary immunodeficiency can result as an adverse effect of immunosuppressive drugs administered to prevent graft rejection or treat autoimmune disease or from infection that causes depletion of immune cells, such as occurs with human immunodeficiency virus-1 (HIV-1) infection. Numerous clinical presentations have the potential to affect anesthesia management in the patient infected with HIV. Percutaneous injury with a hollow-bore needle is the most common mechanism of occupational HIV transmission.

Surgery strongly stimulates the body's stress response, which can produce immunosuppression by release of cortisol from the adrenal cortex and catecholamine secretion from the adrenal medulla. Perioperative lymphopenia commonly occurs in patients undergoing general anesthesia and surgery, and surgical stress may reduce the Th1/Th2 cell ratio and predispose to certain infections. Impaired lymphocyte proliferation has been reported in surgical patients and may be caused by circulating factors such as stress hormones and intravenous and inhalation anesthetic agents. Opioids, in particular morphine, may suppress NK cell activity.

Neuraxial anesthesia may prevent, or reduce the degree of, perioperative immune dysfunction. Spinal and epidural anesthesia have been found to prevent postoperative lymphopenia and adverse changes in lymphocyte subpopulations and NK-cell activity that occur in patients who undergo general anesthesia. Thus one potential advantage of neuraxial anesthesia over general anesthesia may be less postoperative immunosuppression.

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42 CHAPTER Anesthesia and Laser Surgery

◆ *Bernadette T. Higgins Roche*

The term *laser* is an acronym for *l*ight *a*mplification by the *s*timulated *e*mission of *r*adiation. Stimulated emission of radiation was first proposed by Albert Einstein in 1917, and the first laser was developed by Arthur Schawlow and Charles Townes in the late 1950s; Townes went on to win the Nobel Prize in physics for his work on masers and lasers. The first laser, a 694-nanometer (nm) ruby laser, was built by Theodore Maiman in 1960. Lasers now have widespread use in a variety of unrelated fields, including construction, communications, the military, energy production, and the entertainment industry. Lasers are also used in spas and beauty salons for laser hair removal (LHR) by cosmetologists and estheticians.

Medical lasers were introduced in the mid-1960s when the ruby and the argon-ion lasers were first used in retinal surgery. With the development of smaller and more powerful lasers, the use of lasers expanded to all surgical specialties and are frequently used in laparoscopic procedures, surgery of the upper and lower airways, endoscopic arthroscopic procedures, and transmyocardial and transluminal revascularization. Capable of making incisions as small as 0.5 microns, the laser scalpel offers definite advantages over traditional surgery, including improved access to operative sites, greater precision in tissue destruction and removal, increased anatomic preservation, and controlled hemostasis. Surgical lasers have revolutionized the field of dermatology and esthetic surgery.[1] In dentistry, lasers are used for gum reshaping, drilling, and whitening of teeth. Lasers continue to play a major role in ophthalmology, in large part because of the introduction of the excimer laser in the 1980s. In 1995 and 1999, the Food and Drug Administration (FDA) approved excimer lasers for photorefractive keratectomy (PRK) and laser-in-situ keratomileusis (LASIK), respectively. LASIK is now one of the most common surgical procedures in the United States. Medical lasers have other therapeutic applications, including photodynamic therapy (PDT) in which laser-activated drugs are used to destroy cancer cells. Medical lasers are commonly used even in private medical offices.

BASIC PRINCIPLES OF LASERS

Light

Electromagnetic radiation is a broad spectrum of heat energy composed of radio waves, microwaves, infrared waves, visible light waves, ultraviolet waves, x-rays, and gamma rays (Figure 42-1). A wavelength is the distance between two successive points on a periodic wave that has the same phase. The wavelength decreases and the frequency increases as the electromagnetic spectrum moves from radio waves to gamma waves. Ultraviolet, visible, and infrared waves with a wavelength range of 200 to 1000 nm make up the optical portion of the electromagnetic spectrum. Visible light includes a rainbow of colors—red, orange, yellow, green, blue, indigo, and violet—with a very narrow range of wavelengths of 400 nm (violet) to 700 nm (red). The ultraviolet and infrared portions of the optical spectrum are invisible to humans. Infrared radiation is perceived as heat, and ultraviolet radiation causes a chemical reaction in human skin with little heat production.

Light can be described as both a wavelength and a particle of energy called a *photon*. The energy of an electromagnetic wave is proportional to its frequency and inversely proportional to its wavelength. Because of its short wavelength and high frequency, ultraviolet radiation contains a lot of energy that can damage the skin. The energy of a photon is defined as the energy emitted when an electron falls from an excited orbit to one of lower energy; the energy between the two orbits defines the wavelength of the emitted photon. The following equation describes the relationship between the energy and the wavelength of light.

$$E = hc / \lambda$$

(E = energy in joules, h = Planck's constant (6.63×10^{-34} J-s), c = the speed of light (2.998×10^{-8} m/s), and λ = wavelength in meters).

Spontaneous and Stimulated Absorption and Emission of Energy

In an atom, electrons exist in specific locations called orbits or orbitals. A specific level of energy is associated with each orbital. The ground state or orbital closest to the nucleus has the lowest energy state; the higher orbitals have the greatest energy. If an electron is to move to a higher orbital, it must gain the difference in energy between the two orbitals; conversely, it will lose energy if it falls to a lower orbit. Electrons have a tendency to return to the ground state spontaneously, releasing a photon of light energy in the process. This is called *spontaneous emission of radiation*. The energy of the photon and therefore its wavelength is dependent on the energy difference between the two orbits. Light produced by fluorescent lights or incandescent bulbs is a result of electrons changing orbits and returning to ground state. Both the energy of the released photon and the wavelength of the light are proportional to the energy difference between the excited state and the ground state of the atom. Light produced by spontaneous emission is composed of different wavelengths and frequencies; consequently, the photons oscillate randomly (noncoherence), and the light disperses as it travels.

An atom can be "pumped" up to a higher energy level by a stimulating photon if its energy is the same as the energy difference between the two orbitals. A stimulating photon can also cause an atom in an excited state to undergo decay and release energy. When an atom is struck by a stimulating photon, it decays back to its ground state and emits a second photon. If the energy of the stimulating photon is equal to the energy difference between the excited and ground states of the atom, the emitted photon will have the same wavelength, energy, frequency, and direction as the stimulating photon. This process is known as *stimulated emission of radiation* (Figure 42-2). The two photons can strike other excited

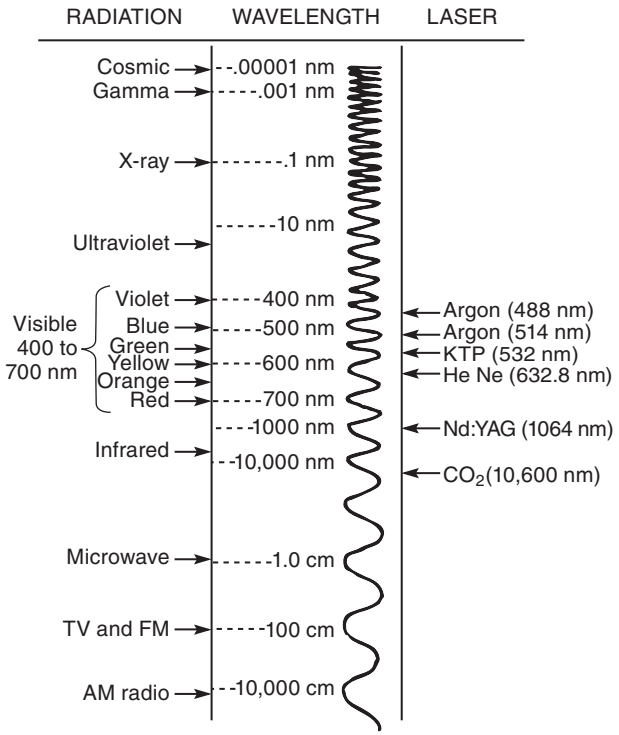

FIGURE **42-1** Electromagnetic spectrum. (Modified from Arndt KA, et al., eds. *Lasers in Cutaneous and Aesthetic Surgery*. Philadelphia: Lippincott-Raven; 1997:4.)

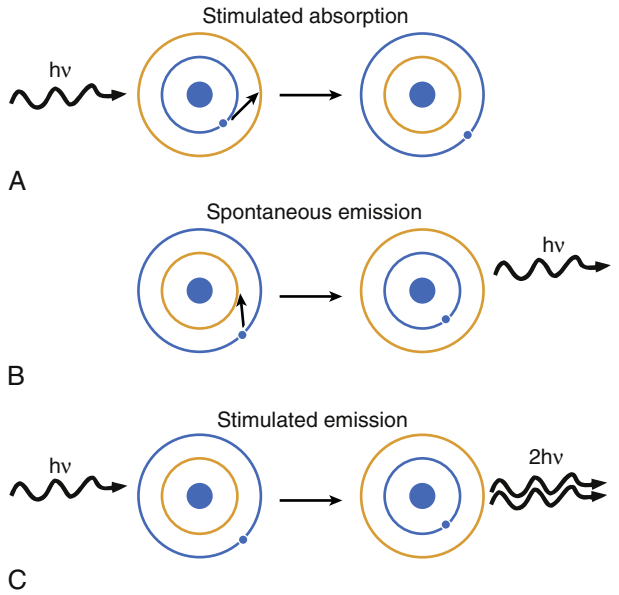

FIGURE **42-2** Absorption, emission, and stimulated emission. Photons may interact with orbital electrons in three ways. **A,** A photon striking an electron may transfer its energy to the electron, pushing the electron into a higher-energy orbit. This interaction is known as *absorption*. **B,** An electron in an orbit higher than the ground (i.e., minimal energy) state may spontaneously lose energy in the form of an emitted photon. **C,** An incoming photon may interact with an electron that is already in a high-energy orbit, with the result that two perfectly coherent, collimated photons leave the electron; this is known as *stimulated emission*. (From Miller RD, et al. *Miller's Anesthesia*. ed 7. Philadelphia: Churchill Livingstone; 2010:2408.)

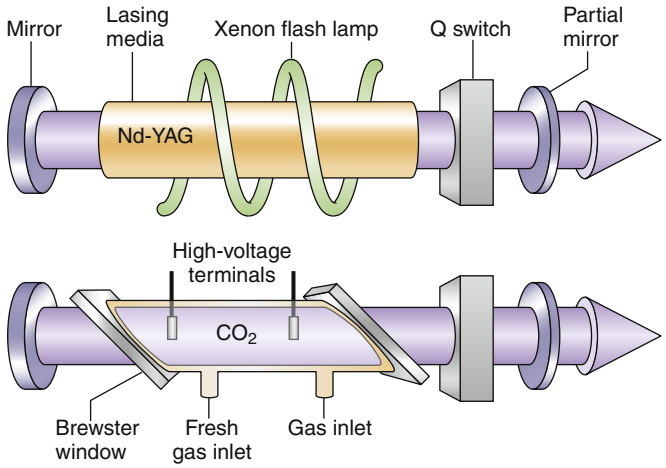

FIGURE **42-3** Generic laser hardware. A laser system consists of several components, regardless of whether the laser is a solid-based, liquid-based, or gas-based device. The central component is the laser medium itself, which may be a solid crystal of yttrium-aluminum-garnet (YAG) with a small concentration of neodymium as dopant, or may be a tube containing carbon dioxide (CO_2). The energy pump provides the means of obtaining a population inversion of orbital electrons; it may consist of a xenon flash lamp or an electric spark generator. A pair of axial mirrors permits repeated passes of collimated photons through the medium, allowing maximum amplification by stimulated emission. The mirror on the right is not 100% reflective, allowing the beam to escape eventually. The optional Q switch increases the efficiency of pulsed lasers by allowing a small delay to increase the pumping. (From Miller RD, et al. *Miller's Anesthesia*. ed 7. Philadelphia: Churchill Livingstone; 2010:2408.)

atoms and stimulate additional emission of photons, resulting in a sudden burst of coherent radiation as all the atoms return to ground state in a rapid chain reaction.

Properties of laser light that differentiate it from fluorescent or incandescent light include coherence, directionality, and monochromaticity. Laser beam photons have the same wavelength and oscillate synchronously in identical phase with one another (coherence). Laser light moves in a parallel, narrow beam (spatial coherence) over long distances and displays minimal dispersion. This spatial coherence, known as *collimation*, allows the laser light to be focused on a very small area (Figure 42-3).

Reflectors placed on the moon allow calculation of the distance to the moon by the length of time it takes for a laser light to return to earth. Reflection of a laser beam can reduce the collimation and increase the dispersion, especially if the reflecting surface has a matte or dull finish; however, the reduction in collimation and increased dispersion of a reflected laser beam is insignificant if the reflecting surface is smooth and shiny.

Laser light is composed of specific and discrete wavelengths; consequently, the light emitted is monochromatic and specific for each laser. Just as white light is composed of multiple colors, some lasers are tunable and can emit light at several different wavelengths. However, tunable lasers can only emit one color or wavelength at a time. A typical light bulb is more powerful than a laser, but its light is not collimated, and the dispersion of the light reduces its intensity. In contrast, the intensity of a 1-milliwatt (mW) laser can be six times that of a 100-watt (W) incandescent bulb. Although a typical laser emits only a few milliwatts of power, from a distance of 100 feet lasers can produce a highly intense beam of 1 to 2 mm that can be 1 million times more concentrated than light from an incandescent source.

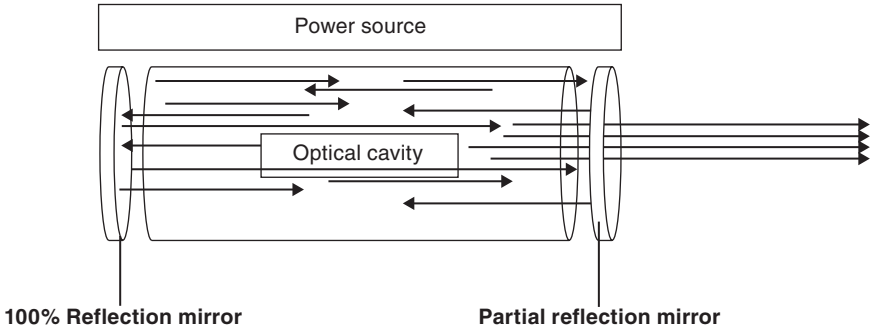

FIGURE **42-4** Basic components of a laser. The optical cavity contains the lasing medium (e.g., solid, liquid, gas). The power source (e.g., flash lamp, electric current, other laser) pumps up the electrons in the lasing medium to a higher energy state. Two mirrors reflect the photons back into the cavity, where they stimulate other excited atoms to emit identical photons. One mirror is partially transparent and allows a portion of the laser beam to exit the cavity in a narrow beam.

Components of a Laser

A laser is a device that creates and amplifies a narrow, intense beam of coherent light. It consists of an energy source, an optical resonating cavity, and a laser medium to create the laser light (Figure 42-4). Lasers require an external energy source to transfer or pump up the energy of the laser medium. The electrons in the lasing medium absorb the energy and move to a higher energy state. Flash lamps, continuous light, high-voltage discharge, diodes, or another laser can be used as the energy source. Electric current is used to excite gas lasers, such as carbon dioxide (CO_2) and argon (Ar) lasers. Liquid and solid state lasers, such as the potassium-titanyl-phosphate (KTP) laser, require activation by a flash lamp or another laser.

The optical resonating cavity, a tubelike structure, provides optimal amplification of the laser beam. It contains the lasing medium and a mirror at each end of the tube. When the lasing medium is excited by the outside energy source (e.g., flash lamp, electric current), the atoms are "pumped" to a higher energy level, increasing the number of atoms in the excited state. Population inversion is necessary for stimulated emission of radiation, and it occurs when more atoms are in an unstable excited state than the resting state. When one of the atoms spontaneously decays back to its ground state, it releases a photon that "stimulates" another excited atom to decay back to its ground state, releasing another photon. The wavelength, frequency, phase, and direction of the second photon are identical to those of the first photon. The mirrors reflect the excited photons back into the resonating cavity at approximately 186,000 miles per second, where they travel back and forth in a parallel fashion, stimulating the release of more photons from other excited atoms and amplifying the resultant laser light. One of the mirrors is partially transparent and allows a very thin beam of the coherent, collimated, and monochromatic laser light to exit and focus on the target tissue.

The laser medium can be a solid, gas, liquid, or semiconductor that is stimulated to a metastable state when pumped with an external energy source. Lasers are commonly named after the laser medium that determines the wavelength output of the laser. Solid-state lasers such as the neodymium: yttrium-aluminum-garnet (Nd:YAG) laser use a solid matrix that is doped with a small amount of impurity (dopant). It is the impurity, that is, Nd, that provides the energy source for the laser. Solid-state lasers are more powerful than gas lasers and require optical pumping. Gas lasers use a variety of gases as lasing media, including argon, CO_2, helium, helium-neon, and krypton and require an electrical source of energy for pumping. Complex dyes, dissolved in a liquid such as alcohol, constitute the lasing media in liquid lasers. Optically pumped, liquid lasers are tunable over a broad range of wavelengths, mostly in the visible spectrum. Excimer lasers use electrical stimulation to produce a dimer of a halogen such as chlorine and fluorine and an inert gas such as argon, krypton, or xenon. The dimer is unstable and quickly breaks down into its constituent atoms, releasing energy in the form of light. Semiconductor lasers, also called *diode lasers*, are composed of semiconductor crystals that are pumped by a high-intensity current. They are commonly used in compact disc players, laser printers, and laser pointers. The gallium-arsenide laser is an example of a semiconductor laser.

Modes of Operation

The majority of medical lasers deliver only one wavelength, and laser selection is dependent on the desired effect on the targeted tissue. The wavelength or color of the laser light is dependent on the laser medium, and the effect on tissue is dependent on the wavelength. In addition to selecting the appropriate wavelength, the surgeon must use the appropriate exposure time and energy density (power setting) to achieve the intended photomechanical, photothermolytic, or photochemical effect.

A laser beam can be delivered in a continuous wave (CW), pulsed-wave, or Q-switched mode. In the CW mode, the laser continues to emit a steady beam as long as the laser medium is excited. Output is measured in watts and can vary significantly among lasers. For example, the power of the helium-neon laser is measured in milliwatts, whereas the output of the more powerful CO_2 laser is measured in kilowatts. Power density of the beam (irradiance or flux) varies from a few watts per square centimeter to hundreds of watts per square centimeter.

Collateral tissue damage can be expected if the laser beam is held on tissue longer than the thermal relaxation time (i.e., time it takes for 50% of the laser energy to be thermally conducted to surrounding tissue). Pulsing the laser beam or scanning a continuous beam allows time for concentration of the energy, limits the exposure time, and minimizes thermal damage. In the pulsed mode, the laser emits peak energy levels in individual pulses from femtoseconds (quadrillionths of a second) to seconds. The power of a pulsed laser is measured in joules, and energy intensity is expressed as joules per square centimeter.

The duration of the laser beam is limited by computerized scanning of the laser beam in a preset pattern before delivery of the beam to the tissue. In the Q-switched mode, the laser emits high-energy, ultrashort pulses (approximately 10 to 250 nanoseconds [nsec]). A shutter is placed in the optical path to allow the buildup

of a large population inversion. After release of the shutter, the electrons fall rapidly to ground state, releasing a large amount of energy that is measured in megawatts.

Laser effects on tissue can be controlled by the mode of delivery. The Nd:YAG laser is used in the CW mode for coagulation of tumors, in the pulsed mode for hair removal, and in the Q-switched mode for tattoo removal. In the CW mode, the CO_2 laser can be focused very tightly and used for incision, much like a scalpel, whereas the defocused CO_2 laser can be used to vaporize a larger area of tissue. When delivered through a scanning device, the laser beam can remove a predetermined thickness of skin.

Fiberoptic cables are used for delivery of laser beams with visible and near-infrared wavelengths. Articulated arms with reflecting mirrors mounted in tubes are used to direct the beam of a far-infrared laser (CO_2). Additional devices may be attached to the fiberoptic cables or articulated arms, including slit lamps for use on the eye, operating microscopes, and insulated fibers for use with endoscopes. Contact laser probes (sapphire) attached to the distal end of a fiberoptic bundle transform the light energy into heat for precise cutting and reduced penetration.

EFFECTS OF LASERS ON BIOLOGIC TISSUES

Lasers are associated with rapid and precise vaporization or coagulation of tissues and are commonly used in a variety of unrelated diagnostic and therapeutic procedures. Laser light is monochromatic and has very selective effects on biologic tissues. The degree of laser light transmission, scattering, reflection, or absorption is dependent on the tissue and the wavelength of the light. Absorption of the light is necessary for the laser to be effective; if the tissue transmits, reflects, or scatters the light, the laser will have little or no effect on the tissue. A specific wavelength may be absorbed by one type of tissue and transmitted by another. Biologic tissues can be thought of as an aqueous solution of light-absorbing molecules. Chromophores, such as hemoglobin and melanin, and water are the main absorbing components, and they determine the reaction of the tissue to the laser light. To be effective, the laser light must match the absorptive property of the tissue. If light absorption occurs, the laser light is converted to heat; vaporization or ablation of the tissue occurs when the temperature reaches 100° C. As the tissue is vaporized, the thermal energy of the laser beam cauterizes capillaries and provides immediate hemostasis. A lower temperature would produce tissue coagulation or denaturation rather than ablation.

A tissue's reaction to light absorption depends on the wavelength, intensity, and exposure time of the light. Powerful, short pulses of laser light cause an explosive tissue expansion (photomechanical reaction), whereas low-power, long pulses cause a rapid increase in temperature (photothermal reaction) that results in tissue vaporization and coagulation. When applied for longer durations, low-power lasers can cause a chemical reaction or change in specific molecules (photochemical reaction). Laser light is also used to activate photosensitizing medications that are selectively absorbed by a specific tissue (photodynamic reaction). The effectiveness of nonthermal laser-assisted techniques is dependent on the ability of special drugs (photosynthesizers) to produce cytotoxicity in the presence of oxygen (O_2) after stimulation with light of an appropriate wavelength.

Tissue absorption is greatest with longer wavelengths such as the far-infrared wavelength of the CO_2 laser (10,600 nm). The CO_2 laser beam is completely absorbed by water in the first few cellular layers, resulting in explosive vaporization of the top layer but little or no damage to the underlying tissues. Excimer lasers (ultraviolet) are associated with an even more superficial effect because of their strong absorption by water. The light from lasers with visible wavelengths, such as the ruby, argon, and krypton lasers, is transmitted by water and absorbed by cells that contain dark pigment. It can penetrate the skin and the cornea to coagulate pigmented or vascular lesions. The light from near-infrared lasers, such as the Nd:YAG, is transmitted rather than absorbed by water. Because they have a greater tissue penetration, near-infrared lasers are better suited for deeper procedures such as tumor debulking. Advantages of lasers include precision, access to remote sites in the body, reduced blood loss, reduced damage to adjacent tissue, and improved patient satisfaction. A disadvantage of laser therapy may be delayed wound healing.

MEDICAL LASERS

The major types of lasers used in medicine are far-infrared (CO_2), mid-infrared (erbium [Er]:YAG, holmium [Ho]:YAG, Nd:YAG), near-infrared (diode), visible (ruby, krypton, argon, copper, and gold vapor), and ultraviolet (excimer). Commonly used surgical lasers are listed in Table 42-1.

Carbon Dioxide Laser

The CO_2 laser has wide application and is the most commonly used surgical laser. The infrared light produced by the CO_2 laser (10,600 nm) is invisible to the human eye, and a low-power helium-neon (He-Ne) laser (633 nm) is incorporated to provide a visible red beam for surgical aim. Because it emits light in the infrared region of the electromagnetic spectrum, the CO_2 laser is a powerful but dangerous laser. Infrared radiation is heat, and this laser basically melts through whatever its beam is focused on, including steel. It is a very precise laser; with the lateral zone of damage less than 0.5 *nanometer* (nm) from the area of incision. The CO_2 laser beam is not transmitted by quartz, glass, or other transparent material and must be delivered as a free beam or through a rigid endoscope with a mirrored, articulated arm. The CO_2 laser light is strongly absorbed by water, and vaporization of cells occurs within the first 100 to 200 μm of the irradiated surface. It can be used in both the CW and pulsed-wave mode. Focused into a tight beam, the CO_2 laser can be used for cutting. Defocusing the beam decreases the power density, and the tissue will be vaporized, or *ablated*. The CO_2 laser is used extensively in general surgery, orthopedics, gynecology, urology, and otolaryngology and is associated with minimal blood loss. When used with a scanning device, thin layers of the skin are ablated for skin resurfacing during cosmetic surgery. Because of its high power, the CO_2 laser is widely used in industry for cutting, drilling, and welding.

Yttrium-Aluminum-Garnet Lasers

The lasing medium of the YAG laser is a YAG crystal rod doped with atoms of rare earth minerals, which accounts for the different properties of the YAG lasers. YAG lasers can be used in the CW, pulsed-wave, or Q-switched mode.

Neodymium: Yttrium-Aluminum-Garnet Laser

The Nd:YAG laser emits a near-infrared invisible light at 1064 nm and requires the addition of a visible aiming beam. It has a penetration of 5 to 7 mm and can be used to cut or coagulate tissue. In the Q-switched mode, the laser removes black tattoo ink and hair. The Nd:YAG laser has important applications in internal debulking and is used to treat gastrointestinal and tracheobronchial tumors and genitourinary lesions. The pulsed and Q-switched Nd:YAG laser is used in ophthalmology. The energy of the Nd:YAG beam is more widely dispersed, and damage to adjacent tissues may not be evident for hours after the laser treatment.

Holmium: Yttrium-Aluminum-Garnet Laser

When doped with holmium (Ho), the YAG laser emits a mid-infrared beam at 2070 nm that is strongly absorbed by water. Output in the mid-infrared spectrum requires a coincident aiming beam. The Ho:YAG laser is used to vaporize, cut, coagulate, and sculpt avascular tissue with a minimal amount of thermal necrosis. The primary applications of the Ho:YAG laser are in endoscopic orthopedic procedures (bone and cartilage ablation) and urology (stone removal and transurethral resection of the prostate [TURP]).

Erbium: Yttrium-Aluminum-Garnet Laser

When a YAG laser is doped with erbium (Er), it emits a mid-infrared beam at 2940 nm (peak absorption of water). Because the infrared beam is not transmitted by quartz or glass, the Er:YAG can be used only as a free beam or through a rigid endoscope. It has limited penetration and excellent precision. It is used extensively in laser resurfacing of the skin and vaporization of fibrous tissue, cartilage, and bone. Because of its ability to penetrate dental tissue, the Er:YAG laser is also used in microdentistry for cavity fillings, root canals, and treatment of gum disease.

TABLE 42-1 Common Surgical Lasers

Laser	Wavelength	Applications
Far-Infrared		
CO_2	10,600 nm	Multiple uses: general surgery, orthopedics, gynecology, urology, otolaryngology, plastic surgery
Mid-Infrared		
Nd:YAG	1064 nm	Multiple uses: gastroenterology, pulmonology, urology, ophthalmology, dermatology
Ho:YAG	2070 nm	Orthopedics, urology
Er:YAG	2940 nm	Dermatology
Near-Infrared		
Diode	800-900 nm	Multiples uses: ophthalmology, otolaryngology, periodontics, cosmetic surgery, pain management Multiple nonmedical applications
Visible		
Argon	488 and 514 nm	Multiple uses: ophthalmology, plastic surgery, dermatology, gynecology, otolaryngology
Krypton	476, 521, 568 nm	Dermatology
Copper bromide	511 and 577 nm	Dermatology, photosynthesizer
KTP	532 nm	Dermatology
Pulsed dye	577-585 nm	Dermatology
Gold	578-628 nm	Oncology
Ruby	694 nm	Dermatology
Alexandrite	755 nm	Dermatology
Ultraviolet (Excimer)		
Argon-fluoride	193 nm	Multiple uses: ophthalmology, dermatology
Krypton-fluoride	249 nm	Dermatology
Xenon-chloride	308 nm	Multiple uses: dermatology, ophthalmology, dermatology
Xenon-fluoride	351 nm	Multiple uses: angioplasty, ophthalmology, dermatology

Er:YAG, Erbium: yttrium-aluminum-garnet; Ho:YAG, holmium:YAG; *KTP*, potassium-titanyl-phosphate; *Nd:YAG*, neodymium:YAG.

Diode Lasers

Diode lasers are semiconductors that emit a near-infrared light (800 to 900 nm) when pumped with a high-intensity electric current. Medical uses include ophthalmology, dermatology (hair removal), and periodontal surgery. Diode lasers are also used to "pump" other laser media such as YAG rods. They have multiple nonmedical applications and are used in laser printers, laser pointers, the entertainment industries, and fiberoptic communication systems.

Visible Lasers

Argon Laser

In an argon laser, the argon gas has lost one or more of its electrons, and the positive ions are excited by a large electrical discharge. The argon ion laser emits visible blue-green light with wavelengths of 488 nm and 514 nm simultaneously. The laser light is transmitted by water and absorbed by hemoglobin and melanin, where the main effect is photocoagulation. Penetration is approximately 1 to 2 millimeters (mm), but this can vary depending on the degree of pigmentation. The beam passes through quartz optical fibers, allowing the laser to be used with a microscope or endoscope. The argon laser is used in ophthalmology, plastic surgery, dermatology, gynecology, and otolaryngology.

Krypton Laser

The active medium krypton is also a rare gas with one or more electrons removed, and the krypton ions are excited by an electrical discharge. The laser produces visible green and blue light at 476, 521, and 568 nm. It is absorbed by hemoglobin and used for photocoagulation of vascular or pigmented lesions.

Ruby Laser

The ruby laser uses a synthetic ruby crystal of aluminum oxide doped with chromium. It emits a red light with a wavelength of 694 nm and has a penetration greater than 1 mm. The ruby laser light is absorbed by melanin and blue, green, and black pigment. It is very effective for tattoo removal, hair removal, and treatment of pigmented lesions such as freckles, liver spots, and nevi (Q-switched mode). Although the ruby laser was one of the first medical lasers, its use in surgery has declined in favor of newer and more powerful lasers.

Alexandrite Laser

Named after Czar Alexander II, the solid-state alexandrite laser contains a rod of synthetic chrysoberyl doped with chromium. It emits a deep red light at 755 nm, and frequency doubling of the alexandrite laser produces a tunable laser output of 360 to 400 nm. Blue and black pigments absorb the beam, with a lesser degree of absorption by melanin. It is used for tattoo removal, and treatment of some pigmented lesions.

Metal Vapor Lasers

The active medium of metal vapor lasers is a neutral metal heated beyond its vapor point. A pulsed electrical discharge is used for excitation of the vapor. Vaporized copper bromide emits green light at 511 nm and yellow light at 577 nm that is used to treat vascular lesions. It also has applications for facial resurfacing. The gold vapor laser (578 to 628 nm) is used in photodynamic therapy for cancer.

Potassium-Titanyl-Phosphate Laser

The wavelength of the Nd:YAG laser is halved when it is passed through a potassium-titanyl-phosphate (KTP) crystal. A solid-state laser, the KTP laser is similar to the argon gas laser. The beam is transmitted by water and absorbed within 1 to 2 mm of vascular or pigmented tissue. A bright green light (532 nm) delivered through fiberoptics, scanners, or microscopes is used to cut tissue (CW mode) and remove vascular lesions (pulsed mode) and red-orange and black tattoo ink (Q-switched mode). Although the power density of the KTP laser is sufficient to cut vascular tissue, it does not provide effective hemostasis.

Dye Lasers

Organic fluorescent materials are dissolved in a solvent such as methanol and are typically pumped with a flashlamp or another laser. The energy levels of the dyes are very close to one another and allow the lasers to release a wide range of wavelengths. In the CW and pulsed mode, dye lasers have wavelengths of 400 to 1000 nm. They can produce extremely short pulses (measured in trillionths of a second [picoseconds]). The major advantage of the dye laser is the ability to tune the wavelength to maximize the laser-tissue interaction. Dye lasers are used in dermatology for excision of vascular and pigmented lesions, in urology for treatment of urinary calculi, and in oncology for photodynamic therapy. The pulsed dye laser (PDL) uses a rhodamine dye to emit a yellow laser beam at 577 to 585 nm (peak absorption of hemoglobin). It is the laser of choice for treatment of port-wine stains and thick, red scars.

Excimer Lasers

Derived from the terms *excited* and *dimer,* excimer lasers use a medium composed of a reactive noble gas (chlorine or fluorine) and an inert halogen gas (argon, krypton, or xenon). When the medium is electrically stimulated, an unstable pseudomolecule (dimer) is produced. As the dimer breaks down to its constituent atoms, it releases light in the ultraviolet range that is strongly absorbed by water. Excimer lasers have a photochemical effect on targeted tissues (pulsed mode), with minimal thermal effect on the underlying tissue. The very short wavelength (ultraviolet) is capable of high resolution and has applications in microscopic surgery. Examples of excimer lasers include the argon-fluoride (193 nm), krypton-fluoride (249 nm), xenon-chloride (308 nm), and xenon-fluoride (351 nm) lasers. They are currently used in ophthalmology for photorefractive keratectomy (PRK) and laser-in-situ keratomileusis (LASIK). Other uses include removal of arterial plaques and treatment of psoriasis.

Cold Lasers

Cold lasers, also known as *low-level laser therapy (LLLT)* and *soft lasers,* use diodes to produce visible to infrared light. The laser beam can penetrate up to 2 inches without damaging tissues or producing a significant amount of heat. Through biostimulation of cellular metabolism, cold lasers speed up the healing process. They are used for treatment of carpal tunnel syndrome and other soft-tissue injuries.

Photodynamic Therapy

Photodynamic therapy (PDT) involves administration of photosensitizers, chemical entities that absorb light and induce a change in another chemical. They are used in the diagnosis of cancer because of their tendency to accumulate in cancer cells. They are also used to treat cancer. Approximately 72 hours after an intravenous administration, when the photosensitizer has left normal cells but remains in cancer cells, the tumor is exposed to laser light with a red wavelength. The photosensitizer absorbs the light and reacts with oxygen to produce free oxygen radicals that destroy cancer cells. Currently PDT is used to treat bladder, esophageal, and pulmonary tumors. It is also used in dermatology (local application) for treatment of acne, psoriasis, and skin cancer. New research supports the use of PDT in antimicrobial therapy because of its ability to target many viral and bacterial pathogens.

LASER SAFETY

Lasers are divided into four classes according to their potential for causing biologic damage (Table 42-2). Class I lasers are incapable of producing damaging radiation and are exempt from radiation hazard controls. This classification includes CD players and laser printers; supermarket laser scanners are classified as IA. Class II lasers emit radiation in the visible portion of the electromagnetic spectrum, but their radiant power is less than 1 mW. The human aversion reaction to bright light will protect the eyes, but injury

TABLE 42-2 Laser Classification

Class	Laser Description
Class I	Do not emit hazardous radiation and are exempt from radiation hazard controls. Typically continuous wave of 0.4 μW at visible wavelengths. *Examples:* CD players and laser printers, CD-ROM devices, geologic survey equipment, and laboratory analytical equipment.
Class IA	Includes lasers that are not intended for viewing. Maximum power is 4.0 mW. *Example:* supermarket laser scanners.
Class II	Do not cause ocular injury unless viewed directly for an extended period. The normal aversion response to bright light protects the eye from a brief exposure. Class II lasers only operate in the visible range (400-700 nm). Maximum power is 1 mW or less. *Examples:* helium-neon lasers and some laser pointers.
Class IIA	Special-purpose lasers not intended for viewing. Power output is less than 1 mW. Ocular injury can occur if viewed directly for more than 1000 seconds over an 8-hour day, not continuous exposure. *Examples:* scanners and bar-code readers.
Class IIIA	Do not pose a serious eye hazard unless viewed through optical instruments (e.g., microscopes). Power outputs for CW lasers operating in the visible range are between 1 and 5 mW. *Examples:* solid-state laser pointers.
Class IIIB	Direct beam viewing or specular reflections result in ocular injury. Power output is between 5 and 500 mW for CW lasers and less than 0.125 J within 0.25 second for a pulsed laser. Do not produce a hazardous diffuse reflection and are not considered fire hazards. *Examples:* spectroscopy, stereolithography, and entertainment light shows.
Class IV	Significant ocular injury can result from direct beam viewing, specular reflections, and diffuse reflections. These lasers require significant controls. Power output is greater than 500 mW for a CW laser and greater than 0.125 J within 0.25 second for a pulsed laser. Skin and fire hazards are also present with Class IV lasers. *Examples:* medical lasers and industrial lasers (drilling, cutting, and welding).

FIGURE **42-5** Danger sign indicating laser procedure in progress.

can occur if the beam is viewed directly for an extended period of time. Class II lasers include laser pointers and scanners. Class III lasers, which include spectroscopy and light shows, can cause eye injury if viewed directly. The direct beam and reflected beam of Class IV lasers are hazardous to the eye and are potential fire and skin hazards. Reflected laser beams are specular and maintain the beam coherence; diffuse beams are scattered when they are reflected from a rough or matte surface. Most medical lasers are Class IV; these lasers also create hazardous airborne contaminants and require a high-voltage power supply.

The U.S. Food and Drug Administration (FDA) regulates the manufacturing and marketing of lasers used in medicine; however, it does not regulate laser safety.[2] The American National Standards Institute's (ANSI) Z136.1–2007 standard addresses medical laser safety and defines control measures for the four laser classifications, which are applicable to medical, industrial, military, and educational laser safety programs.[3] The ANSI requires a laser safety officer (LSO) at institutions that use Class IIIB or Class IV lasers. The LSO is responsible for overseeing education, operation, maintenance, safety, and servicing of medical lasers. Compliance with the ANSI guidelines is voluntary. The Occupational Safety and Health Administration (OSHA) does not have specific regulations governing the safe operation and use of lasers but has identified the hazards associated with the use of medical lasers and developed safety standards to protect patients and operating room personnel.[4] The Association of periOperative Registered Nurses (AORN) and other professional organizations have also developed standards and recommendations for laser safety.[5,6]

When not in use, the laser should be disabled and stored in a secure location. Physicians and other licensed healthcare providers who use lasers should have appropriate training and institutional privileges for laser use. An aiming beam should be used for lasers that do not produce a visible light. Warning signs posted on the inside and outside of all entrances should include the type and wavelength of the laser in use, as well as the specific laser safety eyewear (LSE) required for everyone entering the laser area (Figure 42-5).

Restricted access is ensured through the use of a safety interlock system that will prevent unexpected entry or trigger a shut-off device for the laser if the door is unexpectedly opened. All other optical paths (windows) should be covered to prevent the transmission of a misdirected laser beam. A variety of laser-absorbing glass, plastics, laser safety curtains, and screens are available that attenuate the laser energy. If only CO_2 lasers are used, window coverings are not necessary, because glass absorbs laser energy at 10,600 nm. If a Nd:YAG or a laser with a similar wavelength is used, a laser-blocking shield is necessary to stop accidental exit of the laser beam. A windowless room provides the maximum protection. Surgical cabinets and large surgical instruments should have a matte or dull surface to avoid reflection of a misdirected laser beam. Surfaces of instruments can be made laser safe by sandblasting, ebonization, and anodization.[8] Lasers require high power and carry the potential for electrical injury.

The majority of laser-related accidents and injuries can be attributed to inappropriate use or intentional use of malfunctioning equipment. The most common hazards of medical lasers include thermal trauma, eye injury, perforation of organs or vessels, gas embolization, electrical shock, air contamination, and fire. Beam injuries are due to the direct effects of the laser on the eye and skin; nonbeam injuries are secondary and caused by laser-generated air contaminants (LGACs), fire, electrical shock, and noise.[7]

Thermal Trauma

The most common cause of laser-induced tissue damage is thermal in nature and usually requires exposure to high-energy beams for an extended period of time, resulting in a photochemical change or thermal burn. Tissue proteins are denatured after absorption of the laser energy, and tissue damage can range from mild reddening of the skin to blistering and charring. Skin trauma is dependent on the energy and wavelength of the laser. Longer wavelengths have a deeper skin penetration than shorter wavelengths; shorter wavelengths (400 to 700 nm) are nearly completely absorbed in the first 4 mm of the skin. Burns occur with exposure times greater than 10 μsec and wavelengths ranging from the near-ultraviolet to the far-infrared (315 to 10,300 nm). Ultraviolet-A (315 to 400 nm) exposure causes hyperpigmentation and erythema, but the greatest skin damage is caused by ultraviolet-B (UV-B) radiation (280 to 315 nm). In addition to thermal trauma, carcinogenesis is a potential risk of UV-B exposure. Exposure to ultraviolet-C (UV-C) waves (200 to 280 nm) is less harmful to the skin because they are predominantly absorbed in the outer dead layers of the epidermis. The CO_2 and other infrared lasers penetrate deeper and are associated with first-degree (reddening), second-degree (blistering), or third-degree (charring) burns. Lasers also may precipitate the development of or exaggerate existing skin lesions, including reactivation of viral infections.

Safety interventions to prevent thermal trauma include restricted access to the lasing area; restricted use of the laser system by qualified personnel; application of saline-soaked towels to the area of the patient's skin that surrounds the path of the laser beam, and use of long-sleeved jackets, gloves, and face shields by operating room personnel. Topical sunblock cream will protect against ultraviolet radiation for patients undergoing repeat laser treatments. In addition, liquid gases used for cooling of the laser medium, especially liquid nitrogen, are hazardous if accidentally spilled on the skin. Some of the chemicals used in dye lasers are toxic and hazardous to handle.

Eye Trauma

Because incandescent and fluorescent light are *not* coherent, only a small portion of the energy is spread out over the retina, and these light sources do not harm the human eye. In contrast, the human eye is extremely vulnerable to laser radiation because it *is* coherent, and all of its energy can be focused on a very small portion of the cornea or retina. Eye trauma from laser light is dependent on the power and wavelength of the laser beam, exposure duration, pupil size, retinal pigmentation, and location of the injury. Pulsed-mode lasers present an additional hazard to the eye; laser pulses of

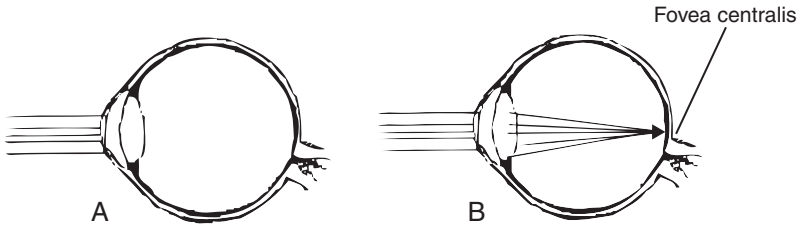

FIGURE **42-6** Laser-associated eye injury. **A,** Mid- and far-infrared wavelengths (less than 400 nm and greater than 1400 nm) are absorbed by the cornea and associated with corneal injury. **B,** Retinal injury is associated with visible and near-infrared (400-1400 nm) wavelengths.

less than 10 microseconds induce shock waves that rupture tissue, resulting in a larger area of permanent retinal damage.

Ultraviolet (200 to 400 nm) and mid-infrared (1400 to 3000 nm) radiation are absorbed by the cornea and can cause corneal photokeratitis (Figure 42-6). Visible lasers and near-infrared lasers (400-1400 nm) are associated with retinal injury. Mid-infrared wavelengths greater than 1400 nm are absorbed by water and cause damage to the cornea and increase the opacity of the lens, resulting in traumatic cataracts; they are also associated with aqueous flare, an increased turbidity of the aqueous humor. Far-infrared radiation (3000 to 10,000 nm) is absorbed by the cornea and can result in corneal burns and potential loss of vision. Inadvertent exposure to the invisible CO_2 laser beam (10,600 nm) causes burning pain of the cornea or sclera. There are no immediate signs of exposure to ultraviolet radiation, but severe eye pain and a sensation of sand in the eye may be present later. After minor injury, regeneration of the epithelium occurs without any permanent abnormality, but corneal scarring and cataract formation may result with more extensive injury. Table 42-3 lists the effect of lasers on eyes and skin.

TABLE **42-3** Effect of Lasers on Eyes and Skin

Laser	Eye Effect	Skin Effect
Ultraviolet C (200-280 nm)	Photokeratitis	Erythema (sunburn)
Ultraviolet B (280-315 nm)	Photokeratitis	Increased pigmentation
Ultraviolet A (315-400 nm)	Photochemical cataract	Darkening/burn
Visible (400-700 nm)	Photochemical and thermal retinal injury	Darkening/burn
Infrared A (700-1400 nm)	Cataract, retinal burn	Burn
Infrared B (1400-3000 nm)	Cataract, corneal burn, aqueous flare	Burn
Infrared C (3000-10,000 nm)	Corneal burn	Burn

The retina is composed of two types of photoreceptors, rods and cones. Rods make up over 95% of the retina; they are sensitive to light but not color. Cones make up less than 5% of the total retinal area and are responsible for detecting color and fine detail. They are heavily concentrated in the fovea centralis, an area associated with the sharpest and most brilliantly colored vision. Retinal damage is associated with visible and near-infrared (400 to 1400 nm) lasers. The beam is transmitted by the cornea and focused by the lens to produce an intense concentration of light energy on a small portion of the pigmented retina. Focusing of the laser by the lens amplifies the irradiance on the retina 100,000 times (see Figure 42-6). The conversion of the light energy to heat can cause retinal burns, visual loss, or total blindness. One milliwatt of visible laser radiation entering the eye deposits 100 W/cm^2 at the retina. Wavelengths less than 400 nm and greater than 1400 nm are not associated with retinal damage.

A visible laser beam produces a bright color flash of the emitted wavelength followed by an afterimage of its complementary color (e.g., a green, 532-nm laser light would produce a green flash followed immediately by a red afterimage). If the individual's cones are damaged by a green laser light, he or she may have difficulty discriminating between blue and green colors thereafter. The Q-switched Nd:YAG laser beam (1064 nm) is especially hazardous to the eye because the beam is invisible, and the retina lacks sensory innervation. Visual disorientation resulting from retinal damage may not be apparent until considerable thermal damage has occurred. Unlike corneal injuries, laser damage to the retina is permanent.

Acute and chronic loss of color sensitivity has been reported in ophthalmologists who frequently use surgical lasers. The Rockwell Laser Industries maintain a voluntary reporting database of laser accidents; in recent years the majority of the reports have involved temporary blindness of in-flight aircraft pilots by the accidental or intentional use of laser pointers from the ground.

All medical lasers are Class IV lasers, and laser safety eyewear (LSE) is required to prevent injury from the direct laser beam or reflected laser light from surgical instruments, cabinets, lights, watches, jewelry, and other smooth reflective surfaces in the operating room.[8] Although LSE will protect against accidental exposure to a laser beam, they will not protect against intrabeam or direct viewing of a laser beam. The eye aversion or blink response of 0.25 second is triggered by bright, visible light only. It will not prevent the trauma of invisible laser beams and provides no protection against lasers with a wavelength of 700 to 1400 nm. In addition, the aversion response is absent or sluggish under general anesthesia and deep sedation. In operating rooms darkened for video and microscope use, the pupils of the eyes will dilate and increase the risk for laser exposure for both surgical personnel and awake patients. During laser procedures, operating room personnel and awake patients must wear LSEs specific for the type of laser in use. An anesthetized patient's eyes should be covered with saline-moistened eye pads and laser shields. Petroleum-based eye ointments should not be used during laser procedures because they may cause severe burns if ignited by a misdirected laser beam.

The maximum permissible exposure (MPE) is the level of laser radiation exposure not associated with biologic changes in the eye. It is directly related to the wavelength and inversely related to the exposure time and expressed as radiant exposure (J/cm^2) or irradiance (W/cm^2). The ANSI Z136.1–2007 standard identifies acceptable MPE levels for medical lasers.[3] The nominal hazard zone (NHZ) refers to the physical space in which the direct,

reflected, or scattered laser radiation exceeds the MPE. During laser procedures, the entire operating room is considered to be within the NHZ; however, it may extend beyond transparent windows for certain lasers.

During laser procedures, LSE must be worn by everyone in the room. The LSE must have the appropriate optical density (OD) and reflective properties for the laser wavelength, the beam intensity, and the expected exposure conditions; it must also have side shields. Optical density (OD) refers to the ability of a material to attenuate or absorb energy of a specific wavelength to a safe level below the MPE while allowing transmission of sufficient ambient light for safe visibility. OD = $\log_{10}$ (E_i /E_t) where E_1 is the incident beam irradiance (W/cm^2) or worst-case scenario, and E_2 is the transmitted beam irradiance (MPE limit in W/cm^2).[3] A LSE with an OD of 2 will allow transmission of 1/100 of the laser energy; in contrast, LSE with an OD of 4 will allow transmission of only 1/10,000 of the laser energy. The OD is rated for a specific wavelength or range of wavelengths; use with a different wavelength will result in a completely different OD value. Because LSE are laser specific, the wavelength and OD are imprinted on the LSE, and users must ensure they are wearing the appropriate LSE for the laser in use. For example, LSE for the ND-YAG laser has an OD of 6 at 1064 nm, whereas LSE for the CO_2 laser has an OD of 7^+ at 10,600 nm. In addition, LSE with an OD of 4 and a wavelength of 755 nm will not protect against a laser beam that requires LSE with an OD of 6 and a wavelength of 755 nm. Lasers also may operate at different wavelengths, for example, doubled Nd:YAG lasers, and tunable lasers, such as the titanium-doped sapphire laser, require different levels of protection at each wavelength and may require the use of two different LSE. Certain lasers require amber-, green-, or red-colored filters, but the color of the LSE lens should not be used for LSE identification. Vision correction glasses may attenuate the effect of the CO_2 laser beam but do not completely protect the eye from direct or reflected laser beams because they lack protective side shields. Medical lasers generally require a LSE of 4 to 7 OD. There are no laser glasses available that protect against all types of laser beams; LSE that cover several wavelengths would require very dark filters, which would interfere with visual acuity.

Perforation

Operator error, such as a misdirected laser beam or failure to check for proper laser function before use, accounts for the majority of laser perforations of a viscus or vessel. A pneumothorax can be a life-threatening complication of a misdirected laser beam, especially during the administration of nitrous oxide (N_2O). Lasers cannot photocoagulate blood vessels larger than 5 mm, and unexpected or excessive bleeding may accompany an accidental perforation with a misdirected beam. Because of greater tissue penetration and dissemination, perforation with the laser beam of the Nd:YAG laser is associated with delayed tissue damage. Perforation, bleeding, or edema may not be apparent for hours to days. Patients undergoing Nd:YAG laser surgery of the airway should be monitored for 24 to 48 hours after the procedure.

Embolism

Some lasers require a coolant to protect the tip of the quartz fibers from overheating. The coolant may be air, CO_2, or a liquid. Although it is a rare event, venous gas embolism is a potential fatal hazard of laser procedures, especially with the gas-cooled Nd:YAG laser.[9] Coronary and cerebral embolisms have occurred during endobronchial Nd:YAG therapy, and transmyocardial laser revascularization is also associated with cerebral microembolization. Fatal venous air embolism has been reported during Nd:YAG hysteroscopies. A liquid coolant will reduce the risk of air embolism. CO_2 emboli appear to be less damaging than air or nitrogen emboli.

Laser-Generated Air Contaminants

Thermal destruction of tissue with a laser or electrosurgical unit (ESU) creates a smoke plume that may contain toxic gases and vapors, including benzene, hydrogen cyanide, formaldehyde, dead and live cellular material, carcinogens, and viruses.[7,10,11,12] It is estimated that approximately 500,000 healthcare workers are exposed to laser or electrosurgical smoke every year.[13] Contaminants in the surgical smoke plume have the potential to cause respiratory, ocular, dermatologic, and other diseases, including cancer, in patients and operating room personnel.

The CO_2 laser produces the greatest amount of smoke. During the use of the CO_2 laser, the amount of smoke produced from 1 gram of tissue is equivalent to the smoke from three to six cigarettes. The smoke plume may contain fine particulates (0.3 μm) that can be deposited in the lower airways. In addition to ocular and respiratory irritation, the smoke plume has the potential for causing cellular mutations. Because lasers are commonly used to vaporize tumors and viral lesions, concern exists that the laser plume may contain infectious material and viral DNA. There are no specific OSHA standards addressing the hazards of the surgical smoke plumes, other than expecting employers to advise employees of the hazards of surgical smoke.[13]

The National Institute for Occupational Safety and Health (NIOSH) recommends the use of a local exhaust ventilation system—for example, a portable smoke evacuator—as the most efficient method to control laser-generated smoke. It should contain a high-efficiency particulate air (HEPA) filter or equivalent for trapping particulates, and the suction nozzle should be kept within 2 inches of the surgical site to effectively capture airborne contaminants.[14] Evacuation tubing, filters, and absorbers should be considered infectious waste, and new filters and tubing should be installed before each procedure.

A triple filtration smoke evacuator is indicated for evacuation of a large smoke plume. Three-stage disposable filter systems include a HEPA filter that can filter 0.3-μm particulate matter, a layer of activated charcoal for odor absorption, and an ultra–low-penetration air (ULPA) filter that can filter particulate matter as small as 0.01 μm. High-filtration masks (0.3 μm) should be worn by operating room personnel to filter out particulate matter and noxious odors. A close-fitting surgical mask can filter particulate matter as small as 5 μm but is ineffective when moist. In addition to high-efficiency mask, AORN recommends the use of protective eyewear and gloves.[10] Despite the support from professional organizations for active smoke evacuation during all laser procedures, the lack of a regulatory OSHA mandate continues to place many operating room personnel at risk for exposure to the laser-generated air contaminants.[11,13]

Reasons for noncompliance with smoke evacuation recommendations include lack of smoke evacuation equipment or supplies, surgeon's refusal to use the devices, increased noise of the smoke evacuators, and lack of training regarding the health risks of surgical smoke.[15,16] Use of an evacuator is less likely to occur during laser procedures in an outpatient or office practice setting. Laser safety precautions can be found in Box 42-1.

Electrical Hazards

Lasers require high-voltage circuits and present a risk for electrical shock and electrocution. Contributing factors include damaged electrical cords, inadequate grounding, inadequate safeguards,

BOX **42-1**

Laser Safety Precautions

- Restrict laser use to qualified personnel.
- Restrict access to laser area during laser operation.
- Close all doors and cover windows.
- Post Laser Warning signs inside and outside the laser area.
- Use appropriate laser safety eyewear (LSE) for personnel and awake patients
- Provide eye protection for anesthetized patients.
- Provide skin protection for patients and operating room personnel
- Minimize the potential for specular reflections by removal of unnecessary shiny surfaces form from the room.
- Maintain room lights as bright as possible to constrict the pupils.
- Adjust brightness of patient monitors to ensure appropriate degree of visibility with LSE.
- Require surgeon to warn of activation of laser and to keep the beam path above or below normal eye level (less than 4.5 feet or greater than 6.5 feet).
- Use an aiming beam or operational warning devices for lasers with invisible beams.
- Avoid looking into the primary beam at all times.
- Place laser in standby mode when it is not in active use.
- Do not leave an active laser unattended.
- Restrict maintenance of laser to authorized individuals who are trained in laser maintenance.

lack of compliance with safety procedures, and use by unqualified personnel. Older laser models that use an external water cooling system present a great electrical hazard. Electrocution is the leading cause of laser-related injury and death in all industries. Laser repair technicians appear to have the highest risk in the healthcare community.[7]

Fire

According to the Emergency Care Research Institute (ECRI), an independent, nonprofit organization that researches the safety, quality, and cost-effectiveness of patient care, there are approximately 600 surgical fires annually in the United States. The ECRI has ranked surgical fires as the ninth-highest technology hazard of 2011.[17] Historically, surgical fires were associated with the use of explosive or flammable anesthetics. When the use of these anesthetics was discontinued in the 1970s, sensitivity of the operating room staff to the possibility of a fire decreased. However, the risk of a surgical fire is still a very real but preventable hazard of modern surgery.[18,19] The number of surgical fires has increased and is primarily associated with the use of electrocautery units (ESUs) and surgical lasers. Unlike ESUs, lasers do not require direct contact to ignite a fuel source.

Electrocautery units and lasers account for 68% and 13% respectively of airway fires. The most common site of surgical fires is the airway (34%) and head or face (28%). In 74% of the cases, an oxygen-enriched environment was a contributing factor. In a survey of otolaryngologists, 25% of respondents had personally witnessed at least one fire in the operating room.[20] Immediate recognition and management of a surgical fire can limit patient injury, whereas delayed recognition and response can be fatal for the patient. In addition to burns, patient injuries include inhalation of toxic products of combustion, namely, carbon monoxide, ammonia, hydrogen chloride, and cyanide, that can cause significant airway and pulmonary damage. In 2003 the Joint Commission issued a Sentinel Event Alter for preventing surgical fires. In 2008 it listed reduction of surgical fires as the 11th National Patient Safety Goal, which addressed the need for education of operating room personnel, control of heat sources and fuels, and minimization of oxygen concentrations under the surgical drapes.[21]

For a fire to occur, three components of the fire triangle must be present: a fuel source, an ignition source, and an oxidizer. All three components are frequently present in the operating room, and a fire can occur any time the three components are allowed to interact. Everyone in the operating room must understand the fire hazards presented by all three sides of the fire triangle, including those not under their direct control.[22-24] Vigilance is key, and communication among all members of the surgical team is mandatory. It is imperative that all surgical personnel are aware of the hazards of fire during laser procedures and know how to prevent and respond to operating room fires.

Fuel Sources

Fuel sources are abundant in the operating room and are predominantly under the control of the nursing staff. They include surgical preparation solutions, petroleum-based ointments, facial hair, surgical drapes, gloves, ointments, sponges, dressings, endotracheal tubes, laryngeal mask airways, breathing circuits, nasogastric tubes, suction catheters, pneumatic tourniquet cuffs, Silastic stents, suction catheters, and tracheostomy tubes. Bowel gas, which contains methane and hydrogen, also provides a fuel source during intraabdominal laser procedures. Volatile organic chemicals such as alcohol, acetone, and ether are common components of skin preparations, tinctures, degreasers, suture pack solutions, and liquid wound dressings. Alcohol and alcohol-based solutions are very volatile and pose a significant fire hazard in the operating room. If adequate drying time is not provided, the laser can ignite the alcohol vapor. This is more likely to occur in a confined space (e.g., tented drapes) and an oxygen-enriched environment. Care must be taken to ensure that the surgical preparation solution does not pool under the patient or saturate the drapes. Alcohol-based hand sanitizers also may release alcohol vapor, which is flammable, and poses a new fire hazard in operating rooms. Although they will resist ignition and slow the spread of a flame in room air, fire-retardant drapes and materials are not fireproof. Materials considered nonflammable may ignite easily and burn more quickly and at a higher temperature when exposed to an oxidizer-enriched environment.

Endotracheal tubes are a fuel source during airway surgery, if the laser beam or reflected laser light comes into direct contact with it. Localized thermal trauma occurs if the fire is contained to the outside of the endotracheal tube. Rupture of the endotracheal-tube cuff allows leakage of anesthetics gases into the path of the laser beam, increasing the risk of an ignition. If the fire burns through to the inner side of the tube, an intraluminal fire occurs, fed by both the anesthetic gases and the volatile products of combustion of the endotracheal-tube wall. The intraluminal flame will travel toward the source of the oxidizer. A secondary flame can shoot out of the distal end of the endotracheal tube like a blowtorch and cause extensive lower airway damage.

During surgical procedures that involve lasers or ESUs, careful attention to possible fuel sources is paramount. A basin of water or normal saline should be available during laser procedures to extinguish a burning endotracheal tube or other material. Two syringes filled with normal saline should be readily available to extinguish an airway fire. Use of excessive tape to secure the endotracheal tube should be avoided to allow easier removal of the tube in the event of an airway fire. Emergency supplies, including

BOX **42-2**

Prevention of Surgical Fires

- Educate surgical personnel on the fire triad and common sources of fuels, ignition, and oxidizers in the operating room (OR).
- Schedule annual mandatory fire drills for the entire OR team and include evacuation of anesthetized patients in the event of an uncontrolled surgical fire.
- Identify location of fire alarms and extinguishers and shut-off valves for pipeline gases.
- Avoid open air administration of supplemental oxygen.
- Administer supplemental oxygen through an ETT or LMA.
- Limit supplemental O_2 to 30%.
- Alert surgical team members to potential sources of fire: oxidizers, fuels, and source of ignition.
- Avoid pooling of preparation solutions and allow adequate drying time before draping patient.
- Coat facial hair with a water-soluble surgical lubricant during head and neck surgery.
- Use flame-retardant drapes and moistened sponges and towels in the area of the laser.
- Use laser-resistant endotracheal tubes during laser surgery of the upper airway. Inflate the cuff with saline and dye to allow early recognition of tube rupture.
- Use moistened sponges to prevent air leaks, especially when using uncuffed tubes during airway surgery. Sponges and pledgets should also be moistened to resist ignition.
- Use a properly applied incise drape to help isolate head, neck, and upper-chest incisions from oxygen-enriched atmospheres and flammable vapors.
- Use continuous suction to minimize the buildup of O_2 in the oropharynx during airway surgery and beneath the drapes during monitored anesthesia care for head and neck surgery.
- Have immediately available a container of water to extinguish burning materials. Two syringes of sterile saline should be available during laser surgery of the airway.
- Have fire extinguishers available in the room or immediately accessible.
- If possible, discontinue supplemental oxygen at least 1 minute before and during laser use for head and neck surgery, and especially surgery of the airway.

ETT, Endotracheal tube; *LMA*, laryngeal mask airway; O_2, oxygen.

a rigid bronchoscope and forceps, should also be readily available. A carbon dioxide fire extinguisher (Class BC) is appropriate for extinguishing surgical fires. The BC fire extinguisher leaves no residue and will not damage human tissue. Dry powder extinguishers (Class ABC) are inappropriate as the first response because the powder (ammonium phosphate) contaminates all surfaces, is a respiratory irritant, and may interfere with visibility. Recommendations for prevention of surgical fires are listed in Box 42-2.

Oxidizers

Oxidizers present in the operating room include air, O_2, and N_2O, and are under control of the anesthetist. Oxygen is heavier than air and tends to accumulate in low-lying areas such as around surgical drapes. In an oxygen-rich environment, materials ignite faster, burn quickly with greater intensity, release more heat, and are more difficult to extinguish.

Ignition Source

The surgeon generally controls the sources of ignition; these include ESUs, fiberoptic light sources or cables, high-speed drills, and lasers. However, electrical sparks from malfunctioning equipment not under the surgeon's control, including monitors and defibrillators, also can result in a fire. Desiccated soda lime is another possible source of ignition in the breathing circuit.

Prevention of a Surgical Fire

Operating room personnel must be educated on the prevention of surgical fires. They need to understand the fire triangle, be able to identify the procedures that present a risk of fire, understand their role in preventing a surgical fire, and know how to respond to a surgical fire. A number of professional organizations have developed practice guidelines and educational resources to assist healthcare institutions develop policies and procedures that address fire prevention and effective response strategies to a surgical fire.[25] In collaboration with the Anesthesia Patient Safety Foundation (APSF), the ECRI developed a clinical guide to surgical fire prevention.[26] The American Society of Anesthesiologists (ASA) have an operating room fire algorithm for both airway and nonairway fires.[27] Fire posters are available on the ECRI website, and a free video on the prevention and management of operating room fires is available on the APSF website.[28,29]

Surgical personnel must be familiar with the location and function of fire alarms, fire extinguishers, and emergency exits and should know how to shut off electrical and medical gas supplies. They should be aware of the fire hazards present in the laser area, such as anesthetic gases, skin preparation solutions, adhesive plastic tape, and surgical drapes. Every operating room should have a fire safety plan in place that includes mandatory fire drills for all operating room personnel including anesthesia providers and surgeons.[26,27] Simulation of a surgical fire scenario in a high-fidelity simulation center provides an excellent opportunity for team training in the prevention and management of a surgical fire.[30]

Anesthetic Gases

Administering an oxygen concentration of less than 30% will reduce the risk of a rapid and widespread propagation of fire, that is, a flash fire. The new clinical guidelines developed by the ASA, ECRI, and the APSF advise against the use of 100% oxygen during head, face, neck, and upper chest surgery.[26 27,29] Air, not oxygen, should be used for open delivery for patients who can maintain a safe oxygen saturation. For patients with normal pulmonary function, low-dose sedatives and narcotics can be administered without supplemental oxygen. Pulse oximetry will identify the patient who may require supplemental O_2, as well as the patient who can tolerate short periods of ventilation with room air. Mild drug-induced respiratory depression that results in a stable decrease in saturation as low as 92% does not require supplemental oxygen. Saturation of 90% or less is undesirable. If supplemental oxygen is necessary, the airway should be secured with a laryngeal mask airway (LMA) or endotracheal tube, and oxygen concentration should be the lowest possible to support acceptable patient oxygenation and should not exceed 30%.[26,27,29,31] Buildup of oxygen should be minimized by scavenging the operative site with suction. During airway surgery, the oropharynx should be suctioned throughout the procedure.

If supplemental O_2 via a mask or nasal cannula is necessary, it should be discontinued at least 1 minute before and during laser use; this will close communication between the anesthetist and the surgeon who must give adequate notice of his intent to activate the laser. Nitrous oxide readily supports combustion and should be avoided in cases with potential for fire. Suitable gases include O_2 and air, O_2 and nitrogen, and O_2 and helium. Helium has a high thermal conductivity and is more resistant to ignition. In addition, its lower viscosity can help overcome the increased resistance resulting from smaller internal diameter (ID) tubes or airway obstruction.

TABLE 42-4 Gas Mixtures That Deliver 30% Oxygen or Less

Air (L/min)	Oxygen (L/min)	Total Gas Flow (L/min)	O_2 Concentration
0.89	0.11	1	29.7%
1.78	0.22	2	29.7%
2.7	0.30	3	28.9%
3.60	0.40	4	28.9%
4.45	0.55	5	29.7%

Volatile anesthetics are nonflammable, but their use is not recommended during airway laser procedures because they may deteriorate to potentially toxic compounds in the presence of a fire.[3] Gas mixtures that deliver 30% oxygen or less are listed in Table 42-4.

Endotracheal Tubes

Polyvinyl chloride (PVC) tubes ignite easily and produce toxic materials that can increase the amount of damage to the airway. PVC tubes appear to be more susceptible to damage by the CO_2 laser; however, the presence of blood on the tube makes a PVC tube also susceptible to damage by the Nd:YAG laser. The radiopaque barium sulfate strip found on most PVC tubes has a faster ignition rate than the PVC. Red rubber tubes appear to be more resistant to initial ignition, have a slower rate of burn, and produce less toxic smoke. However, they tend to melt and can produce carbon monoxide. Although silicone tubes are also less combustible, inhalation of silica ash may produce pulmonary damage.

Laser-resistant endotracheal tubes should be used during laser surgery of the airway.[32] The Laser-Flex tracheal tube (Nellcor) is a flexible stainless steel tube with a matte finish that is resistant to the CO_2 and KTP lasers. In the event of a proximal-cuff rupture with a laser beam, the distal cuff will maintain a tracheal seal and prevent anesthetic gases from leaking into the path of the laser beam. The Lasertubus (Rüsch) is a soft, white rubber tube that is resistant to the argon, Nd:YAG, and CO_2 lasers. The lower 17 cm of the tube is covered with a Merocel Laser Guard wrap that dissipates the laser light and prevents backscatter. Soaking the tube in water will reduce ignition potential. The Lasertubus has two high-volume cuffs, one inside the other. The Bivona Fome-Cuf (Portex), a silicone and aluminum spiral tube, is designed for use with the CO_2 laser. It has a polyurethane self-inflating foam cuff covered with silicone that is designed to maintain a tracheal seal in the event of a cuff rupture. Inability to deflate the foam after cuff rupture is a recognized problem with this tube. The Laser Shield II (Medtronic), a reflective aluminum-wrapped silicone tube with a smooth fluoroplastic covering, is specific for use with CO_2 and KTP lasers. The cuff is designed to be inflated with saline, and methylene blue is present in the inflation valve for immediate detection of cuff rupture. The Laser-Trach (Kendall/Sheridan) is a red rubber tube with an embossed copper foil for use with CO_2 and KTP lasers.

Application of a metallic foil wrap (aluminum or copper) or a thin metal-coated plastic tape has been used to protect PVC and red rubber endotracheal tubes during laser surgery of the airway, but this practice should be discouraged. Recognized problems with foil wrappings include laser reflection damage, potential areas of exposed tube, unprotected cuff, the need to use a smaller ID tube, and airway damage from the sharp edges of the foil wrap. Only the Merocel Laser-Guard endotracheal tube wrap (Medtronic) has FDA approval for endotracheal-tube protection.

Laser-resistant endotracheal tubes are not laser-proof and carry the inherent risk of ignition. Cuff rupture is often the prelude to an airway fire. The cuffs should be inflated with normal saline; addition of methylene blue may alert the surgeon to cuff rupture.[27] The endotracheal-tube cuff should be fully inflated and a stethoscope used to confirm the absence of a leak before the laser is used. Saline-moistened cotton gauze should be placed proximal to the endotracheal-tube cuff. The gauze and the attached cotton strings should be constantly remoistened. At least 1 minute should elapse before a laser is used after reinflation of an endotracheal-tube cuff or repositioning of the endotracheal tube for correction of a leak.

LMAs have been tested with the KTP and Nd:YAG lasers. The tube of the standard silicone mask is more resistant to the laser beams than the disposable PVC tube, but the PVC cuff is more resistant than the silicone cuff. The intubating LMA (silicone and steel) is more sensitive to the KTP laser. The presence of blood increases the vulnerability of all the LMAs, especially with the KTP laser. Additional precautions for use of an LMA during laser procedures include inflation of the cuff with saline and methylene blue and protection of the cuff with moistened gauze. The use of 5 to 10 cm H_2O positive end-expiratory pressure (PEEP) has been advocated during laser surgery of the airway to prevent the hot, toxic gases from reaching the lower airways.

Management of a Surgical Fire

Fire must be anticipated during any laser procedure. Communication among all members of the surgical team is vital for the prevention of and coordinated response to a surgical fire. Fire management includes early recognition, halting of procedure, extinguishing the fire, evacuation if appropriate, and postoperative care of the patient.[26,27] For a nonairway fire, all gases should be discontinued and all drapes and burning material removed from the patient and extinguished with saline, water, or by smothering. The patient should be immediately assessed for thermal trauma or smoke inhalation. In the event the fire spreads, the acronym *RACE* is applicable: ***R***escue the patient, ***A***lert other staff and ***a***ctivate the fire alarm systems, ***C***onfine the fire by shutting doors, closing off gas supplies and electrical power, and using fire extinguishers, and ***E***vacuate the room.

In the event of an airway fire, the anesthetist has approximately 6 seconds for recognition and removal of an endotracheal tube that has ignited. Signs of an airway fire include darkening of the endotracheal tube or breathing circuit with soot, an orange or red glow to the endotracheal tube, and the presence of flames in or around the endotracheal tube. The endotracheal tube acts like a blowtorch, with high concentrations of O_2 adding to the intensity of the fire. Within seconds the flames can reach a height of 5 to 10 inches. Intraluminal fires will spread toward the proximal end of the tube—the source of the O_2. Severe thermal or chemical trauma is unlikely to occur if the flame is vented through the tube or oropharynx. Downstream gases contain the products of oxidation and little O_2, but a free-end fire can occur if the products of oxidation ignite in the O_2-rich alveoli.

In rapid succession, the endotracheal tube should be removed, all flammable and burning material removed from the airway, all gases discontinued, and saline poured into the patient's airway to extinguish any residual smoldering material and cool the tissues.[26,27] Ventilation should be resumed, but an oxygen-enriched gas mixture should be avoided until all risk of re-ignition is eliminated. The endotracheal tube should be examined for intactness, and direct visualization of the tracheobronchial tree with a rigid bronchoscope is recommended for assessment of thermal injury and removal of foreign material including endotracheal tube fragments. A flexible bronchoscope may be necessary for evaluation

BOX **42-3**

Management of Airway Fires

- Discontinue use of laser.
- In rapid succession, remove ETT, turn off all gases, remove sponges and any flammable material, and pour saline into airway.
- Extinguish burning ETT/LMA in basin of water.
- Resume ventilation with air. Ventilate with 100% O_2 only when the fire is extinguished.
- Examine airway and remove residual debris with rigid bronchoscope. Consider lavage with normal saline. Examine small and distal airways with flexible fiberoptic bronchoscope.
- Administer humidified O_2 by mask if airway damage is minimal and risk of laryngeal edema is low.
- If indicated, reintubate with a smaller ETT.
- Assess extent of thermal trauma with ABG, carboxyhemoglobin levels, and CXR.
- Keep patient intubated and administer 40% to 60% humidified O_2 if airway burn is present or suspected.
- Consider tracheostomy and mechanical ventilation for postoperative management.
- Consider administration of steroids.
- Admit patient to ICU for a minimum 24-hour observation.
- Retain all equipment and materials involved in the fire for further inspection.
- Reassemble surgical team to identify the sequence of events that led to the surgical fire.
- Report fire as a sentinel event to The Joint Commission, ECRI, and the FDA.

ABG, Arterial blood gas; *CXR*, chest x-ray; *ECRI*, Emergency Care Research Institute; *ETT*, endotracheal tube; *FDA*, Food and Drug Administration; *ICU*, intensive care unit; *LMA*, laryngeal mask airway; O_2, oxygen.

of distal airways, and tracheobronchial lavage with saline solution should be considered. If reintubation is indicated, a smaller endotracheal tube should be used; a chest x-ray (CXR) and arterial blood gases (ABGs) are indicated to guide postoperative management. Carboxyhemoglobin (CoHgb) levels are needed for assessment of smoke inhalation.

After an airway fire, 24-hour observation of the patient is indicated. For minor burns, the patient should be monitored for development of laryngeal-tracheal edema. A patient with severe burns should remain intubated and receive 30% to 60% humidified O_2. A tracheostomy and mechanical ventilation with PEEP should be a definite consideration. Corticosteroids have been recommended for the treatment of both smoke inhalation and the bronchospasm that may be precipitated in patients with irritable airways. Additional treatment is dependent on the extent of the injury and the response of the patient. Complications may be delayed, and tracheal stenosis can occur months after an airway fire. A monthly laryngoscopy or bronchoscopy may be indicated for up to 6 months. All equipment and materials involved in a surgical fire should be retained for further inspection; surgical fires should be reported to The Joint Commission as sentinel events. Recommendations for management of an airway fire are listed in Box 42-3.

ANESTHESIA FOR LASER PROCEDURES

Anesthesia is frequently required for laser procedures, and most anesthetic techniques are suitable for laser procedures. Although they may appear to be less invasive, laser procedures have complications similar to those of traditional surgery. Continuous use of LSE is mandatory during laser surgery. The lenses of CO_2 LSE are usually clear and do not affect color perception, but tinted or colored LSE are required for other lasers and can affect color perception. Some Nd:YAG LSE can significantly dim the green color on monochrome monitors, tempting the anesthesia provider to remove the LSE while the laser is in use. Prior to anesthetizing a patient for a laser procedure, the anesthetist should observe the monitors through the LSE to ascertain the effect of the tinted LSE on the visibility of the displayed parameters. Display lights and alarms of patient monitors should be set to maximum brightness or otherwise adjusted to compensate for the color restriction. Audible alarms should be adjusted to the loudest setting.

Major anesthetic concerns exist when the airway is shared between the anesthetist and the surgeon during a laser procedure. The proximity of the endotracheal tube and anesthetic gases to the laser beam creates a very real hazard of airway fire.[25,27,33] Communication between the surgeon and the anesthetist is paramount to ensure patient safety, maximize surgical access, and avoid complications. Ventilation techniques during laser procedures of the airway depend on the surgeon preference and the site of the laser application.

For the patient receiving supplemental O_2 during monitored anesthesia care (MAC), good communication between the surgeon and anesthetist is mandatory. To reduce the risk of fire, buildup of oxygen should be minimized during head and neck surgery by continuous scavenging of the operative site with suction. Supplemental O_2 should be discontinued 1 minute before and during laser use. Pulse oximetry will allow monitoring of the patient's response to the decrease in O_2 concentration. To maximize surgical view and access, small-sized endotracheal tubes are necessary, and the anesthetist must be prepared to deal with the associated increase in resistance to ventilation. During airway surgery, the oropharynx should be continually suctioned throughout the procedure. Some surgeons may prefer an apneic technique, in which case the airway is alternately shared between the surgeon and the anesthetist. After induction of general anesthesia and the administration of a muscle relaxant, the patient is hyperventilated by mask after brief periods of laser application. The pulse oximeter must be monitored closely and ventilation immediately resumed if oxygenation decreases 2% to 3% below the patient's initial saturation or when 1.5 to 2 minutes have elapsed. However, this technique is to be discouraged; during periods of apnea there are still high O_2 concentrations in the upper and lower airways that are susceptible to ignition by the laser beam. Because of their potential to deteriorate toxic compounds in the presence of a fire, volatile anesthetics are best avoided during laser surgery of the airway.[3]

SUMMARY

Because of their ability to cut, coagulate, vaporize, and selectively destroy abnormal tissue, medical lasers have numerous applications in all medical and surgical specialties. They are an integral part of a surgeon's armamentarium, and newer and more powerful lasers are finding expanded use in surgery. Anesthetists are involved on a daily basis with patients undergoing laser procedures in the hospital operating rooms and off-site locations, ambulatory surgeries and clinics, and private practice offices. Safe provision of anesthetic care requires knowledge of laser physics, as well as the potential hazards associated with the use of medical lasers. Continuous use of eye and skin protection for both the patient and the operating room personnel and continuous use of a smoke evacuator is mandatory. The anesthetist must be acutely aware of the risk of fire during laser procedures, especially laser surgery of the airway, and must be prepared to both prevent and respond to a surgical fire. This can be accomplished by fire safety education and participation in annual fire drills with the other members of the operating room team.

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43 CHAPTER Obesity and Anesthesia Practice

◆ *John J. Nagelhout*

OVERVIEW

Obesity is a complex, multifactorial, chronic disease that develops from an interaction between the genotype and the environment.[1-6] It is the second leading cause of preventable death in the United States.[1] The prevalence of overweight and obesity has increased significantly during the last three decades. Obesity is associated with an increased incidence of a wide spectrum of medical and surgical conditions and morbidity. As a result, anesthetists can expect to encounter overweight and obese patients frequently in their practices. These patients may present a considerable challenge due to the multiple pathophysiologic changes associated with obesity. A thorough understanding of the pathophysiology, pharmacology, and specific anesthetic considerations associated with obesity will promote optimal anesthesia care.

Statistics

The prevalence of obesity around the world continues to rise, and in the United States, millions of Americans are considered to be severely obese. Current estimates are that 200 million or 66% of U.S. adults are classified as overweight or obese, and more than 34% of adults are classified as obese. In nationwide data from 2004, 7% of women and 3% of men were extremely obese.[7] There are an estimated 26 million people in the United States with a body mass index (BMI) of no less than 35 kg/m^2, and 15 million with a BMI of 40 kg/m^2 or higher.[1,4]

For persons ages 20 years and older, there has been an increase in the proportion of obese adults from a previous level of 23% in 1994 to a new level of approximately 35% (Figure 43-1).

Obesity is not confined to the United States; it is a health problem that is increasing at an alarming rate throughout the world. Globally there are approximately 2 billion individuals documented as overweight (BMI of 25 kg/m^2 to 29.9 kg/m^2), which approximates the number of individuals who are starving worldwide.[8,9] It is estimated that there are more than 300 million obese people worldwide,[10] and three countries report that more than 50% of their population is obese. The World Health Organization (WHO) has predicted that the number of severely overweight adults is expected to double by 2025. Concerns about the global obesity crisis are growing, and WHO reports that obesity accounts for more than 400,000 deaths annually, second only to tobacco-related disease as a cause of preventable and premature death.[11]

In the United States, individuals who are obese have a 10% to 50% percent greater risk of death from all causes, compared with healthy-weight individuals (BMI 18.5 to 24.9). Obesity is associated with about 112,000 excess deaths per year.[12] Most of the increased risk is due to cardiovascular causes.[13]

Cost of Obesity

Public awareness of the problems that arise from obesity is corroborated by the $147 billion spent annually on medical treatment, weight-reduction programs, exercise equipment, low-fat diet products, pharmacologic agents, advertising, and marketing.[4] Obesity is a major health concern, and obese patients admitted for surgery may exhibit one or more medical conditions in addition to the primary underlying problem.[14] Clearly, identification of obesity-related conditions is vital to the safe administration of an anesthetic.

Definitions

BMI is the accepted measure of body habitus that normalizes adiposity for height.[1] BMI can be calculated according to the following formulas:

- BMI = Weight (in kilograms)/height (in meters)^2
- BMI = (Body weight [in pounds]/height [in inches]^2) × 703

Overweight is defined as a BMI of 25 to 29 kg/m^2, and *obesity* as a BMI of 30 kg/m^2.[1-3] The rationale for these definitions is based on epidemiologic data that reveal increasing mortality with BMIs over 25 kg/m^2.[6] For individuals with a BMI greater than 30 kg/m^2, mortality rates for a number of conditions, especially those associated with cardiovascular disease, are increased 50% to 100% above rates in individuals of normal weight. A person's degree of obesity is commonly defined using the body mass index, as classified in Table 43-1. A BMI greater than or equal to 25 is considered "overweight," a BMI of greater than or equal to 30 is considered "obese," and a BMI greater than or equal to 40 is classified as "morbidly obese." We are now seeing references to "super-obese" (BMI greater than 50) and "super-super-obese" (BMI greater than 60).[15]

Ideal body weight (IBW) is a term used interchangeably with the terms *normal weight* and *desirable weight*.[1-3] IBW is a measurement of height and body mass that exhibits the lowest morbidity and mortality for a given population.[2] Determination of IBW is especially useful in calculating drug and intravenous infusion doses in morbidly obese patients. Certain drugs, if administered according to actual body weight, can produce toxicity, renal damage, or hemodynamic instability. Conversely, some drugs must be given according to actual body weight if therapeutic effects are to be achieved. Simplified weight calculations for ideal and lean body weight (LBW) are as follows:

- For men: IBW = Height (in centimeters) − 100
- For women: IBW = Height (in centimeters) − 105
- LBW = IBW × 1.3

Risk Factors

Obesity is associated with an increase in the incidence of many medical conditions (Box 43-1). The risk for cardiovascular disease, certain cancers, diabetes, and overall mortality is linearly related to weight gain. Type 2 diabetes, coronary heart disease, hypertension, and hypercholesterolemia are prominent conditions in overweight and obese patients.[1-3] With increasing weight gain and increased adiposity, glucose tolerance deteriorates, blood pressure rises, and

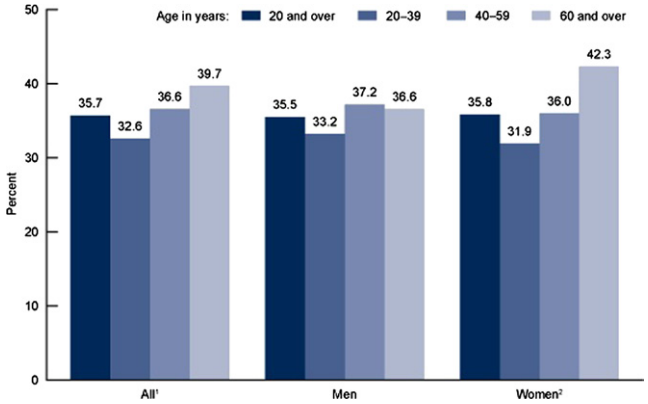

FIGURE **43-1** Prevalence of obesity among adults aged 20 and over by sex and age in 2009-2010. (From Ogden CL, et al. *Prevalence of Obesity in the United States, 2009-2010. NCHS Data Brief, No 82.* Hyattsville, Md: National Center for Health Statistics; 2012.)
[1]Significant increasing linear trend by age (ρ<0.01).
[2]Significant increasing linear trend by age (ρ<0.001).
NOTE: Estimates were age adjusted by the direct method to the 2000 U.S. Census population using the age groups 20–39, 40–59, and 60 and over.

TABLE 43-1 Classification of Overweight and Obesity by Body Mass Index

	Obesity Class	Body Mass Index (kg/m²)
Underweight	—	Less than 18.5
Normal	—	18.5-24.9
Overweight	—	25-29.9
Obesity	I	30-34.9
	II	35-39.9
Morbid obesity	III	Greater than 40

the lipid profile becomes more atherogenic.[2] Using BMI, age, and gender as independent variables, a multiple logistic regression model established that males (P = 0.021), those with higher BMI (P <0.0001), and those of older age (P <0.0001) tended to have more comorbid illness. These data suggest that age, male gender, and extent of obesity are risk factors because they are markers for sicker patients.[16] Hormonal and nonhormonal mechanisms contribute to the greater risk of breast, gastrointestinal, endometrial, and renal cell cancers.[6] Psychological health risks often stem from social ostracism, discrimination, and impaired ability to participate fully in activities of daily living. Coexistent feelings of worthlessness and low self-esteem can lead to depression that not only magnifies anesthetic morbidity, but also contributes to an increased incidence of suicide among morbidly obese persons.

ADIPOSE TISSUE

Adipose tissue has major integrative physiologic functions, secretes numerous proteins, and is considered an endocrine organ.[2] Its major functions as an organ are to provide a reservoir of readily convertible and usable energy and to maintain heat insulation.[2,3,17] Functions associated with liver fat metabolism include degradation of fatty acids into usable units of energy, synthesis of triglycerides from carbohydrates and proteins, and synthesis of other lipids from fatty acids, particularly cholesterol and phospholipids.[17] The ability of the liver to desaturate fatty acids is tremendously important because all cells contain some unsaturated fats synthesized by the liver.

BOX 43-1
Conditions Associated with Obesity

Cardiovascular System
- Coronary heart disease
- Hypertension
- Dyslipidemia
- Cerebrovascular disease
- Thromboembolic disease
- Cardiomegaly
- Congestive heart failure
- Pulmonary hypertension

Endocrine System
- Type 2 diabetes
- Thyroid disorders

Respiratory System
- Restrictive lung disease
- Obesity hypoventilation syndrome
- Obstructive sleep apnea

Gastrointestinal System
- Hiatal or inguinal hernia
- Gallbladder disease
- Nonalcoholic fatty liver disease: steatosis, cirrhosis, hepatomegaly
- Gastroesophageal reflux disease (GERD)

Other Systems
- Gout
- Infertility
- Impaired immune response
- Wound infections
- Osteoarthritis
- Malignancy: esophageal, gallbladder, colon, breast, uterine, cervical, prostate, renal
- Urinary incontinence
- Pancreatitis
- Low back pain
- Obstetric complications

Body fat is also important in heat regulation and insulation. Fat cells, which arise from modified fibroblasts, enlarge and fill with liquid triglycerides to nearly 95% of their storage capacity.[17,18] During exposure of the skin to cold (several weeks), the fatty acid chains of the triglycerides shorten, or become more unsaturated.[3] This phenomenon lowers their melting point, which allows the fat in the fat cells to maintain a liquid state. Metabolically, this is significant. Only liquid fat can be hydrolyzed and transported from the cells to be used for energy.[3]

Body Fat Distribution

In early childhood, fat-cell formation occurs rapidly.[2] Overfeeding during this time accelerates fat storage and triggers hyperproliferation of fat cells. During adolescence, the number of fat cells stabilizes and remains constant throughout adult life. Children become obese through an increase in fat-cell numbers, whereas adults become obese through hypertrophy of existing fat cells.[2,3] The distribution of body fat, however, is a clearer indicator of increased health risk.[18]

Central, android, or abdominal visceral obesity ("apple" shape), with a waist/hip ratio greater than 0.85 in men and 0.92 in women, is perceived as a malignant form of fat accumulation[2,19]

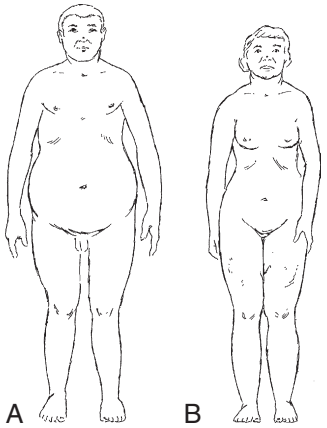

FIGURE **43-2** Obesity. **A,** Central android, or abdominal visceral. **B,** Peripheral gynecoid, or gluteal.

(Figure 43-2, *A*). Waist/hip ratio is calculated by dividing the narrowest waist measurement by the broadest hip measurement while the patient is standing.[2] Waist circumference is the newly established standard used as a marker for abdominal obesity. In men a waist circumference greater than 102 cm (40 inches) and in women a waist circumference of 88 cm (35 inches) denote increased risk for certain diseases and conditions.[2,17] These include ischemic heart disease, diabetes mellitus, hypertension, dyslipidemia, and death.[1-3]

Peripheral gynecoid, or gluteal femoral obesity ("pear" shape), with a waist/hip ratio below 0.76 is associated with varicose vein development, joint disease, and reduced incidence of non–insulin-dependent diabetes mellitus (Figure 43-2, *B*). Medical risks accompanying gynecoid fat deposition are less perilous than those associated with the android pattern.[1,20]

Differences in morbidity between android and gynecoid fat distribution are caused by metabolic attributes of the adipose and tissues adjacent to it. Gynecoid repositories of fat, found primarily in women, are metabolically static and are proposed to function as energy depots for pregnancy and lactation.[3,20] Android fat distribution, typically seen in males, is metabolically active with regard to free fatty acid (FFA) release.[2] When elevated levels of FFAs are mobilized from adipose tissue, portal venous drainage delivers high concentrations of FFAs to the liver. Continual delivery of excessive FFAs stimulates hepatic synthesis of very-low-density lipoproteins (VLDLs) and circulation of low-density lipoproteins (LDLs). Hepatic exposure to high concentrations of FFAs also increases gluconeogenesis and inhibition of insulin uptake, which induces non–insulin-dependent diabetes mellitus. Although VLDLs, LDLs, and hyperglycemia are catalysts for the formation of associated cardiovascular and cerebrovascular disease, some studies support the possibility that hyperinsulinemia alone may cause hypertension.[2,3]

CAUSES OF OBESITY

Body size is dependent on genetic and environmental factors. Genetic predisposition, believed to be a primary factor in the development of obesity, explains only 40% of the variance in body mass.[6] The significant increase in the prevalence of obesity has resulted from environmental factors that result in increased calorie intake and reduced physical activity.[6,17] Other factors such as socialization, age, sex, race, and economic status affect its progression. In the United States, food consumption has risen as a result of the "super-sizing" of portions and the availability of high-fat fast food and snacks. Physical activity has been reduced as a result of modernization (e.g., television and computers) and sedentary lifestyle and work activities. Cultural and lifestyle variations play an important role in the development of obesity.[6] For example, some ethnic foods contain high levels of fats and carbohydrates, whereas others (e.g., Asian) focus on low-fat foods such as fish and vegetables.

There is increased interest in the role of inflammation in obesity. Several inflammatory mediators such as angiotensinogen (AGT), transforming growth factor beta (TGF-β), tumor necrosis factor alpha (TNF-α), and interleukin 6 (IL-6) are elevated in morbidly obese patients. Weight loss results in a reduction in both the inflammatory mediators and comorbidities associated with obesity.[21] Continued investigation into genetic-environmental interactions may provide further understanding and treatment of obesity.[19,20]

PATHOPHYSIOLOGY OF OBESITY

A number of pathophysiologic changes occur as a result of overweight and obesity.[22] These changes involve all of the major body organ systems, leading to an increase in morbidity and premature death. The risk of many of the medical conditions associated with obesity increases linearly with BMI.[2-4]

Cardiovascular Considerations

Cardiovascular considerations are predominantly a reflection of the progressive compensatory processes that evolve to meet the increased metabolic demands of the fat organ.[23,24] Cardiovascular disease dominates the morbidity and mortality in obesity and manifests in the form of ischemic heart disease, hypertension, and cardiac failure.[14] Development and sustenance of the fat mass necessitates formation of extra blood vessels and increased circulatory, pulmonary, central, and peripheral blood volume.[2-4] For every 13.5 kg of fat gained, an estimated 25 miles of neovascularization occurs to provide blood flow at a rate of 2 to 3 mL/100 g of tissue per minute. This represents an increased cardiac output of 0.1 L/min for each kilogram of fat acquired.[3] Expansion of blood volume, stimulated by hypoxia-induced chronic respiratory insufficiency, is seen in severe obesity. Accelerated renin-angiotensin activity and the perfusion requirements of the fat organ further increase the vascular fluid compartment.[2-4,23,24]

Movement of the expanded blood volume through extensive vascular tissue, under compression by adipose tissue, places greater demand on the myocardium. Increased workload caused by elevation of the basal metabolic rate is reflected in increased cardiac output, increased oxygen (O_2) consumption, increased carbon dioxide production, and normal or slightly abnormal arteriovenous O_2 difference.[2,25] Chronically elevated cardiac output precedes increased left-sided heart pressures and left ventricular hypertrophy. Because heart rate usually remains the same, cardiac output must be augmented by an increase in stroke volume. Therefore, cardiomegaly, atrial and biventricular dilation, and biventricular hypertrophy ensue. These contribute to the development of hypertension and eventual congestive heart failure.[2-4,26]

Hypertension is defined as a systolic pressure greater than 140 mmHg, a diastolic pressure greater than 90 mmHg, or both.[3] The prevalence rates of hypertension in obese patients are more than twice as high as those in lean men and women.[26,27] Blood pressure has been shown to increase 6.5 mmHg for every 10% increase in body weight.[28] In the nonhypertensive remainder of the severely obese, decreased systemic vascular resistance may serve to facilitate forward blood flow through the doubled body habitus.[2,4] Hypertension is precipitated by increased blood viscosity, catecholamine kinetics, and possibly increased estrogen

concentrations. Hyperinsulinemia, elevated mineralocorticoids, and abnormal sodium reabsorption are also implicated as causes of hypertension. Hypercholesterolemia (i.e., cholesterol levels greater than 240 mg/dL) often coexists with hypertension, thereby predisposing obese patients to atherosclerosis and cerebrovascular accident.[25,27] Arrhythmias may occur as a result of hypoxemia, hypercapnia, electrolyte disorders, sleep apnea, ventricular hypertrophy, hypertension, and coronary artery disease.[23,24]

Coronary artery disease in the obese is a frequently associated but independent risk factor. It appears with or without hypertension, hypercholesterolemia, diabetes mellitus, hyperlipidemia, or sedentary lifestyle.[2-4,29] Obesity coincident with coronary artery disease results in frequent angina, congestive heart failure, acute myocardial infarction, and sudden death.[14,25,26] Ischemic heart disease is more common in those obese individuals with a central distribution of fat.[25]

Respiratory Considerations

Compromise of respiratory function results from the compression of fat on abdominal, diaphragmatic, and thoracic structures. Over time, thoracic kyphosis and lumbar lordosis develop, resulting in impaired rib movement and fixation of the thorax in an inspiratory position.[1,3] As a result, chest wall, lung, parenchyma, and pulmonary compliance is reduced to 35% of predicted values.[29,30] Metabolic needs of the fat organ and the greater mechanical work of breathing stimulate increased myocardial O_2 consumption. Increases in carbon dioxide production and retention, coupled with decreased ventilation, coincide with reduced respiratory muscle efficiency.[2] Lung inflation is inhibited, which causes declinations in functional residual capacity (FRC) to less than closing capacity. Premature airway closure increases dead space and causes carbon dioxide retention, ventilation-perfusion mismatch, shunting, and hypoxemia.[1,19] Morbid obesity is associated with reductions in FRC, expiratory reserve volume (ERV), and total lung capacity.[29-31] FRC declines exponentially with increasing BMI.[2] A recent study of pulmonary function in morbidly obese patients indicates that forced vital capacity varies inversely with BMI, and patients with a very high BMI, even when asymptomatic, will have major reductions in lung function.[32]

Concomitant diminution of vital capacity, total lung capacity, ERV, and inspiratory capacity are demonstrated by rapid, shallow breathing. These ventilation patterns are characteristic of restrictive lung disease.[2,30,31] Eventual hypoventilation, hypercarbia, and acidosis result from depression of central nervous system responsiveness to chronic hypoxia.[3] Recurrent hypoxemia leads to secondary polycythemia and is associated with an increased risk of coronary artery disease and cerebrovascular disease.[18] Respiratory muscle dysfunction also has been reported with obesity[33] and may result from an inefficiency secondary to changes in chest-wall compliance or the lower lung volumes found in obesity. These abnormalities predispose obese patients to respiratory failure in the setting of even mild pulmonary or systematic insults.[34]

Obstructive Sleep Apnea

Obesity is a well-established risk factor for sleep apnea, with the incidence of obstructive sleep apnea (OSA) increasing in direct proportion with the level of obesity. Patients characterized with OSA have a BMI greater than 30 kg/m^2, abdominal fat distribution, and a large neck girth (greater than 17 inches in men and greater than 16 inches in women).[2] For patients with clinically severe obesity (BMI 35 kg/m^2 or greater) who present for bariatric surgery, the incidence of sleep apnea ranges from 71% to 77%.[35-57]

OSA is characterized by excessive episodes of apnea (10 seconds) and hypopnea during sleep that are caused by complete or partial upper airway obstruction.[38] Up to 25% of all surgical patients are at risk of OSA.[39] Obstructive sleep apnea is characterized by intermittent closure or narrowing of the upper airway during sleep, which leads to episodes of apnea-hypopnea, arousal, and oxygen desaturation.[40] This disorder is pervasive and affects nearly 18 million Americans.[41] As many as 80% to 95% of persons with OSA are undiagnosed.[42]

Apnea is the cessation of airflow at the nose and mouth for more than 10 seconds.[43] Apnea is considered obstructive if there is continued respiratory effort despite airflow cessation. Hypopnea is defined as a 50% reduction in airflow for 10 seconds for 15 or more times per hour of sleep associated with snoring and a 4% decrease in oxygen saturation. It connotes a transient reduction in airflow caused by increased upper airway resistance.[42] OSA syndrome is diagnosed by polysomnography using an apnea-hypopnea index (AHI).[44] There are different definitions of OSA. The AHI is the number of abnormal respiratory events per hour of sleep. Classically, the accepted minimal clinical diagnostic criteria for OSA are an AHI of 10 plus symptoms of excessive daytime sleepiness. The American Academy of Sleep Medicine defines mild OSA as AHI between 5 and 15, moderate OSA as AHI between 15 and 30, and severe OSA as AHI more than 30. The Medicare guidelines diagnose OSA with an AHI of 15, or an AHI of 5 with 2 comorbidities.[35]

The pathogenesis of OSA is likely multifactorial.[45] Contributing factors include airway anatomy, the state-dependent control of the upper airway dilator muscles, and ventilatory stability. The site of upper airway obstruction typically lies in the pharynx. The pharyngeal luminal area during inspiration reflects a balance between collapsing intrapharyngeal negative suction pressure and dilating forces provided by the pharyngeal muscles.[46] In awake human subjects, the patency is maintained by the central nervous system's continually mediated contraction of the tensor muscles. These dilator muscles oppose the negative collapsing force developed during inspiration.[42] This activation of muscle tone is typically reduced during sleep and in many individuals leads to compromised patency of the upper airway with turbulent airflow and snoring. In obese patients, more adipose tissues in the pharyngeal structures increase the likelihood that relaxation of the upper airway muscles will cause collapse of the soft-walled oropharynx between the uvula and the epiglottis. Extraluminal pressure is increased by superficially located masses, and the upper airway is compressed externally.[40,42,47,48]

While sleeping, any and all of these mechanical, neural, and structural factors may contribute to upper airway collapse that either interferes with or eliminates ventilation, which results in a surge of pharyngeal dilator muscle activity that subsequently opens the airway. A period of hyperventilation then follows, which reverses hypercarbia, and then correspondingly the central respiratory drive is reduced. The process can repeat itself continually throughout the night, causing intermittent hypoxia and hypercarbia, fragmenting sleep, and triggering adrenergic surges with each cycle.[42,43,46] Clinically significant episodes of 5 or more per hour or more than 30 per night result in hypoxia, hypercapnia, systemic and pulmonary hypertension, and cardiac arrhythmias.[20,30,31,38]

Patients undergoing electrocardiogram (ECG) Holter monitoring showed that nocturnal paroxysmal asystole, episodic bradycardia, and sinus node dysfunction were more prevalent in patients with OSA.[49] Study of OSA patients with permanent atrial pacemakers demonstrated that subjects had fewer episodes of OSA if their pacemakers were set to increase their heart rate during the

BOX 43-2

STOP-Bang Scoring Model for Screening for Obstructive Sleep Apnea

1. Snoring: Do you snore loudly (loud enough to be heard through closed doors)?	Yes	No
2. Tired: Do you often feel tired, fatigued, or sleepy during daytime?	Yes	No
3. Observed: Has anyone observed you stop breathing during your sleep?	Yes	No
4. Blood Pressure: Do you have or are you being treated for high blood pressure?	Yes	No
BMI: BMI more than 35 kg/m^2?	Yes	No
Age: Age more than 50 years old?	Yes	No
Neck circumference: Neck circumference greater than 40 cm?	Yes	No
Gender: Male?	Yes	No

High risk of OSA: Answering yes to 3 or more items.
Low risk of OSA: Answering yes to fewer than 3 items.

Adapted from Seet E, Chung F. Obstructive sleep apnea: preoperative assessment. *Anesthesiol Clin*. 2010;28(2):199-215.
BMI, Body mass index; *OSA*, obstructive sleep apnea.

night. It is hypothesized that the increased vagal tone accompanying bradycardia also affects airway patency.[50]

Patients with OSA also have a higher incidence of comorbidities. Approximately 50% to 60% of patients with OSA are hypertensive, and an estimated 50% of hypertensive patients have sleep apnea.[51]

Because 80% to 95% of all patients with OSA are undiagnosed and untreated, many patients who present for surgery will not be diagnosed. During preanesthetic evaluation, patients should be asked about their sleeping patterns, and anesthesia providers should have a high index of suspicion for OSA in all obese patients.[52] Some advocate that all obese patients, or those who observe them while they sleep, be routinely asked about nocturnal snoring or apnea, arousals, and diurnal sleepiness.[53] Several screening tools have been developed for preoperative use. The STOP-Bang screening tool (Box 43-2) is easy to use and has a sensitivity of up to 93%.[39,54,55]

Suggestions for the management of obstructive sleep apnea patients are listed in Table 43-2.

Obesity Hypoventilation (Pickwickian) Syndrome

Obesity hypoventilation syndrome (OHS), or pickwickian syndrome, is a complication of extreme obesity characterized by OSA,

TABLE 43-2 Perioperative Anesthetic Management of the Patient with Obstructive Sleep Apnea

Phase	Anesthetic Concern	Principles of Management
Preoperative period	Cardiac arrhythmias and unstable hemodynamic profile	Indirect evidence advocating the usefulness of PAP to reduce cardiac arrhythmias, stabilize variable blood pressure, and decrease myocardial oxygen consumption
	Multisystem comorbidities	Preoperative risk stratification and patient optimization Individualized intraoperative anesthetic management tailored to comorbidities
	Sedative premedication	α_2-Adrenergic agonist (dexmedetomidine) premedication may reduce intraoperative anesthetic requirements and have an opioid-sparing effect
	OSA risk stratification, evaluation, and optimization	Preoperative anesthesia consults for symptom evaluation, airway assessment, polysomnography if indicated, and formulation of anesthesia management
Intraoperative period	Difficult intubation	Ramp from scapula to head Adequate preoxygenation ASA difficult airway algorithm
	Opioid-related respiratory depression	Opioid avoidance or minimization Use of short-acting agents Regional and multimodal analgesia (e.g., nonsteroidal antiinflammatory drugs, acetaminophen, tramadol, ketamine, gabapentin, pregabalin, dexamethasone)
	Carry-over sedation effects from longer-acting intravenous sedatives and inhaled anesthetic agents	Use of propofol for maintenance of anesthesia Use of insoluble potent anesthetic agents (sevoflurane and desflurane)
	Excessive sedation in monitored anesthetic care	Use of capnography for intraoperative monitoring
Reversal of anesthesia	Postextubation airway obstruction and desaturations	Verification of full reversal of neuromuscular blockade Ensure patient fully conscious and cooperative before extubation Semiupright posture for recovery
Immediate postoperative period	Suitability for outpatient surgery	Lithotripsy, superficial, or minor orthopedic surgeries using local or regional techniques may be considered for outpatient surgery No requirement for high-dose postoperative opioids Transfer arrangement to inpatient facility should be available
	Postoperative respiratory event in known and suspected high-risk patients with OSA	Longer monitoring in the PACU Continuous oximetry monitoring and PAP therapy may be necessary if recurrent PACU respiratory events occur (e.g., desaturation, apnea, bradycardia)

Adapted from Seet E, Chung F. Obstructive sleep apnea: preoperative assessment. *Anesthesiol Clin*. 2010;28(2):199-215.
ASA, American Society of Anesthesiologists; *OSA*, obstructive sleep apnea; *PACU*, postanesthesia care unit; *PAP*, positive airway pressure.

hypercapnia, daytime hypersomnolence, arterial hypoxemia, cyanosis-induced polycythemia, respiratory acidosis, pulmonary hypertension, and right-sided heart failure. At its extreme, there is evidence of nocturnal episodes of central apnea, apnea without respiratory efforts, reflecting progressive desensitization of the respiratory centers to nocturnal hypercarbia.[30,31,38,47]

OHS is defined as obesity (body mass index greater than 30 kg/m2), daytime hypoventilation with awake P_{CO_2} greater than 45 mmHg, and sleep-disordered breathing in the absence of other causes of hypoventilation. About 90% of patients with OHS also have OSA. The prevalence of OHS in patients with OSA is uncertain but is estimated to be between 4% and 20%.[56]

OHS, which occurs in 8% of the obese population, is clinically distinct from simple obesity.[31] With simple obesity, the partial pressure of arterial carbon dioxide, pH, and pulmonary compliance are within normal ranges.[29] Hypoxia may be present, but no evidence of cardiac failure or arterioalveolar O_2 difference exists. In contrast, OHS is diagnosed when the morbidly obese patient exhibits inappropriate and sudden somnolence, sleep apnea, hypoxia, and hypercapnia.[3] A P_{CO_2} greater than 45 during wakefulness on arterial blood gas testing with compensatory metabolic compensation and hypoxemia (P_{O_2} less than 70) is suggestive of OHS.[56] Alveolar ventilation is reduced because of shallow and inefficient ventilation related to decreased tidal volume, inadequate inspiratory strength, and inadequate elevation of the diaphragm. Cardiac enlargement, cyanosis, polycythemia, and twitching also are evident on physical examination.[4] Activities of daily living are altered by the somnolent episodes. Operating machinery or driving a vehicle may cause injury or death.

Gastrointestinal Disease

The incidence of gastroesophageal reflux disease, gallstones, and pancreatitis increases with obesity. Obesity is associated with a number of liver abnormalities referred to as *nonalcoholic fatty liver disease* (NAFLD).[57] NAFLD includes steatosis, steatohepatitis, fibrosis, cirrhosis, hepatomegaly, and abnormal liver biochemistry. Patients with NAFLD are at risk for developing cirrhosis, hepatic decompensation, and hepatocellular carcinoma. The pathogenesis of NAFLD is not fully understood, although researchers have found that a combination of environmental, genetic, and metabolic factors lead to advanced disease. There have been improvements in noninvasive radiographic methods to diagnose NAFLD—especially for advanced disease. However, liver biopsy is still the standard method of diagnosis for NAFLD.[58]

The prevalence of NAFLD is up to 30% in developed countries and nearly 10% in developing nations, making NAFLD the most common liver condition in the world. The pathogenesis of NAFLD is related to insulin resistance and it is frequently found in individuals who have central obesity or diabetes. Insulin resistance and excess adiposity are associated with increased lipid influx into the liver and increased hepatic triglyceride accumulation. Defects in lipid use via mitochondrial oxidation and lipid export also may contribute to hepatic lipid build-up. Clinically, NAFLD is commonly asymptomatic and usually detected incidentally by liver function tests or imaging performed for other reasons. Subjects with NAFLD have a higher mortality rate than the general population and are at increased risk of developing cardiovascular disease and diabetes in the future.[57] In obese patients, the mortality rate from liver cirrhosis is 1.5 to 2.5 times higher than in nonobese persons.[18]

Gallstones

Gallstones are 30% more prevalent in obese than nonobese women, and this prevalence increases linearly with BMI.[4] Higher concentrations of cholesterol in the bile and an increased ratio of bile salts to lecithin are responsible for the development of gallstones.[59] Jaundice also may accompany bile duct obstruction. Laparoscopic and open cholecystectomies are commonly performed in this group of patients because of the increased incidence of gallbladder disease in the obese. Although technically more difficult for both surgical and anesthesia teams, the benefits of laparoscopic gallbladder removal (e.g., reduced postoperative pain, shorter hospitalization, earlier return to activities of daily living) outweigh the risks.

Endocrine and Metabolic Disease

Obesity is seldom the result of primary endocrine dysfunction. Thyroid, adrenocortical, and pituitary function should be investigated with obesity that manifests atypical symptoms.[3] Menstrual problems such as oligomenorrhea, amenorrhea, menorrhagia, and the presence of hirsutism may herald hypothalamic-pituitary abnormalities. Obese men may experience decreased libido or impotence indicative of hypogonadism. Low serum follicle-stimulating hormone and testosterone levels are frequently evident.[20]

Within groups of individuals demonstrating non–insulin-dependent diabetes mellitus, 80% are obese. The risk of type 2 diabetes increases linearly with BMI.[20]

There is a 35% to 40% prevalence of the metabolic syndrome in the U.S. population. Patients with obesity and metabolic syndrome may have complicated medical histories including diabetes, heart disease, and OSA. Metabolic syndrome comprises an array of conditions including glucose intolerance and/or type 2 diabetes mellitus, hypertension, dyslipidemia, and cardiovascular diseases. Patients with the metabolic syndrome have increased risks for developing coronary artery disease, stroke, peripheral vascular disease, and type 2 diabetes mellitus, and greater mortality from coronary disease and other causes. These patients also have a proinflammatory and prothrombotic state. Whether this syndrome is a disease itself or is composed of discrete disorders is the subject of much investigation and controversy. Individuals with the metabolic syndrome have a cardiovascular risk 50% to 60% higher than normal. The definition and characteristics of metabolic syndrome is noted in Box 43-3.[60]

BOX 43-3

Metabolic Syndrome Definition

The American Heart Association and the National Heart, Lung, and Blood Institute defines metabolic syndrome as the presence of three or more of the following criteria:

1. Elevated waist circumference
   - Men: 40 inches (102 cm) or greater
   - Women: 35 inches (88 cm) or greater
2. Elevated triglycerides
   - 150 mg/dL or greater
3. Reduced HDL cholesterol
   - Men: less than 40 mg/dL
   - Women: less than 50 mg/dL
4. Elevated blood pressure
   - 130/85 mmHg or greater
5. Elevated fasting glucose
   - 100 mg/dL or greater

Adapted from Levin PD, Weissman C. Obesity, metabolic syndrome, and the surgical patient. *Anesthesiol Clin*. 2009;27(4):705-719.

Orthopedic and Joint Disease

Obese persons often develop osteoarthritis from continued mechanical stress on weight-bearing joints. A linear relationship between degree of arthritis and weight exists.[2-4] Ankles, hips, knees, and lumbar spine are frequently burdened. Bone resorption secondary to limited physical activity also may reduce bone density and contribute to stress fractures. Reduction of weight can curb orthopedic injury and lessen the discomfort in the back and lower extremities.

PEDIATRIC OBESITY

Obesity is a growing problem among U.S. children. In 1994, one in five children between the ages of 6 and 17 was overweight, tripling the rate of 30 years ago.[61] The 2004 National Center of Health Statistics (NCHS) report shows 20% of children and adolescents 2 to 19 years of age are overweight, and that 4% of adolescents have BMIs greater than 40. Adolescents are more overweight than preschool children.[62,63] These adverse trends in obesity have potentially profound effects on children's health now and for their long-term health outlook.

Obesity is clinically diagnosed as a weight-for-height greater than the 90th percentile or a BMI greater than or equal to the 95th percentile, age and sex specific. Pediatric obesity is recognized by BMI greater than the 95th percentile on the Centers for Disease Control and Prevention (CDC) growth chart. Evidence-based guidelines and expert committee recommendations have repeatedly stressed that the BMI for age should be the basis of our definitions of pediatric overweight and obesity.

Studies document links between early childhood and adolescent obesity and adult obesity:

- Obese adolescents have a 70% to 80% chance of being obese adults.[64]
- Childhood obesity is associated with a higher chance of premature death and disability in adulthood, particularly in urban areas.[65]
- Childhood and adolescent overweight and obesity are linked with adult cardiovascular and endocrine problems.[66]
- Obese children are three to five times more likely to suffer a heart attack or stroke before they reach the adult age of 65.[66]
- Being overweight as young as age 18 could be the strongest predictor of future hip replacement because of osteoarthritis.[67]

Determinants of obesity are multifactorial and include genetics, biology, and social and environmental behaviors that may begin in early childhood. The escalating national and global epidemics of obesity and sedentary lifestyle warrant increased attention by physicians and other healthcare professionals. The health goals for obese children and adolescents should be to develop healthy eating habits, maintain weight or reduce the rate of gain, and to be active rather than sedentary.[68]

Some specific problems obese children face related to the healthcare community are the following:

- Pediatric obesity is more common than diabetes, human immunodeficiency virus (HIV), cystic fibrosis, and all childhood cancers combined.
- Primary hypertension in children has become increasingly common in association with obesity and risk factors such as a family history of hypertension and an ethnic predisposition to hypertensive disease. Obese children are at approximately a threefold higher risk for hypertension than nonobese children.[69]
- Most children with type 2 diabetes are overweight or obese at diagnosis and usually have a family history of type 2 diabetes. Americans of African, Hispanic, Asian, and American Indian descent are disproportionately represented.[70]
- OSA sleep disorder was very common in a clinical sample of overweight children. OSA is not associated with abdominal obesity. On the contrary, higher levels of abdominal obesity and fat mass are associated with central sleep apnea.
- Bariatric surgery may be useful but only with carefully selected obese children with serious comorbidities and unresponsiveness to interventions. The biggest barrier seems to be the psychosocial aspect, although complications from child bariatric surgery may include leaks, deep vein thrombi, micronutrient deficiency, bleeding, and infection.[71]
- Psychosocial disorders may result when obese children are treated differently. This may be the most devastating effect of obesity on children. They may feel isolated and lonely and have self-esteem and identity problems. It is important for the healthcare professional to be sensitive to this issue and understand that an individual's confidence, especially a child's, is affected by self-image and perceptions of peers.[72]

Unfortunately, children with long-standing obesity (especially morbidly obese) develop medical problems previously seen only in adulthood. Medical effects of obesity such as hypertension, insulin resistance, coronary artery disease, and metabolic syndrome previously reserved for adults are on the rise in children and adolescents.[73,74]

The prevalence of the metabolic syndrome is high among obese children and adolescents and increases with worsening obesity. Diagnosis of metabolic syndrome in children and adolescents is only now receiving greater attention, and there does not seem to be consensus on precise standards of treatment. As with adults, the dominant underlying risk factors for this syndrome appear to be abdominal obesity, insulin resistance, hypertriglyceridemia, hypertension, and proinflammatory and prothrombotic states.[74]

Studies show that obesity increases the burden of disease for children and adolescents, and special attention has been given to clinical complications for that population. These include cardiovascular disease (dyslipidemia and hypertension), respiratory disease (sleep apnea, snoring, asthma), orthopedic conditions (Blount's disease, slipped capital femoral epiphysis), gastrointestinal disease (gallbladder, steatohepatitis), and endocrine disease (insulin resistance, hyperinsulinism, impaired glucose tolerance, and type 2 diabetes that is normally reserved for adults). Other conditions in adolescent females include polycystic ovarian syndrome and menstrual irregularity. Studies also include psychosocial conditions such as depression, eating disorders, and social isolation.[75]

MATERNAL OBESITY

Obstetric complications of maternal obesity correlate more to pregravid obesity rather than excessive weight gain during gestation. Maternal obesity, not diabetes, seems to be the most important link to the nation's increase in mean birth weight. Mean increase in birth weight in the past 30 years was 116% at 37 to 41 weeks' gestation.[76] Prepregnancy obesity significantly increases the parturient risk for cesarean delivery.

Both first and second stages of labor are longer in obese women. Obesity is a risk factor for developing gestational hypertension, insulin-treated gestational diabetes, and hydramnios. However, neonatal outcome of obese women is comparable to women with normal prepregnancy body mass index.[77]

The National Institutes of Health (NIH) recognizes many risk factors associated with maternal obesity. Outcomes in pregnancy complicated by obesity include gestational diabetes, preeclampsia, preterm labor, cesarean delivery, postpartum hemorrhage, infection, pregnancy-induced hypertension (PIH), and macrosomic

infants. The American College of Obstetricians and Gynecologists (ACOG) reports increased risk for spontaneous abortion and miscarriage rates of almost double that of nonobese women in the first 6 weeks of pregnancy.[76] Metabolic syndrome in pregnancy manifests as preeclampsia, gestational hypertension, insulin resistance, and diabetes. Preeclampsia increases further in obese women with gestational diabetes mellitus (GDM) that is poorly controlled, a previous history of GDM, family history of type 2 diabetes, and history of a macrosomic fetus.[73]

Newborns considered large for gestational age (LGA), or macrosomic, are at long-term risk for adolescent and adult obesity. Weiss et al.[78] defined *fetal macrosomia* as birth weight greater than 4000 g. The study found the rate of macrosomia to be 8.3% in nonobese parturients, 13.3% in those who were obese, and 14.6% in the morbidly obese. These increased birth weights have been linked to increased adolescent metabolic syndrome and type 2 diabetes. By age 4, 25% of these children have impaired glucose tolerance. Children born to mothers with BMIs greater than 30 in the first trimester are more likely to show fetal overgrowth and adiposity beginning in utero and continuing into the first years of life. The results of one study demonstrated that at ages 2, 3, and 4, growth was increased by 15.1%, 20.6%, and 24.1%, respectively.[79]

Peripartum risks associated with maternal obesity include the following:

- Cesarean delivery and associated morbidity (approaches 40% in severely obese)
- Difficult placement of epidural and spinals, requiring multiple attempts
- Difficult intubation risk, usually in an emergent setting (twice the risk of nonobese women)
- Decreased ability of ultrasound to detect cardiac and craniospinal abnormalities
- Increased postoperative complications, longer surgery times, wound infection and breakdown, endometritis, antepartum venous thrombi/emboli (VTE), and excessive blood loss during surgery but no increased risk of postpartum hemorrhage

Bariatric Surgery for Obese Women: Gestational Considerations

Owing to limited success with lifestyle changes, more obese women of reproductive age are seeking bariatric surgery as an alternative. Previous reports showed complications during pregnancy after these malabsorptive procedures, including increase in premature rupture of membranes, small bowel ischemia, nutrient deficiencies, and fetal abnormalities.[76] Cesarean deliveries increased in women who had previous bariatric surgery. Gestational diabetes and PIH disorders were significantly reduced in women having laparoscopic adjustable gastric banding procedures. There were no significant differences in placental abruption and previa, labor dystocia, or perinatal complications with bariatric surgery prior to conception.

Recommendations by ACOG[80] include weight screening annually, especially for women of childbearing age with a family history of cardiovascular disease and diabetes mellitus. They recommend physical activity, proper diet, behavioral therapy, and bariatric surgery for women with BMIs greater than 40 with comorbidities prior to pregnancy. After delivery, continued exercise and diet, as well as breastfeeding the infant, are beneficial. During pregnancy, weight gain should be limited following the Institute of Medicine (IOM) suggestions: 25- to 35-lb increase in nonobese women, 15 to 25 lb in overweight women, and 15 lb in obese women.

Genetic predisposition, physiology, and mechanisms related to maternal and fetal-placental interaction are important to the growth and development of children. Maternal obesity is shown to be a significant risk factor in adverse outcomes in pregnancy. Higher birth weights have a definite connection to overgrowth in children and obesity in adolescents.

TREATMENT OF OBESITY

A multimodal approach in the treatment of obesity includes dietary intervention, increased exercise, behavior modification, drug therapy, and surgery. Weight-loss programs are individualized to each patient based on the degree of obesity and coexisting conditions. Drug therapy is initiated in patients with a BMI greater than 30 kg/m^2 or a BMI between 27 and 29.9 kg/m^2 with a coexisting medical condition.[2-4] Medications that promote weight loss have limited efficacy. Despite the enormous potential market, efforts to develop effective drug therapies have been disappointing. The FDA guidance for long-term weight loss drugs recommends that a 5% weight reduction be maintained for 12 months after treatment initiation. Orlistat (Xenical; Alli) is the only over-the-counter medication currently approved for obesity treatment. Orlistat is a lipase inhibitor that decreases the absorption of fat in the gastrointestinal tract. Side effects are minor and mostly related to gastrointestinal discomfort. It may inhibit the absorption of fat-soluble vitamins A, D, E, and K, requiring supplementation. Occasionally monoamine oxidase inhibitors are used off label.[81] The Food and Drug Administration (FDA) has recently approved one new drug and a new combination of two old drugs for chronic weight management. Lorcaserin (Belviq) is a selective serotonin 2_C receptor agonist. Activation of the serotonin 2_C receptor, found mainly in the central nervous system, is thought to suppress appetite. Qsymia (Vivus) is a fixed-dose combination of the weight-loss drug phentermine and an extended-release formulation of topiramate. The new products are approved for use in obese patients (body mass index [BMI] of ≥30 kg/m^2) and for patients who are overweight (BMI ≥27 kg/m^2) and have one weight-related risk factor such as hypertension, dyslipidemia, or type 2 diabetes. Both drugs have some success taken as adjuncts to diet and exercise and may be effective in increasing weight loss in the first year of use.[82]

Surgical Treatment

Besides common surgeries performed within the general population, obese persons undergo additional procedures to ameliorate obesity-related diseases (Box 43-4). The four most common bariatric procedures at present are the Roux-en-Y gastric bypass (RYGB), laparoscopic adjustable gastric bypass (AGB), sleeve gastrectomy (LSG), and the biliopancreatic diversion with duodenal switch (BPD with DS). All are safe, effective, minimally invasive, and relatively cost-effective. Surgical approaches

BOX 43-4

Obesity-Related Diseases Requiring Surgery

- Cholelithiasis
- Thromboembolism
- Peripheral vascular disease
- Urolithiasis and urinary incontinence
- Osteoarthritis-related orthopedic procedures
- Varicose veins
- Hiatal and abdominal wall hernias
- Cancer (endometrial, breast, prostate, colorectal, renal)
- Uterine fibroma
- Ovarian cysts
- Cesarean section

designed to treat obesity can be classified as malabsorptive or restrictive.[81] Malabsorptive procedures are not commonly used. Restrictive procedures include the largely historic vertical banded gastroplasty (VBG) and the increasingly common gastric banding, including laparoscopic adjustable gastric banding and laparoscopic sleeve gastrectomy The mechanisms of various bariatric procedures are shown in Box 43-5. Despite the technically demanding nature of the Roux-en-Y gastric bypass procedure, it has become the procedure of choice for clinically severe obesity. Laparoscopic adjustable gastric banding is greatly increasing in frequency in the United States.[81,83-87]

Advances in laparoscopic surgery have significantly improved surgical procedure times, morbidity, and mortality related to bariatric surgery. If the operation is performed using the "closed" method, the negative impact of pneumoperitoneum on respiratory system mechanics and oxygenation during laparoscopy can be seen. Ezri [88] demonstrated that the endotracheal tube moves more often in obese patients undergoing laparoscopy compared with those having open abdominal surgery. Patients appreciate laparoscopic bariatric surgery because it reduces postoperative pain and the duration of convalescence.[89] Many studies show reductions in overall morbidity when a laparoscopic technique is used.[90-93]

Indications for bariatric surgery are noted in Box 43-6. Postoperatively, patients must stay in close contact with multidisciplinary team members. Rehabilitation of previous lifestyle patterns is achieved through counseling and support provided by psychologists, dietitians, physical therapists, and internists.[84-86] Most patients who are monitored for as long as 5 years postoperatively achieve losses from their original weight of as much as 30% to 60%.[98]

BOX 43-5

Mechanism of Action of Select Bariatric Operations

Restrictive
- Vertical banded gastroplasty (VBG; historic purposes only)
- Laparoscopic adjustable gastric banding (AGB)
- Laparoscopic sleeve gastrectomy (LSG)

Largely Restrictive, Mildly Malabsorptive
- Roux-en-Y gastric bypass (RYGB)

Largely Malabsorptive, Mildly Restrictive
- Biliopancreatic diversion (BPD)
- Duodenal switch (DS)

Adapted from Richards WO. Morbid obesity. In: Townsend CM, et al, eds. *Sabiston Textbook of Surgery: The Biological Basis of Modern Surgical Practice*. 19th ed. Philadelphia: Saunders; 2012:358-388.

BOX 43-6

Indications for Bariatric Surgery

Patients must meet the following criteria for consideration for bariatric surgery:
- BMI greater than 40 kg/m^2 or BMI less than 35 kg/m^2 with an associated medical comorbidity worsened by obesity
- Failed dietary therapy
- Psychiatrically stable without alcohol dependence or illegal drug use
- Knowledgeable about the operation and its sequelae
- Motivated individual
- Medical problems not precluding probable survival from surgery

Adapted from Richards WO. Morbid obesity. In: Townsend CM, et al, eds. *Sabiston Textbook of Surgery: The Biological Basis of Modern Surgical Practice*. 19th ed. Philadelphia: Saunders; 2012:358-388.
BMI, Body mass index.

PHARMACOLOGIC CONSIDERATIONS

Obesity causes physiologic changes that can affect the pharmacokinetics and pharmacodynamics of anesthetic agents. An overview of these changes are listed in Box 43-7. The common approach to anesthetic drug administration is to give water-soluble drugs according to ideal body weight (IBW) and lipid-soluble drugs according to total body weight (TBW). Lean body mass increases approximately 20% to 40% in obesity, so adding 30% to the ideal body weight is a convenient dose adjustment. Contradictory results from individual drug studies in small patient groups are common; therefore specific recommendations are frequently conflicting. A few general observations can be made. Postoperative respiratory depression is especially problematic in obese patients; therefore most clinicians favor short-acting drugs, which allow for fast recovery. The newer inhalation agents desflurane and sevoflurane produce excellent recovery profiles in obese patients. Although desflurane is less soluble than sevoflurane, clinical differences are minimal. Nitrous oxide can be safely used in patients where a requirement for high oxygen concentrations does not preclude its administration. Succinylcholine doses for intubation are given according to TBW to ensure excellent intubating conditions, whereas the nondepolarizing muscle relaxants used for operative maintenance are given according to IBW. Use of a nerve stimulator to guide relaxant administration assists in minimizing residual paralysis and reversal concerns. Remifentanil infusion is an especially popular analgesic due to titratability and rapid offset and is administered according to IBW. Dexmedetomidine is also a useful adjunct for sedation, amnesia, and analgesia. Specific dosing recommendations for some common anesthetic agents in obesity are listed in Table 43-3.[81,94,95]

ANESTHETIC MANAGEMENT: PREANESTHETIC EVALUATION

The goals of the preanesthetic evaluation are to obtain pertinent data regarding the patient's medical or surgical history, to optimize current physiologic functioning, and to determine an appropriate anesthetic plan (see Chapter 19). Of paramount importance is the need to establish a nonjudgmental and trusting relationship with the patient. Explanations of anticipated events during preoperative preparation (e.g., multiple venipunctures, central and arterial line insertions, awake intubation, pain management) and protection of the patient's privacy will allay anxiety.

BOX 43-7

Pharmacokinetic Changes Associated with Obesity

- Increased fat mass
- Increased cardiac output
- Increased blood volume
- Increased lean body weight
- Changes in plasma protein binding
- Reduced total body water
- Increased renal clearance
- Increased volume of distribution of lipid-soluble drugs
- Abnormal liver function
- Decreased pulmonary function

Medications

Obese persons must be queried for concurrent use of weight-reducing substances, herbal supplements, and anorexiant drugs. Patients who take over-the-counter drugs, including herbal medications, often forget or are afraid to reveal that they are taking these preparations, which can have deleterious consequences on induction. Patients' usual medications should be continued until the time of surgery, with the exception of insulin and oral hypoglycemics.[96] Recommendations for preoperative management of antidiabetic drugs are given in Chapters 19 and 33. Antibiotic prophylaxis is important because of an increased incidence of wound infections in the obese.[97]

Laboratory Tests

Given the current climate of cost-consciousness and cost-efficiency, only the laboratory tests appropriate in light of the patient's history, physical examination, and planned surgery should be ordered.[14] In morbidly obese patients, baseline studies that may be directly affected by associated medical conditions are performed. Routine testing includes assessment of a complete blood count, electrolyte panel, glucose and hemoglobin A_{1c}, coagulation profile, liver and renal function tests, and a lipid profile. Complete blood cell counts may reveal a hematocrit as high as 65%, which can result from contracted blood volume or polycythemia associated with cardiopulmonary disease.[14,29] Leukocytosis (greater than 11,000 µL) is a strong predictor of risk for acute myocardial infarction independent of tobacco smoking.[17]

Arterial blood gas analysis that compares samples taken with the patient lying supine and sitting while breathing room air provides baseline values and can distinguish simple obesity from OHS. The renal panel may reflect abnormal glucose and potassium levels, which are indicators of insulin resistance and potentiation of myocardial irritability. Concomitant use of diuretics and certain cardiac medications can exacerbate electrolyte disturbances.[14] Blood urea nitrogen (BUN) and creatinine levels may be elevated in response to dehydration or renal dysfunction. Liver function tests are typically elevated in obese patients. This is generally not the result of hepatic disease but of infiltration of the hepatocytes with triglycerides (e.g., fatty liver, liver steatosis). The severity of fatty infiltration may alter pharmacologic effects of many anesthetic drugs, thereby requiring dose reductions.

Coagulation studies are necessary, especially if regional anesthesia is planned or if coagulopathy exists. Patients taking anticoagulants for treatment of deep vein thrombosis or atrial fibrillation may exhibit elevated prothrombin and partial thromboplastin times. Use of nonsteroidal antiinflammatory drugs (NSAIDs) may prolong bleeding times and affect surgical hemostasis.

In obese patients undergoing abdominal or thoracic surgery, pulmonary function tests are invaluable and essential for anesthetic planning; for selected procedures, the tests may be waived.[18] Chest radiography is necessary to determine the presence of cardiomegaly, pulmonary infiltrates, and evidence of chronic obstructive pulmonary disease.

Cardiac Assessment

Evaluation of cardiac function is essential in overweight and obese patients undergoing surgery. Investigation of prior myocardial infarction and the presence of hypertension, angina, or peripheral vascular disease is crucial. Limitations in exercise tolerance, history of orthopnea, and paroxysmal nocturnal dyspnea may indicate left ventricular dysfunction.[94] A careful elicitation of drug history is invaluable in garnering clues about the patient's coexistent diseases. When possible, cardiac medications should be continued up to and including the morning of surgery.

An electrocardiogram (ECG) is essential for determination of resting rate, rhythm, and ventricular hypertrophy or strain. Because of the increased incidence of coronary artery disease (CAD) and myocardial infarction in this population, the preoperative ECG is also helpful in providing a reference for comparison in the event that myocardial ischemia is suspected in the perioperative period. Beyond this, there is no reason to believe that extensive preoperative testing to detect CAD is indicated based solely on a patient being obese.[98] The ECG may be of low voltage because of the excess overlying tissue and therefore might result in underestimation of the severity of ventricular hypertrophy. Axis deviation and atrial tachyarrhythmias are relatively common.[4]

QT-interval prolongation, discovered retrospectively in severely obese patients who died from refractory dysrhythmias, is a marker for sudden cardiac arrest.[3] In cases of fatal and nonfatal dieting, prolonged QT intervals were also exhibited on patient ECGs.[4] In addition, sudden cardiac death is more prevalent in morbidly obese patients with left ventricular hypertrophy and

TABLE 43-3 Guidelines for Dosages of Intravenous Anesthetics in Obese Patients

Drug	Dose Recommendation	Comments
Propofol	Induction dose based on LBW Maintenance dose based on TBW	Increased fat mass does not affect initial distribution/redistribution during induction; cardiac depression at high doses is a concern
Succinylcholine	Intubating dose based on TBW	Increased fluid compartment and pseudocholinesterase levels require higher doses to ensure adequate paralysis
Rocuronium Vecuronium Cisatracurium	All doses based on IBW	Hydrophilic drugs given according to IBW will ensure shorter duration and a more predictable recovery in this respiratory-challenged population
Fentanyl Sufentanil	Loading dose based on TBW Maintenance doses based on LBW and response	Increased distribution volume and elimination time correlate with degree of obesity
Remifentanil	Infusion rates based on IBW	Distribution volumes and elimination rates are similar to normal-sized individuals; fast offset requires planning for postoperative analgesia
Dexmedetomidine	Infusion rates of 0.2 mcg/kg/min	Useful as an adjunct; lower than usual infusion rates are recommended to minimize adverse cardiac side effects

IBW, Ideal body weight; *LBW*, lean body weight; *TBW*, total body weight.

ventricular ectopy.[5] If ventricular hypertrophy or cardiomyopathy is suspected, echocardiography is useful. Tricuspid regurgitation on echocardiography is the most confirmatory test of pulmonary hypertension when combined with clinical evaluation.[99]

Exercise testing may elicit valuable information about myocardial function in morbidly obese patients. Most are physically unable, however, to achieve adequate levels of exercise stress to make the studies worthwhile.[14] In addition, echocardiography is useful for determining whether akinesis or wall-motion abnormalities are present in the obese myocardium.

Cardiomegaly, pulmonary congestion, elevated diaphragm, and a tortuous aorta can be identified by use of chest radiography. Results of radiographic studies serve to guide preoperative pharmacologic and medical management (e.g., diuretics, β_1-agonists, antibiotics). Repeated radiographs may be required to obtain adequate penetration and visualization of all lung fields. Unfortunately, standard stationary and portable x-ray machines cannot accommodate massively obese persons. As a result, diagnostic x-ray examinations or evaluation of central line placement may be impossible. Under these circumstances, clinical expertise and management of subtle symptoms are invaluable. If it is indicated, the patient should be referred to a cardiologist for further investigation and optimization of his or her condition (e.g., control of blood pressure, treatment of heart failure, or treatment of coronary pathology).[100]

Respiratory Evaluation

Careful preoperative evaluation of the patient's respiratory function identifies potential problems. A patient who becomes dyspneic and desaturates when recumbent experiences the same symptoms during induction in the supine position. Questions must elicit information regarding the presence or absence of OSA, orthopnea, wheezing, sputum production, or smoking history. Pulmonary function tests are valuable for assessing the presence of respiratory impairment. Recent upper respiratory infection, snoring, or sleep disturbances may indicate obstructive processes. The potential for difficult mask ventilation also should be considered during the preoperative visit. Obesity has been identified as an independent risk factor for difficult facemask ventilation. Increasing this risk would be findings such as presence of a beard, lack of teeth, and history of snoring.[101] Room air pulse oximetry saturations and blood gases obtained in supine and upright positions may reflect disturbances in cardiac compensation.[102]

Airway Evaluation

A thorough airway evaluation is warranted for determination of the optimal airway management technique in overweight and obese patients.[103] A variety of assessment criteria have been evaluated for prediction of difficult intubation in obese patients. Most practitioners use evaluation of multiple patient physical characteristics to identify potential airway problems indicative of the unanticipated difficult airway. These include measurement of interincisor distance, thyromental distance, head and neck extension, Mallampati classification, body weight, and, most importantly, a history of difficult airway.[104-106] Inspection of the oropharynx is necessary to determine Mallampati classification for intubation difficulty.[104] The value of oropharyngeal Mallampati classification alone is low. Evaluation of the length of upper incisors, visibility of the uvula, shape of the palate, compliance of the mandibular space, and length and thickness of the neck provide further criteria for assessment.

Opinions differ about the use of a patient's weight (BMI) as an independent predictor of difficulty in intubation. Some have demonstrated that difficult intubation is more common in obese patients.[107] Others have demonstrated that increased BMI per se is not a predictor of difficult intubation.[108] Variables determined likely to predict difficulty in intubation of the obese patient include increased neck circumference, Mallampati classification greater than 3, increased age, male sex, temporomandibular joint (TMJ) pathology, a history of OSA, and abnormal upper teeth.[108,109] Of these, a high Mallampati score (3 or greater) with a large neck circumference and a history of sleep apnea were in the aggregate found to be good predictors of difficulty in intubation.[104]

Fat rolls around the neck (restricting neck motion) and fat in the airway (decreasing glottic opening) together increase the difficulty of successfully intubating the trachea. The larger the neck circumference, the more difficult the laryngoscopy and intubation. Neck circumference of 40 cm was associated with a 5% probability of difficult intubation, and neck circumference of 60 cm was associated with a 35% probability of difficult intubation. A normal neck circumference in a 70-kg man is about 35 cm. Other researchers, using ultrasound to quantify the amount of anterior neck soft tissue, produced data that support these findings.[110]

Anatomic aberrations of the upper airway induced by severe obesity include reduced temporomandibular and atlanto-occipital joint movement. Unsatisfactory mouth opening, presence of neck or arm pain, or inability to place the head and neck into "sniffing position" may indicate the need for awake fiberoptic intubation. Extreme airway narrowing in conjunction with shortened mandibular-hyoid distance (less than three fingerbreadths) can complicate mask ventilation and intubation. Presence of a short, thick neck, pendulous breasts, hypertrophied tonsils and adenoids, or a beard can contribute to a difficult airway. Marginal room air pulse oximeter saturations, abnormal arterial blood gases, and history of complicated airway management also indicate a potentially difficult intubation.[104-106] (Refer to Chapter 22 for a full description of the assessment and management of a difficult airway.) Airway management techniques should be explained to the patient, with emphasis on awake intubation and the need for postoperative ventilation.[111,112]

Vascular Access

Venipuncture can be challenging in overweight and obese patients with excessive fat that obscures blood vessels from visualization and palpation.[14] Central cannulation of vessels is impeded by distortions of the underlying anatomy by adipose tissue.[113] Hemorrhage, hypothermia, and trauma further reduce the likelihood of accessing vessels with ease. Use of a portable ultrasound machine may improve central venous catheter placement. As in all patients, iatrogenic pneumothorax must be avoided. Morbidly obese patients are less able than nonobese patients to tolerate the ensuing respiratory impairment.

ANESTHETIC MANAGEMENT: PREPARATION

Operating Room Equipment

In preparation for either emergent operating room procedures or nonemergent hospital admission, appropriate equipment must be readied. Newer-model operating room tables can accommodate up to 600 lb of weight. Older-model standard operating room tables could hydraulically elevate 300 to 350 lb of weight. In cases of extreme morbid obesity, "big boy" hydraulic beds are obtained and used in the operating room. Heavy-duty stirrups, extra-large retractors, elongated instruments, arm sleds, doubled armboards, and extremity tourniquets must be obtained. Sometimes a sanitized engine crane or other hoisting device must be used to suspend the panniculus adiposus for optimal surgical exposure.

Extra-large thigh cuffs can be used on the upper arm or the lower leg (over the posterior tibial artery). A regular-size or large blood pressure cuff can be used on the forearm over the radial artery until arterial cannulation for blood pressure monitoring can be performed. Bed-warming devices, fluid warmers, and warm airflow blankets should be used to prevent hypothermia, which can occur rapidly when large areas of body surface are exposed.

Airway Equipment

An equally important part of airway assessment is the preparation of equipment and personnel necessary to ventilate and intubate the morbidly obese patient. An assortment of blades, laryngoscopy handles, endotracheal tubes, masks, oral and nasopharyngeal airways, and stylets should be assembled. Laryngeal mask airways (LMAs), intubating laryngeal mask airways (ILMA), GlideScope, fiberoptic and bronchoscopic devices, Eschmann introducers, a jet ventilator (or Venturi apparatus), and emergency tracheotomy and cricothyrotomy kits must be available in the event that ventilation by mask or endotracheal tube is unsuccessful. Most departments have a difficult-airway cart that has all of the available equipment that should be placed in the operating room. Recently the ILMA and LMA CTrach (a modified version of the intubating LMA that allows continuous videoendoscopy of the tracheal intubation procedure) have been advocated as particularly useful tools for ventilating and intubating morbidly obese patients.[114,115]

Monitoring

Intraoperative monitoring, both basic and advanced, should address the specific needs of the patient. Selection of electrocardiographic leads, when possible, should enhance detection of myocardial ischemia and pathology (leads II and V_5). Needle electrodes may be useful for obtaining a better tracing. Cuffs with bladders that encircle a minimum of 75% of the upper arm circumference, but preferably the entire arm, should be used. Forearm measurements with a standard cuff overestimate both systolic and diastolic blood pressures in obese patients.[116] Placement of an arterial catheter is appropriate for monitoring hemodynamic status and is advocated for all but the most minor procedures in the morbidly obese.[18] Use of central venous and pulmonary artery catheters are not standard but should be considered in patients undergoing extensive surgery or those with serious cardiorespiratory disease.[94,113]

Aspiration Prophylaxis

Anesthesia providers have traditionally considered obese patients to be "full-stomach" patients and at risk for regurgitation and subsequent pulmonary aspiration.[117-119] It is known that gastroesophageal reflux and hiatal hernia are more prevalent in the obese, and this may predispose them to esophagitis and pulmonary aspiration. More recent data, however, have demonstrated that obese patients (BMI greater than 30 kg/m^2) may have a lower incidence of "at-risk" stomach contents compared with lean patients.[120] The actual incidence of clinically significant aspiration in these patients has not been conclusively determined, but is likely quite low. The airway should be secured expeditiously, but use of a "rapid-sequence induction" should be individualized and not routinely performed.[94] In one study, researchers evaluated gastric contents of 232 surgical patients. Only 20 of 75 obese patients (27%) had high-volume, low-pH stomach contents, compared with 66 of 157 (42%) of lean patients. More recent studies have also demonstrated that obese patients who are fasting may not have gastric pH and volumes that would put them at risk for pulmonary aspiration.[121,122]

There is no consensus on whether obese patients have delayed, normal, or accelerated gastric emptying.[123] Current recommendations are that obese patients should follow the same fasting guidelines as nonobese patients. All patients should be allowed to drink as much as 300 mL of clear liquids until up to 2 hours before elective surgery; that volume has been demonstrated to not adversely affect the pH and volume of gastric contents at induction of anesthesia.[124]

Obesity is significantly related to gastroesophageal reflux disease (GERD).[125,126] Although increased body mass has been shown by some researchers to correlate directly with an increased incidence of reflux symptoms,[127] others have demonstrated the opposite and question the routine use of rapid-sequence induction on all patients who present with a diagnosis of GERD.[128]

Owing to the more recent and favorable data, some advocate the avoidance of rapid-sequence induction technique on obese patients as standard protocol, citing that it is a common misperception that all obese patients should be viewed as "full-stomach" patients, and in the event of failed intubation, obese patients may have poorer outcomes.[129,130] Although obese patients and patients with sleep apnea syndrome are prone to GERD, and both groups may also have an increased risk of difficult intubation, in the case of elective surgery in a fasted patient with no risk factors other than obesity or sleep apnea syndrome, the requirement for rapid-sequence induction is debatable.[131]

However, if symptoms are present in obese patients with GERD disease, the potential increased risk of aspiration should be discussed with the patient, and prophylactic measures (e.g., cricoid pressure, H_2 blockers, and proton-pump inhibitors) should be considered.[132] Although rapid-sequence induction may be safe for some obese patients, its safety in superobese patients has been questioned. For patients with a BMI greater than 50 kg/m^2, or lower but with risk factors such as OSA or large neck circumference, either an awake intubation (with local anesthesia) on spontaneous respiration of the patient or intubation without relaxants (after only propofol administration) is suggested.[133]

Patient Positioning for Induction

Obese patients are more difficult to intubate in the "sniffing" position, but placed in the "ramped" position there is no evidence that this risk is greater than in the general population.[134] It is essential that optimal patient positioning for laryngoscopy is ensured prior to induction of anesthesia. This includes the placement of towels under the patient's shoulders and head and putting the operating room table in reverse Trendelenburg position to increase the patient's FRC. The term *HELP* (*h*ead *e*levated *l*aryngoscopy *p*osition) reminds clinicians of the importance of patient positioning for successful laryngoscopy.[135] This position generally improves the view during laryngoscopy and contributes to increasing the safety period until patients demonstrate signs of oxygen desaturation. This position is also a better patient position for using rescue ventilation techniques, such as bag-valve mask ventilation or insertion of an LMA, should they be required.

One study described positioning morbidly obese patients with the head, upper body, and shoulders significantly elevated above the chest, such that an imaginary horizontal line could connect the patient's sternal notch with the external auditory meatus. Positioning patients in this manner resulted in successful intubation in 99 of 100 morbidly obese patients, with all having a Cormack grade I view.[136]

Others have also concluded that the "ramped" position (with blankets used to elevate both the upper body and head of the patient) improves laryngeal view in obese patients when compared

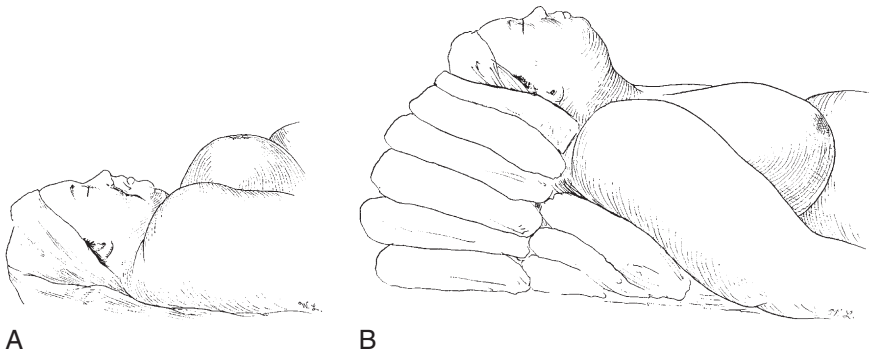

FIGURE **43-3** **A,** Supine position. **B,** Sniffing position.

with a conventional 7-cm cushion under the patient's head (sniffing position), which should result in fewer failed intubations[137] (Figure 43-3). Without proper support and alignment of the oropharynx and trachea (see Figure 22-13), ventilation may be obstructed, and visualization of the laryngeal structures may be obscured.

The importance of proper positioning and the difficulty of repositioning morbidly obese patients during failed intubation can be underestimated by practitioners who are not experienced in airway management in obese patients. If direct laryngoscopy is unsuccessful, LMAs can be effective for establishing ventilation and should be immediately available.[111,124] In one study, the use of an intubating laryngeal mask resulted in better patient oxygenation compared with intubation through direct laryngoscopy in morbidly obese patients.[115]

During a rapid-sequence induction, cricoid pressure is applied while the patient's trachea is intubated. There is much discussion regarding the effectiveness of cricoid pressure and the advantages and risks associated with the technique.[138]

In theory, when pressure is applied to the cricoid cartilage, it causes an occlusion in the esophagus between the cricoid cartilage and the vertebral body. However, it has been demonstrated that the application of cricoid pressure results in a reduction in lower esophageal sphincter pressure in anesthetized patients, but gastric pressure is reportedly less than the esophageal pressure, and the barrier to reflux remains intact.[139]

Researchers have determined that during rapid-sequence induction, gastric pressure is about 14 mmHg or less and that gastric barrier pressure is less than 15 mmHg. These researchers concluded that the amount of cricoid pressure that is adequate to protect most anesthetized patients from regurgitation is 20 Newtons (N), increasing the force to 30 N as loss of consciousness occurs.[140]

The theory, however, has been challenged. In a recent study of awake patients using magnetic resonance imaging (MRI), it was demonstrated that when applying cricoid pressure, the esophagus may actually be displaced laterally. The lateral laryngeal displacement was noted in 67% of the subjects with cricoid pressure, and airway compression of at least 1 mm was demonstrated in 81% of the subjects as a result of cricoid pressure.[141]

ANESTHETIC MANAGEMENT: MAINTENANCE

Intubation

For airway management to be facilitated, the obese patient should be positioned with the head elevated (reverse Trendelenburg position) on the operating room table. This position promotes patient comfort, reduces gastric reflux, provides easier mask ventilation, improves respiratory mechanics, and helps maintain FRC. The reduced FRC in obese patients contributes to the rapid desaturation that occurs with induction of general anesthesia.[142] To attenuate the desaturation and maximize O_2 content in the lungs, patients are preoxygenated with 100% mask O_2 for at least 3 to 5 minutes.[143] Adequate preoxygenation is vital in obese patients because of rapid desaturation after loss of consciousness secondary to increased oxygen consumption and decreased FRC. Application of positive-pressure ventilation during preoxygenation decreases atelectasis and improves oxygenation in morbidly obese patients. A study in morbidly obese individuals (limited to 160 kg by the weight limit of the computed tomography [CT] scanner) has demonstrated that the administration of continuous positive airway pressure (CPAP) during the preoxygenation period and gentle ventilation with positive end-expiratory pressure (PEEP) during anesthetic induction significantly reduce atelectasis, as documented by chest CT scans.[144] An associated benefit to the reduced atelectasis was a significantly increased average Pa_{O_2} (457 ± 130 pascals [Pa] versus 315 ± 100 Pa, P = 0.035) in those subjects who received CPAP-PEEP versus the control subjects. Theoretically, the increase in Pa_{O_2} would increase the apneic time to oxygen desaturation if an airway event were to occur.[145]

Some practitioners advocate the use of an "awake look" to visualize the difficulty of the airway.[104-106,111,112] Careful administration of sedative drugs and application of topical anesthesia to the oropharyngeal structures, possibly including transtracheal and superior laryngeal nerve blocks, are performed. Nasal O_2 is used as a supplement during awake laryngoscopy. If the epiglottic and laryngeal architecture is easily visualized, successful asleep intubation can be done. If the airway structures cannot be visualized, an intubating LMA, awake fiberoptic, or other type of intubation should be used.[111,146,147] Many clinicians advocate the use of a modified rapid-sequence induction when aspiration is a consideration.[148] This is a technique with preoxygenation and cricoid pressure as usual, but the lungs are lightly ventilated prior to securing the airway. This avoids the rapid desaturation that frequently occurs in the obese patient with no or a minimal increased risk of aspiration. The endotracheal tube must be safely secured to prevent movement during positioning and surgery.[88]

The surgeon and another skilled anesthesia provider also must be in attendance during the induction. Muscle hypotonus in the floor of the mouth, followed by rapid occurrence of soft-tissue obstruction and hypoxia, requires one person to support the mask and airway while another person bag-ventilates the patient. In the case of inability to ventilate or intubate, the American Society of Anesthesiologists' difficult airway algorithm should be followed (see Chapter 22). Intubation of the obese patient can be safely accomplished with careful assessment and planning and use of modern airway techniques.

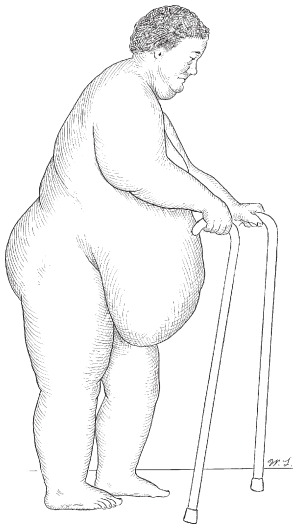

FIGURE **43-4** Panniculus in a standing patient.

Effects of General Anesthesia on Respiration

General anesthesia depresses respiration in normal subjects, so any preexisting pulmonary dysfunction is exaggerated by anesthesia.[18] The type of surgery, positioning, and underlying disease pathology further compound the undesirable respiratory responses caused by obesity and anesthesia.[149-154] General anesthesia causes a 50% reduction in FRC in the obese anesthetized patient, as compared with a 20% reduction in anesthetized nonobese patients.[88] Airway collapsibility is likely due to the decreased lung volume associated with deeper anesthesia as the end-expiratory esophageal pressure is reduced with lighter planes of anesthesia.[155] FRC can be increased by ventilating with large tidal volumes (15 to 20 mL/kg), although this has been shown to improve arterial O_2 tension only minimally.[83,149] In contrast, the addition of PEEP achieves an improvement in both FRC and arterial O_2 tension, but only at the expense of cardiac output and O_2 delivery.[151,152] Current ventilation recommendations include using tidal volumes of 10 to 12 mL/kg to avoid barotrauma.[83] During laparoscopic surgeries, the respiratory rate should be 12 to 14 breaths per minute.[80]

Prolonged (longer than 2 to 3 hours) and extensive procedures (those involving the abdomen, thorax, and spine) negatively influence respiratory function. Subdiaphragmatic packing, cephalad displacement of organs, and surgical retraction cause decreased alveolar ventilation, atelectasis, and pulmonary congestion.[149,150] Recumbent or Trendelenburg positioning further reduces diaphragmatic excursion, which is already impaired by the weight of the panniculus (which can be very large) (Figure 43-4). Trendelenburg positioning also causes elevated filling pressures, which then increase right ventricular preload. Subsequently, myocardial O_2 consumption, cardiac output, pulmonary artery occluding pressures, peak inspiratory pressures, and venous admixtures are increased above upright-sitting values.[151]

In a normal-weight person, cardiac output increases in response to supine posturing to maintain hemodynamic stability. By increasing left ventricular output, the centrally located circulating volume is propelled forward, thereby minimizing pulmonary congestion and hypoxia. In a severely obese patient, positive-pressure ventilation (which impedes venous return) and inability to increase cardiac output may result in cardiopulmonary decompensation.[152,153] This is exhibited intraoperatively by hypoxia, rales, ventricular ectopy, congestive heart failure, and hypotension.[154] Bag ventilation by hand may be useful to attenuate hypotension resulting from positive pressure.

Use of ventilators powerful enough to inflate the morbidly obese thorax is critical to minimizing hypoxia. Pressure- or volume-controlled ventilators can be used to maintain adequate oxygenation and normocapnia. Avoidance of prolonged prone, Trendelenburg, or supine positioning also decreases ventilation-perfusion mismatch. Optimization of oxygenation by using no less than 50% flow of inspired O_2 is emphatically recommended.[18,31,83] Intermittent manual "sighs" of large volume can also augment the FRC.

Application of PEEP can reduce venous admixture and support adequate arterial oxygenation. PEEP, however, can impair arterial oxygenation in some patients when it is superimposed on large tidal volumes.[153] For these reasons, PEEP that exceeds 15 cm H_2O is not recommended.

Other intraoperative events, such as hemorrhage or hypotension, further impair ventilatory homeostasis and result in hypoxemia that extends into the postoperative period.[30] A vertical abdominal incision, compared with a horizontal (transverse) incision, also prolongs postoperative hypoxia.[103] Pain causes further reductions in diaphragmatic excursion and vital capacity, leading to atelectasis and ventilation-perfusion mismatch.[18,83] For these reasons, 24-hour postoperative admission to a monitored bed is prudent for severely obese patients, who already exhibit higher morbidity and mortality apart from anesthesia and surgery.

Some suggested ventilatory strategies are listed in Table 43-4.

Choice of Anesthetic Technique

Selection of the anesthetic technique is dependent on the patient, coexisting history, planned surgical procedure, and anesthetist and patient preference. Diverse anesthetic techniques have been described for use with obese patients undergoing surgical and diagnostic procedures.[94,134,156-161] Anesthetic management of obese patients can include local or monitored anesthesia, general (e.g., narcotic, inhalation) anesthesia, regional blocks, or a combination of techniques.

No demonstrable difference in emergence from inhalation versus narcotic technique has been discerned in the obese patient.[18] The use of short-acting anesthetics facilitates smooth anesthetic induction, maintenance, and emergence from anesthesia. Objectives for maintenance of anesthesia in the obese patient include strict maintenance of airway, adequate skeletal muscle relaxation, optimum oxygenation, avoidance of the residual effects of muscle relaxants, provision of appropriate intraoperative and postoperative tidal volume, and effective postoperative analgesia. Depending on the patient's condition and the type of surgery, these can be achieved by either general or regional anesthesia. An epidural anesthetic with concomitant "light" general anesthesia is frequently chosen. A light general anesthetic can facilitate management of the airway, ventilation, and the patient's level of consciousness, whereas the epidural provides surgical analgesia and anesthesia. The epidural catheter can be used for postoperative analgesic administration and will enhance earlier resumption of deep breathing and coughing maneuvers.

Volume Replacement

Despite the augmentation of circulatory fluid that accompanies morbid obesity, the estimated blood volume is actually diminished.[22] Fat, which contains only 8% to 10% water, contributes less fluid to total body water than equivalent amounts of muscle. The normal adult percentage of total body water is 60% to 65%.[18] In the severely obese, it is reduced to 40%. Therefore, calculation

TABLE 43-4 Ventilatory Management of the Morbidly Obese Patient

Goal/Recommendation	Rationale/Additional Information
Prevent Hypoxemia During Induction	
HOB elevated (back-up Fowler or reverse Trendelenburg) 30 degrees Use of CPAP during induction Preoxygenate with 100% O_2	May increase the safe apnea period during induction
Prevent/Reverse Atelectasis	
Restrict the use of Fio_2 to less than 0.8 during maintenance of anesthesia	Use of a high Fio_2 concentration during anesthesia accelerates the onset and the amount of atelectasis
Recruitment ("vital capacity") maneuver after intubation by using sustained (8-10 seconds) pressure of 40 cm H_2O or greater	Monitor for adverse effects (bradycardia, hypotension)
Maintain Lung Recruitment	
Use PEEP (10-12 cm H_2O)	Monitor for hypotension or decreasing arterial oxygenation (PEEP-induced increase in pulmonary shunt fraction)
Prevent Reoccurrence of Atelectasis	
Intermittent intraoperative re-recruitment	Monitor highest oxygenation and respiratory system compliance achieved after recruitment: a decline may be a sign of redeveloping atelectasis
Avoid Lung Overdistension	
Use tidal volume 6-10 mL/kg of ideal body weight Keep end-inspiratory pressure below 30 cm H_2O Consider mild permissive hypercapnia if necessary	Increase the ventilation rate to control excessive hypercapnia instead of using large tidal volumes or high ventilatory pressures
Maintain Postoperative Lung Expansion	
Use CPAP or BiPAP immediately after tracheal extubation Keep the upper body elevated Maintain good pain control Use incentive spirometry Encourage early ambulation	

Adapted from Thompson J, et al. Anesthesia case management for bariatric surgery. *AANA J*. 2011;79:2:147-160.
BiPAP, Bi-level positive airway pressure; *CPAP*, continuous positive airway pressure; *Fio_2*, fractional inspired oxygen concentration; *HOB*, Head of bed; *PEEP*, positive end-expiratory pressure.

of estimated blood volume should be 45 to 55 mL/kg of actual body weight rather than the 70 mL/kg apportioned in nonobese adults.[17] Use of reduced parameters for volume replacement and avoidance of rapid rehydration lessen cardiopulmonary compromise. Fluid management is guided by the usual clinical parameters such as blood pressure, heart rate, and urine output measurements. Fluid requirements for bariatric procedures may be greater than anticipated to maintain renal perfusion. Although rare, acute renal failure occurs in approximately 2% of bariatric procedures. Predisposing factors include hypovolemia, a BMI greater than 50 kg/m^2, prolonged surgery time, intraoperative hypotension, and preexisting renal disease.[162] Adequate intraoperative fluid replacement also helps reduce postoperative nausea and vomiting after bariatric procedures.[163] Volume expanders, such as hetastarch (Hespan), should not be administered at greater than recommended volumes per kilogram of IBW (20 mL/kg). Dilutional coagulopathy, factor VIII inhibition, and decreased platelet aggregation can result from excessive administration. Albumin may be used as indicated to support circulatory volume and oncotic pressure. No difference in the criteria between the administration of blood products in normal-weight patients versus severely obese patients has been identified.

Intraoperative Positioning

Surgical positioning of morbidly obese patients necessitates extra precautions for the prevention of nerve, integumentary, and cardiorespiratory compromise. The type of surgery, combined with inordinate stretching or compression of nerve plexuses and prolonged immobility, cause local tissue ischemia and damage, which begins at the cellular level. Hypothermia, hypotension, table positioning, and the pressure effect the adipose tissue places on orthopedic or cardiopulmonary structures potentiate impairment.[165]

Although many peripheral nerves are subjected to possible ischemia or necrosis, the ulnar, brachial plexus, radial, peroneal, and sphenoid nerves are the most vulnerable to injury in any anesthetized patient. In morbidly obese patients, the incidence may be increased because of excessive weight on the anatomic structures.[164] Care is necessary when one is positioning obese extremities in slings, draping them on Mayo stands, or securing them in lithotomy stirrups. Excess weight and loose skin may "strangle" or macerate tissues on the dangling ankle or wrist. Draping of heavy upper extremities atop poorly secured Mayo stands can cause cuts, bruises, or abrasions of the arm, breast, or abdomen, as well as obscure early signs of skin breakdown or circulatory compromise.

Prolonged hyperextension, external rotation, or abduction greater than 90 degrees overstretches the brachial plexus and can cause postoperative muscle pain, nerve palsies, or paralysis. Often obese patients do not have the range of motion that nonobese individuals possess. Therefore, less flexion or abduction and rotation of hips, legs, and arms may be necessary. Frequent palpation of pulses, generous padding, correct alignment, and repeated inspection of extremities for color and temperature can help diminish the incidence of positioning-related injuries.[165,166]

Lower back pain can be aggravated by both spinal and general anesthesia because of ligamentous relaxation that results in loss of lumbar curvature. Surgical towels placed under the lumbar spine before induction will enhance lordosis and reduce postoperative discomfort.[164]

Treatment of the panniculus is often a major concern for both anesthetist and surgeon. Extra-long straps and wide adhesive tape can secure the panniculus and reduce shifting when the operating table is changed. If Trendelenburg positioning is anticipated, some means to prevent the panniculus from sliding cephalad must be devised. The head-down position, coupled with the crushing weight of the thorax and panniculus, compresses the brachial neurovascular bundle between the clavicle and first rib. If the patient requires a fracture table, ensure that sufficient padding encircles the pole adjacent to the patient's vulva or penis.[166] Genital and pudendal nerve injury can be profound if adipose tissue surrounding the thigh is not carefully distracted to reveal proper placement of the padding.

Integumentary Concerns

Decubitus ulcers, skin infection, and wound dehiscence are exceedingly common in the severely obese. Decubitus ulcers arise

from prolonged immobility and compression of the fat on bony prominences and vessels. Traction, external fixation devices, and straps may cause certain types of injury. Creases of the skin are subject to erosion and ulceration from sweat and constant friction of opposing skin surfaces. Inability to perform hygiene under the breasts, between neck folds, or beneath the abdominal pannus accommodates organism proliferation. Concomitant diabetes further accelerates the growth of bacterial or fungal infections. As a result, wound dehiscence, particularly in the abdomen, can occur after suboptimal surgical closure in compromised skin. A poorly vascularized panniculus and torsion on the wound by the weight of the fat apron also contribute to malunion of the tissue.[166] Although atelectasis and hypoxia are less frequent with a horizontal laparotomy, a vertical laparotomy approach is often preferred by the surgical team. Compression of abdominal contents on superficial wound layers is lessened during ambulation and therefore may reduce the occurrence of dehiscence.[85]

Extubation

The risk of airway obstruction after extubation is increased in obese patients.[167] A decision to extubate depends on evaluation of the ease of mask ventilation and tracheal intubation, the length and type of surgery, and the presence of preexisting medical conditions, including OSA. Criteria for extubation must include all of the standard objective and subjective criteria used by every clinician. Patients are usually placed with the head up or in a sitting position prior to extubation. If doubt exists regarding the ability of the patient to breathe adequately, the endotracheal tube is left in place and extubation over an airway exchange catheter or via a fiberoptic bronchoscope may be performed.[167,168]

Regional Anesthesia

Regional anesthesia can be used as the primary anesthetic in selected cases or as an accompaniment to postoperative pain and mobility management.[18,25,166] Difficulties are frequently encountered, though, in severely obese patients. Anatomic landmarks used to guide conduction blockade are not easily visualized, palpable, or identifiable with ultrasound. Brachial plexus anesthesia can be hampered by adipose tissue in the axillary region, inability to position the arm, and an undetectable pulse. Full-term pregnancy, obesity, and the coincident discomfort of active labor further inhibit the discernment of spinous processes and posterior iliac crests. Redundant rolls of fat, unsatisfactory ventilation, and inability of the patient to sustain optimal positioning make neuraxial anesthesia even more challenging.

For subarachnoid or epidural anesthesia, it is recommended that the patient sit upright so that landmarks such as C7 or L3 to L4 can be more easily identified.[86] In addition, skin-fat folds will fall toward the operating table, and respiratory ventilation will be enhanced. A selection of longer needles (7 inches) should also be available before anesthetic administration is begun. Generous infiltration with local anesthetic will provide greater patient comfort during insertion of the "finder," Tuohy, or spinal needle. The importance of generous administration of local anesthetic cannot be overemphasized because repeated insertions and repositioning of the needle or introducer may be required before access to the epidural (or subarachnoid) space is achieved.

Another consideration regarding subarachnoid or epidural anesthesia in severely obese pregnant or surgical patients is the lack of predictability of spread of local anesthetic. Obese patients will also experience greater respiratory embarrassment from a high regional block than normal-weight patients.[169] Successful laparotomy procedures have been described after epidural anesthesia.[170]

In obese parturients, a cesarean section can be performed under spinal or epidural anesthesia. A significant correlation exists with increased body mass and rostral spread of epidural subarachnoid anesthetics when a patient is positioned supine. Undesirable cephalad spread of local anesthetics can be obviated by reducing the volume and increasing the patient's upright sitting time.

ANESTHETIC MANAGEMENT: POSTOPERATIVE CARE

Pain Management

Optimal postoperative pain management is facilitated by the use of oral analgesics, NSAIDs, patient-controlled analgesia, local infiltration of the surgical site, and epidural anesthesia. Obese patients are more sensitive to the respiratory-depressant effects of opioid analgesics; therefore caution and close monitoring are warranted.[171] Supplemental O_2 and pulse oximetry monitoring are mandated. If the patient was on CPAP (nasal or facemask) preoperatively, CPAP should be applied at all rest times in the early post–general anesthetic period. The CPAP protects the patient with OSA against airway obstruction during sleep by pneumatically splinting the oropharynx.[43,172,173] Postoperative opioids must be used judiciously.

Postoperative Complications

Morbidity and mortality rates are higher in obese patients than in normal-weight patients. Various studies have reported that the mortality rate during the perioperative period has decreased among morbidly obese patients.[174] Older age, a high BMI, and male gender have been confirmed as proven surgical risk factors for obese patients undergoing gastric bypass surgery.[175,176] Other factors that have been shown to increase mortality risk include hypertension, diabetes, postoperative leak with bariatric procedures, and thromboembolism.[177] Those with major comorbid diseases had a higher BMI, a higher mortality, a greater leak rate, and a higher rate of surgical site infections.[178] Ventilation abnormalities are exacerbated in obese patients with OSA and OHS and may last for several days. The maximum decrease in partial pressure of arterial oxygen occurs 2 to 3 days postoperatively.[29] In one study, morbidly obese subjects had a mean maximal oxygen uptake that was similar to patients with severe heart failure (mean ejection fraction 21.5 ± 8%).[179] The same investigators studied cardiorespiratory fitness in 109 patients prior to laparoscopic gastric bypass. They found that severe complications and mortality were more common in patients whose maximum oxygen uptake was less than 15.8 mL/kg/min than in those whose maximum oxygen uptake was more than 15.8 mL/kg/min ($P = 0.02$).[180] This may be a promising way to identify high-risk patients and perhaps monitor their preoperative progress. Blouw et al.[181] tried to identify factors influencing the frequency of respiratory failure in patients with morbid obesity. They found that a higher rate of respiratory failure is associated with BMI greater than 43 kg/m^2.

Rhabdomyolysis is a complication in about 1.4% of bariatric surgeries, owing to high pressures exerted on deep tissues. Serum creatinine phosphokinase (CPK) measured pre- and postoperatively aids in early diagnosis and treatment, which helps reduce further complications such as myoglobinuric acute renal failure that can be as high as 30% with serum CPK greater than 5000 units/L.[182] A recent report[183] describes rhabdomyolysis of the gluteal muscles leading to renal failure in several morbidly obese patients who were supine for 5-hour gastric bypass operations. Another case report[184] describes rhabdomyolysis leading to renal failure and death after bariatric surgery.

The risk of thromboembolism, wound infections, and atelectasis is amplified in patients with increased BMI.[29,168]

Thromboembolism is facilitated by immobility (venous stasis), increased blood viscosity (polycythemia, hypovolemia), increased abdominal pressure, and abnormalities in serum procoagulants and anticoagulants.[6] Obesity is an independent risk factor for development of venous thromboembolism (VTE).[185] Thromboembolism is reported to be the most common cause of postoperative mortality after bariatric surgery, accounting for as many as 50% of all deaths.[186]

Four important risk factors, namely, venous stasis disease, BMI of 60 or more, truncal obesity, and obesity hypoventilation syndrome (OHS) or sleep apnea syndrome (SAS) are significant in the development of postoperative venous thromboembolism, and if present, preoperative prophylactic placement of an inferior vena cava (IVC) filter should be considered. Venous stasis disease, BMI greater than 60, truncal obesity, OHS, OSA, a previous incidence of pulmonary embolism, and hypercoagulable states have been suggested as factors that increase the baseline risk of perioperative pulmonary embolism in obese patients after bariatric surgery.[187] Administration of minidose heparin (5000 units administered subcutaneously twice per day), low-molecular-weight heparin, antiembolic stockings, and correctly fitting pneumatic compression boots can lessen the occurrence of deep vein thrombosis in the early postoperative period. Early ambulation and maintenance of vascular volume further attenuate the likelihood that clots will develop. Wound infections and pulmonary embolism are 50% higher in obese patients than in normal-weight patients.[188-190]

Post–Gastric Bypass Anastomotic Leaks

In a recent series of more than 3000 gastric bypass patients from four centers, the anastomotic leak rate was 2.1%.[191] The most common signs and symptoms of a leak were tachycardia (72%), fever (63%), and abdominal pain (54%). An upper gastrointestinal series was positive in 17 of 56 patients. Tachycardia is the most sensitive sign of an anastomotic leak, and a heart rate greater than 120 beats per minute should prompt an investigation, even if the patient looks and feels well. Tachypnea or decreasing oxygen saturations can also signal early sepsis from a leak and may be clinically indistinguishable from pulmonary embolism. Signs and symptoms of an anastomotic leak are shown in Box 43-8.[81,192,193]

In general, morbidly obese patients have higher rates of postoperative and intensive care unit (ICU) complications and may require more intensive care and increased staffing requirements.[194] Investigations in surgical/trauma ICU patients universally report an adverse effect of obesity on outcomes. In a surgical ICU, investigators reported that morbid obesity conferred elevated odds of death after 4 days of ICU stay,[195] and among blunt-trauma patients, obese patients suffered more frequent complications (e.g., multiple-system organ failure, acute respiratory distress syndrome, myocardial infarction, and renal failure), including the need for more vasopressors, additional days of ventilator support, and more often failed extubation. Among survivors, obese patients had a higher ICU and hospital length of stay.[196]

BOX 43-8

Signs and Symptoms of Anastomotic Leak

- Unexplained tachycardia (sustained heart rate greater than 120 bpm)
- Shoulder pain (usually left)
- Abdominal pain
- Pelvic pain
- Substernal pressure
- Shortness of breath
- Fever
- Increased thirst
- Hypotension
- Unexplained oliguria
- Hiccups
- Restlessness

Adapted from Thompson J, et al. Anesthesia case management for bariatric surgery. *AANA J*. 2011;79(2):147-160.

SUMMARY

Obesity is a complex and multifactorial disease, and its incidence is continuing to increase in the U.S. patient population. Through an understanding of the implications of associated conditions in obesity, the anesthetist can promote more favorable anesthetic outcomes. Consideration of the physiologic and pharmacologic changes and their implications for optimal anesthetic management guides clinical practice.

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44 CHAPTER Regional Anesthesia

Spinal and Epidural Anesthesia

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Spinal and epidural blocks are known collectively as *central neuraxial blockade* (CNB) because they involve the placement of local anesthetic solution onto or adjacent to the spinal cord. Both spinal and epidural blocks share much of the same anatomy and physiology but are distinct from one another due to their unique anatomic, physiologic, and clinical features.

The person most credited with introducing spinal anesthesia is Augustus Bier, who in 1898 described the injection of cocaine into the spinal column and its potential for use as a surgical anesthetic technique. When cocaine was introduced into the subarachnoid space, anesthesia lasted approximately an hour. With the development of newer and safer anesthetic drugs, needles, and techniques, regional anesthesia expanded to include many neural blocks for the enhancement of surgery and obstetrics and the management of pain.[1,2] Modern procedures have simplified, refined, and increased the safety and success of regional anesthesia techniques.[2]

APPLIED ANATOMY AND PHYSIOLOGY OF THE CENTRAL NEURAXIS

Knowledge of anatomic landmarks and underlying structures aids the anesthetist in forming a three-dimensional "mind's-eye" picture. This picture, coordinated with the "feel" of the structures and tissues against the needle and a steady, sensitive hand, facilitates accurate placement of the needle tip and administration of appropriate techniques and medications. Although anatomy is the oldest of medical sciences (with detailed descriptions of the spinal column dating from the nineteenth century), modern imaging methods such as computed tomography (CT), magnetic resonance imagining (MRI), and endoscopic examination have permitted in vivo investigations that further our understanding of spinal anatomy. The following is therefore a current review of applied anatomy of the central neuraxis.

The sequential interconnectivity of the 33 bones called *vertebrae* form the spinal, or vertebral, column, which anesthetists use as a bony reference during the placement of various anesthetics or analgesics. This column is located in the posterior midline of the trunk and allows for truncal flexibility because movable joint surfaces and cartilaginous vertebral bodies exist between 24 of the 33 vertebrae (Figure 44-1). The vertebral column extends from the base of the skull and the foramen magnum to the tip of the coccyx. The vertebral bodies are stacked on top of one another, separated by fibrocartilaginous intervertebral disks that provide support for the cranium and trunk. In general, each vertebra can be visualized as having two parts. The anterior, cylindric portion of the vertebra is solid and called the *body*. This heavier portion of the vertebra forms the anterior portion of the vertebral arch. The body of each vertebra is contiguous with two pedicles that stretch in a posterior and slightly lateral direction, joining to two laminae that stretch posteriorly and medially to complete an arch, creating an oval-triangular foramen. This foramen, known as the *vertebral foramen*, allows for the passage and protection of the spinal cord. Transverse processes on both sides of the pedicles allow for muscular attachments and the control of movement. A spinous process projects along the median plane from the union of the laminae in a posteroinferior direction. The spinous process is the long, slender, bony prominence that can often be seen and felt along the midline of the back. The spinous process also provides a place for muscular attachment and movement control. In addition, the inferior angle of the bone creates an overlap that further protects the spinal cord (Figure 44-2).[3]

The pedicles and processes of each vertebra have superior and inferior articular surfaces and lateral notches. The superior notch is shallow when compared with the deeper inferior notch. When the vertebrae are stacked, the notches and the articulating surfaces, known as *zygapophyseal* or *facet joints*, form the intervertebral foramina. The intervertebral foramina provide safe passage for spinal nerves passing from the spinal cord to the rest of the body. The articular surfaces of the facet joints are covered with hyaline cartilage, which permits a gliding motion between the vertebrae. Because the facet joints are innervated by branches from closely associated spinal nerves, these joints often become clinically important. When the joint is injured, the associated spinal nerves also may be affected, leading to pain along associated dermatomes or muscle spasm along associated myotomes.[3]

The size and shape of vertebral lamina and spinous processes differ among the thoracic, lumbar, and sacral regions, and variation exists within each region. Knowledge of these variations is important in the practice of regional anesthesia and in selection and administration of spinal and epidural anesthesia. For instance, cervical and thoracic vertebrae have spinous processes that angle acutely in a caudad direction such that the process of the superior vertebra overlaps the inferior vertebra and its process. This construction adds protection to the spinal cord when an individual stands erect. When attempts are made to insert a needle into the cervical or thoracic regions, the tight construction and angles of the vertebral column must be considered.

In the lumbar region the vertebrae are larger, and the spinous processes become shorter and broader and have a posterior orientation with less overlap than in other vertebrae. Relatively large gaps, bridged by ligaments, exist between the spinous processes in the lumbar area. This provides the anesthesia practitioner easier access for needle placement, catheter passage, and the instillation of anesthetic into the epidural or subarachnoid space for surgical or obstetric procedures.

The sacrum is a triangle-shaped section of fused bodies of vertebrae. The broader portion is the base, which tapers as it approaches the coccyx. The sacrum is shaped so the weight of the body forces the base of the sacrum downward and forward. It is wedged tightly between the two iliac crests by the downward forces exerted on the spinal column. The lamina of the last sacral vertebra is incomplete

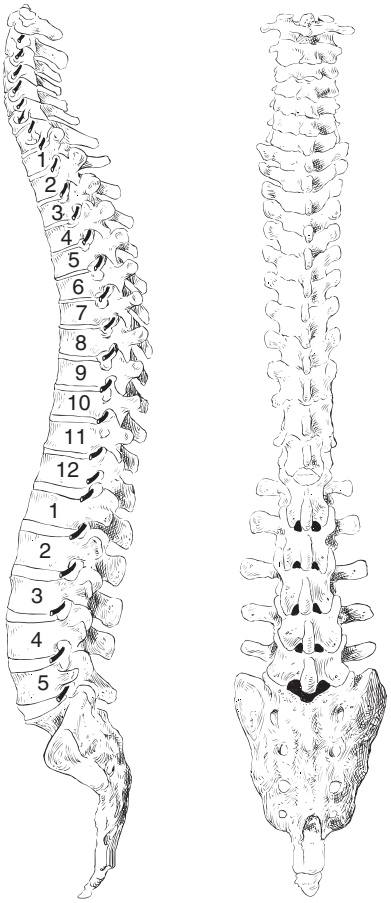

FIGURE **44-1** The spinal, or vertebral, column with its 33 vertebrae.

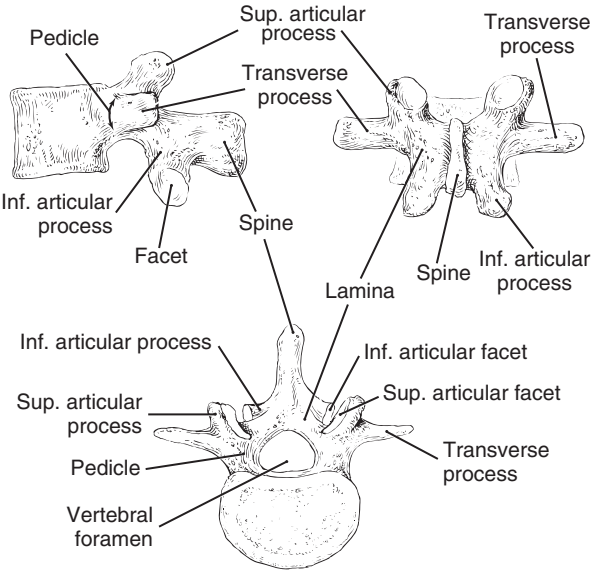

FIGURE **44-2** Articular surfaces, transverse processes, and spinous process. *Inf*, Inferior; *Sup*, superior.

and bridged only by ligaments. This area is known as the *sacral hiatus* (Figure 44-3). The coccyx is composed of four small segments of bone that become fused into two bones as an individual ages; between the ages of 25 and 30 years, fusion is complete. The bodies of the vertebrae can be identified with the transverse processes and articular processes. No pedicles or spinous processes are present. The last, or fourth, bone is small and is similar to a nodule.

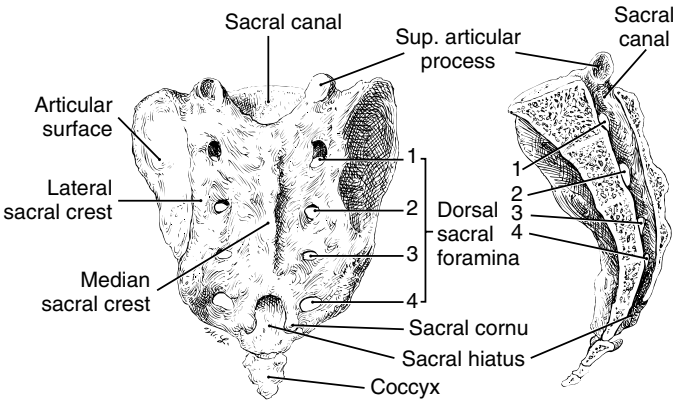

FIGURE **44-3** Sacrum and coccyx.

The changing size of the bone from the first to the fourth vertebra gives the coccyx the appearance of a triangle. The projections of the rudimentary articular processes are known as the *cornua*, and the superior pair is the most pronounced. These sacral cornua are the "horns" or bony protuberances that guard the area of the sacral hiatus.[3] Because they can be easily palpated in children and in most adults, they are important surface anatomic landmarks for the performance of a caudal anesthetic procedure.

Of the more than 35 pairs of muscles and ligaments in the back, the supraspinous ligaments, the interspinous ligaments, and the ligamentum flavum (yellow ligaments) are of special significance to the anesthesia practitioner. These three structures act as landmarks that help in identification of and access to the epidural and subarachnoid spaces. The supraspinous ligament is a strong cordlike ligament that connects the apices of the spinous processes; it is thick and serves as the major ligament in the cervical and upper thoracic regions. The supraspinous ligament consists of three layers: the superficial layer extends over several vertebral spinous processes, the middle layer connects two or three spinous processes, and the inner layer connects only the neighboring spinous processes. The ligament blends at all levels with the thin interspinous ligaments that run between adjacent spinous processes. The interspinous ligaments are usually absent or of poor quality in the cervical region and can be exceptionally thin in the lumbar area, even in young people. The ligamenta flava are the strongest of the posterior ligaments. These broad elastic bands join the vertebral arches through vertical extensions from adjacent lamina. The ligamenta flava are paired flat ligaments that run caudad from the inferior border of one lamina to the upper border of the lower lamina on both sides of the midline. The two ligaments almost fill the space, leaving only a separation in the midline and thereby creating a V or wedge that points posteriorly to align with the interspinous and supraspinous ligaments. The V is thin on the lateral edge and thickest midline—in an adult approximately 3 to 5 mm at the L2-L3 interspace. The ligaments extend from each lamina with an overlapping of fibers that creates the appearance of a contiguous ligament from one vertebral body to the next. The ligament is thicker in the lumbar area than in the cervical area and is responsible for maintenance of upright posture. The ligaments' color comes from their high content of yellow elastic tissue.[4]

The spinal cord itself is a cylindrical structure extending from the medulla oblongata through the spinal foramen to the level of the L2 vertebra in most adults and ranges from 42 to 45 cm in length (Figure 44-4). Because the vertebral column grows more rapidly than the spinal cord, the spinal cord in children extends

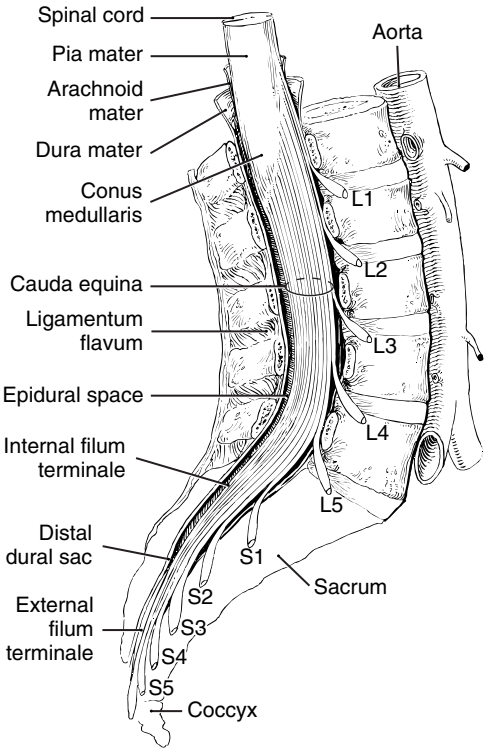

FIGURE **44-4** Extension of the spinal cord to the second lumbar vertebra.

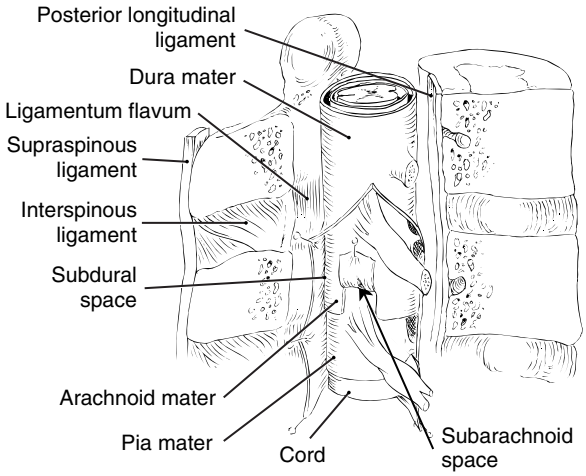

FIGURE **44-5** The linings of the spinal cord and the posterior ligaments of the spinal column.

initially to the level of the third lumbar vertebra. In approximately 1% of adults, the spinal cord may extend below L2 and rarely to the level of L3. The spinal cord tapers to the conus medullaris, and nerve pathways continue in a collection of rootlets called the *cauda equina* or *horse's tail*, which extends from L1 to S5. The spinal cord is enlarged in two regions. The first, called the *cervical enlargement*, extends from the spinal segments C4 to T1. The ventral rami of the spinal nerves in this enlargement form the brachial plexus of nerves that innervates the upper limbs. The second enlargement stretches from segments L2 to S3. This lumbosacral enlargement contributes corresponding nerves to create the lumbar and sacral plexuses. It is important to note that the spinal cord levels do not directly correspond with vertebral levels. For example, in adults the lumbosacral enlargement (L2 to S3) usually extends from the body of the T11 vertebra to the body of the L1 vertebra.[3]

The spinal cord is enveloped by the same three membranes that line the cranium, and they are collectively called the *meninges*. The meninges are nonnervous support tissues that provide a protective covering for the cord and nerve roots from the foramen magnum to the base of the cauda equina. The linings are identified as the *dura mater*, the *arachnoid mater*, and the *pia mater*. The dura mater is the outermost layer. It is a thick, tough membrane that provides most of the protection for the central cord structures. The nerve roots are covered with dura mater while inside the spinal canal. As the roots exit the canal via the intervertebral foramen, the dura blends into the root at a junction referred to as a *dural cuff* or *root sleeve*. The arachnoid mater is a thin, spiderweb-like covering that forms the middle layer. Beneath the arachnoid mater is a space that is continuous with the central canal of the cord and the ventricles. This space, which is filled with cerebrospinal fluid (CSF), is known as the *subarachnoid space*. This mater and the fluid protect the spinal cord from shock injuries and are the medium for the interaction with local anesthetics and opioids that occurs during the administration of regional anesthesia. The innermost layer, the pia mater, is thin and is in direct contact with the outer surface of the spinal cord (Figure 44-5).[3]

The epidural space is a potential space outside the dural sac but inside the vertebral canal and is continuous from the base of the cranium to the base of the sacrum at the sacrococcygeal membrane. The epidural space contains epidural veins, fat, lymphatics, segmental arteries, and nerve roots. Fat in the epidural spaces is physiologically fluid, acting as a pad and lubricant for the movement of neural structures within the canal. The posterior epidural space, as it is approached by the anesthetist's advancing needle, is protected by the ligamenta flava, the lamina, and the spinous processes. It is easy but inaccurate to depict the epidural space as a uniform column surrounding an equally uniform and tapering spinal cord. A better mental picture is provided by a "look" along the longitudinal axes. The epidural space can be envisioned as a series of lateral, posterior, and anterior compartments existing among the vertebral body, lamina, and pedicles. The compartments, occupied mostly by fat but also by nerves and fibrous tissue, repeat at each segment in a metameric fashion. Of greatest interest to the anesthetist, the posterior epidural space is a series of fat-filled tripodial pads, shaped like a three-sided sand dune. The pad stretches and narrows in a caudad direction as it approaches the next inferior lamina. In areas of the vertebral canal surrounded by bone, the dura actually contacts bone, leaving only a potential epidural space that physically separates the epidural fat-containing compartments. The posterior epidural space, therefore, is a discontinuous group of tapering fat pads that repeat throughout the length of the spinal canal and are separated by a potential space that allows the passage of fluids or small catheters.[4-7]

The distance from the skin to the epidural space and the depth of the epidural space, or the distance to the dura, is of interest to one wishing to avoid needle injury of neural and vascular tissues. The distance to the epidural space varies with vertebral level and is loosely correlated with patient weight. The distance from skin to the lumbar epidural space using a midline approach varies from 2.5 cm to 8 cm, with an average of 5 cm. Because the space itself is not uniform in shape, the depth of the epidural space from the ligamenta flava to the dura varies considerably. Given the tripodial, dunelike shape of the epidural space, expect the space to narrow considerably when approaching laterally to the midline and in more caudad areas in the space. The depth of the epidural space is also relative to the vertebral level of approach and angle of needle entry, but some clinical generalizations can be made. The epidural

space is largest (posterior to anterior) in the midline of the midlumbar region, at 5 to 6 mm. The midline thoracic region epidural space may be 3 to 5 mm deep and is narrower there (lateral width). Caution must be exercised when one approaches the lower cervical region because the epidural space is very small (only 1.5 to 2 mm), leaving little room for error.[5]

In addition to a larger epidural space, another anatomic reason to stay midline with an approaching anesthetic needle is the presence of the epidural veins. The epidural veins are valveless veins that form a plexus draining the blood from the spinal cord and the linings of the cord. The plexus is most prominent in the lateral portion of the epidural space. In pregnant or obese patients, the epidural veins become engorged and swollen as increased intraabdominal pressure results in venous congestion of the lumbar and sacral vessels. The potential for injury or accidental cannulation of these vessels is increased because of this physiologic compensation.[3,4,6]

A final anatomic consideration for neuraxial anesthesia is the existence of normal and abnormal curvatures of the spinal column. A median-plane longitudinal view of the vertebral column reveals four curvatures in the normal adult. The thoracic and sacral curvatures have posterior curvatures (concave anteriorly), whereas the cervical and lumbar regions have anterior curvatures (concave posteriorly). In a supine patient, the apex of the lumbar curve is usually at L3 to L4, and the trough of the thoracic curve is at T4.[8] *Scoliosis*, the most common abnormal curvature, is a lateral curvature of the spine, and *kyphosis* is an excessive posterior curvature or hump, usually of the thoracic region. Excessive *lordosis*, or hollowing of the back, may occur as a result of obesity as the body attempts to restore the center of gravity. A temporary lordosis may also occur during pregnancy. Changes in these anatomic curves will challenge the anesthesia practitioner during the performance of epidural or spinal anesthetic techniques. Clear knowledge of the curves is also important when anticipating the spread of local anesthetics in the subarachnoid space relative to the site of injection and the patient's position.[9]

Neuroanatomic Mapping and Evaluation of Neuraxial Anesthesia

The goal of neuraxial anesthesia is to block pain transmission from areas of injury, disease, or surgical intervention. Therefore, it is clinically useful to have knowledge of the innervations of body structures being operated on in relation to spinal nerve location within the vertebral column. Anatomic maps have been generated based on cutaneous sensation alone. These sensation maps are referred to as *dermatomal maps*, *charts*, or *levels*. A *dermatome* is defined as the area of cutaneous sensation supplied by a spinal nerve that is anatomically identified as it passes through an intervertebral foramen. For example, the umbilical area is directly anterior to the L3 vertebra but receives cutaneous innervations from T7 to T11, depending on the dermatomal map consulted (Figure 44-6).

For the practical clinician, use of accepted anatomic landmarks and test methods is perhaps the best method for documenting the functional level of blockade—the level of the loss of sensation achieved. The level of anesthetic can be evaluated in many ways, and tests can be used to evaluate several components of the neuraxial anesthetic. For motor function, a straight leg raise or a request to "step on the gas" works well as a clinical measure. Cutaneous sensation can be evaluated through use of a Wartenberg pinwheel, a Semmes-Weinstein monofilament aesthesiometer, or (more practically and simply) with the stylet from the spinal or epidural needle, a portion of a broken wooden tongue blade, or

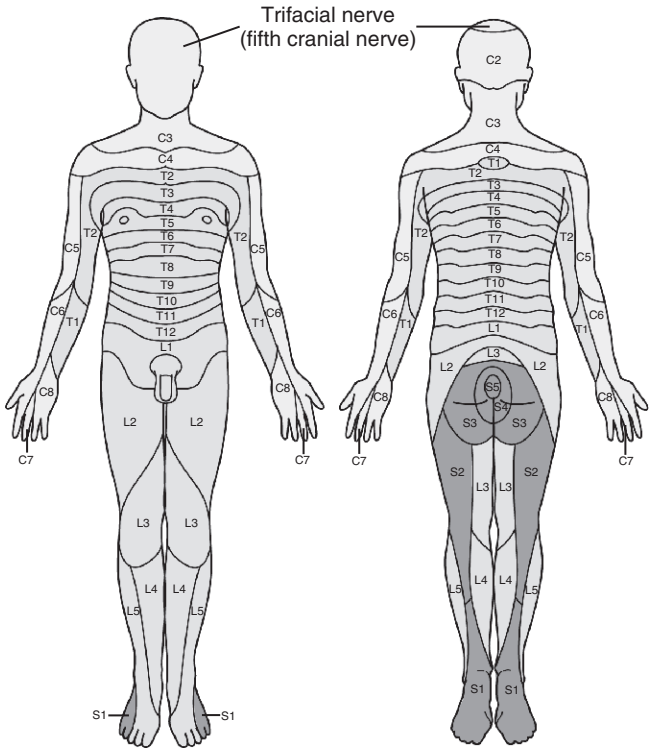

FIGURE **44-6** Dermatomes.

even a peripheral nerve stimulator. Such "pressure" or "scratch" tests are done using two surface-anatomy points for comparison. Inform the patient that the sensation on a normal area, such as the skin surface of the shoulder, is scratchy or sharp. Next, scratch or press an area expected to be numb, such as the lateral thigh. Gradually work cephalad in 2- or 3-inch bands until the patient notices a change in sensation. Note the level of the change in sensation relative to a dermatomal map. This approximates the upper level of sensory loss. Skin refrigerant, ice cubes, and alcohol pads can be used in a similar manner to identify changes in temperature sensation.

Physiology and Mechanisms of Action

Despite more than 90 years of research and experience with spinal and epidural anesthesia, much speculation remains regarding the exact cellular locations and molecular mechanisms involved when local anesthetics, opioids, and other pharmacologically active agents bind to produce spinal analgesia and anesthesia.[10,11] For a thorough review of local anesthetics and details on mechanism of action please see Chapter 10. What is known and clinically important about spinal and epidural anesthesia is that the primary site of action for local anesthetics is on the nerve roots within the spinal cord. When a drug is injected directly into the CSF, the drug distributes through the subarachnoid space based on the physical and chemical properties of that injectant and the characteristics of the space in which it must spread. When the drug concentration reaches a minimal effective concentration, neuronal transmission is altered in a manner that clinically provides anesthesia. Neurons—some myelinated, others not; some relatively large, others smaller—differ in susceptibility to drugs such as local anesthetics, and these pharmacodynamic relationships are not easily explained (Table 44-1). The processes involved at the cellular level are complex, and *blockade* is perhaps a confusing term. It is more accurate to say that anesthetic drugs alter nerve transmission, predominantly by affecting sodium ion channels and

TABLE 44-1 Classification of Nerve Fibers

		CONDUCTION		
Nerve Fiber	Myelination	Diameter (μm)	Velocity (m/sec)	Function
A-α	Heavy	15-20	70-120	Motor
A-β	Moderate	5-12	30-70	Touch and pressure
A-γ	Moderate	5-10	30-70	Proprioception
A-δ	Light	2-5	12-30	Pain and temperature
B	Light	1-4	3-15	Preganglionic, autonomic
C	None	0.5-1	0.5-2	Pain and temperature

inhibiting the units of information that are transferred along the spinal cord. Complete blockade or a "chemical transection" of the cord is an oversimplification. For example, somatosensory evoked potentials have been recorded in individuals made functionally insensate from lidocaine epidural anesthesia. This suggests that neural transmissions are reaching the brain without causing sensory perceptions.[4,12]

When a local anesthetic interrupts nerve transmission of autonomic nerves but not sensory nerves or motor nerves (because of a variation in susceptibility), a "differential block" is said to have occurred. A differential block is seen in the more rostral spinal segments of a spinal anesthetic. As the spinal anesthetic spreads from the epicenter of injection, the distal reaches of drug distribution are presumably of lesser concentrations. A differential block is clinically important when sensory anesthesia is desired at a specific level; however, sympathetic blockade could be deleterious in a patient with coexisting disease. The level of sympathetic blockade could be as high as six or more dermatomal levels above the level of sensory blockade and therefore contribute to hypotension and bradycardia.[11]

Drug injected into the epidural space is distributed to the same sites of action as a spinal anesthetic but in a slightly different manner. The drug must first distribute along the epidural space then diffuse through the meninges and dural cuffs to reach the nerve roots or reach the spinal cord through absorption into the radicular arteries.[13] Data exist to support the clinical impression that spinal anesthesia is generally more effective or complete from the patient's perspective than epidural anesthesia and therefore referred to as a more "dense" anesthetic. Epidural local anesthetics first act at sites such as the dural cuffs, at which spinal nerves pass through the peridural spaces. This is consistent with the segmental onset often associated with epidural anesthesia. If the concentration and volume of the anesthetic agent are increased, or if time is allowed for the drug to diffuse into the CSF or pass via radicular arteries into the spinal cord, the epidural anesthetic can become more dense.[4,8]

Central Neuraxial Blockade: Indications and Preoperative Considerations

Spinal and epidural anesthesia (central neuraxial blocks) can be used successfully for a variety of inpatient or ambulatory surgical procedures involving the lower extremities, perineum, and abdomen. In addition, spinal and epidural anesthesia or analgesia is used for the treatment of acute and chronic pain syndromes, for obstetric procedures and labor analgesia, and can be applied in patients at the extremes of age.[14] Spinal anesthesia techniques also may be used in combination with other techniques, such as epidural catheter techniques, general or intravenous anesthetic techniques, and with the use of a laryngeal mask airway, to provide anesthesia during surgery. Such combinations, or balanced techniques, minimize the side effects of any one anesthetic technique, maximize the benefits, and offer options in the selection of anesthesia or analgesia for surgical or obstetric procedures.[15]

As with any anesthetic plan, proper preparation, patient selection, education, and collaboration with surgeons and nurses are the keys to success. Often the best time to obtain a truly informed consent is during the preoperative visit. It is important to establish rapport with patients to gain their trust and cooperation. Patients eager to be involved in their own care often have the emotional maturity to understand the benefits of their anesthetic options and make rational choices. Anticipate patients' fears and anxieties; they are often easily dealt with through education and the reassurance provided by the calm voice of a confident and competent anesthetist.

Before presenting the option of a regional anesthetic to the patient, the anesthesia practitioner should answer the following three important questions about the procedure:

1. Will the patient be comfortable having this surgical procedure performed with the proposed regional anesthetic technique?
2. Will the patient be able to remain in the required position without difficulty for the length of the procedure?
3. Does this regional anesthetic technique outweigh the risks of performing this procedure using an alternate anesthetic technique?

The answers to these questions directly affect the choice of anesthetic techniques offered to the patient. When recommending any anesthetic technique to the patient, the practitioner has a responsibility to educate the patient, the patient's family, and other interested parties about the anesthesia procedure and the potential outcomes. One can then obtain an informed consent and garner the trust of the patient before performing any technique. Without this trust, even the best anesthetic technique may be a failure.

Potential advantages of neuraxial anesthesia include less nausea, vomiting, and urinary retention; a reduced total opioid requirement; and greater mental alertness compared with patients who have received general anesthesia alone. After regional anesthesia, patients are quick to eat, void, and ambulate. Ambulatory surgical patients may or may not be discharged any sooner after spinal anesthesia when compared with those who have undergone general anesthesia, but they can avoid unnecessary overnight admissions resulting from complications of general anesthesia. A growing body of evidence also supports improved outcomes for selected patients and situations. Spinal and epidural anesthesia blunt the body's stress response to surgery and may offer preemptive analgesia. In addition, studies have shown neuraxial anesthetics to decrease intraoperative blood loss, lower the incidence of postoperative thromboembolic events and postoperative ileus, increase patency of vascular grafts, improve respiratory function and cardiac stability, and improve outcome in high-risk surgical patients.[16-20] "Walk-in, walk-out" spinals with a low dose of lidocaine and opioids for ambulatory surgery created the concept of selective spinal anesthesia. Because lidocaine spinals are no longer used, single lower limb anesthesia can be produced with a low dose of hyperbaric bupivacaine. Spinal techniques produce a reliable block, with low incidence of side effects and rapid home-readiness. Reintroduction of chloroprocaine may provide a solution for bilateral, short-acting spinal anesthesia in the future.[21] Although headache remains a small concern, this risk is greatly reduced.[22,23]

Another group of patients well known to benefit from the use of CNB techniques are patients who require anesthesia for obstetric procedures. One primary example is the administration of an epidural anesthetic to the patient in labor. No other modality can

provide the parturient with relative relief from the most severe discomfort and still permit the baby and mother to interact immediately after delivery, all with minimal possibility of respiratory distress or depression. Also, epidural techniques in labor allow a safe conversion of the analgesia to a surgical anesthetic if a cesarean section becomes necessary.[24,25]

Patient safety also may be increased with spinal or epidural anesthesia. Urologic procedures such as cystoscopic examinations and transurethral resections of the prostate (TURP) are most often performed with the use of spinal anesthesia. When awake and anesthetized to the level of the dome of the bladder (T10), the patient may verbally respond to bladder overdistention, thereby helping the urologist minimize the potential for bladder rupture. In addition, the mental status and sensorium of a responsive patient can easily be monitored and the development of conditions associated with TURP syndrome such as hypervolemia, hyponatremia, and ammonium toxicity are more readily detected.[19,26]

Safety is also an issue when the patient is placed in the prone or jackknifed position as for perianal procedures. A patient in such a position under general anesthesia is at risk for inadvertent extubation and positioning injury. A hypobaric spinal anesthesia technique offers several advantages. The anesthetic procedure can be performed after the patient is positioned and has verbalized that he or she is comfortably padded. With hypobaric spinal anesthesia, the spread of the local anesthetic is controlled, and spontaneous ventilation is maintained.

Additionally, patients often fear postoperative discomfort.[27] Therefore, another advantage of spinal anesthesia is the ability to administer long-acting opioid analgesics or clonidine. Epidural catheter placement allows for opioids, low concentrations of local anesthetics, or mixtures containing both solutions to be continuously infused or administered by patient-controlled devices, thereby keeping patients comfortable well into the postoperative period. Because the total doses of opioids and local anesthetics are small, the patient remains alert and possibly ambulatory while receiving analgesia with minimal side effects.[4,8] The patient's right to be fully informed also necessitates a discussion of the disadvantages of CNB. Consider the patient's perspective, and keep in mind that the disadvantages and risks inherent in any anesthetic plan are relative only to those of another anesthetic option. For example, patients with a history of headaches or backaches are at increased risk for experiencing these problems after spinal and epidural analgesia but also may have exacerbations of these problems after a general anesthetic. Such patients should be evaluated and counseled regarding this potential problem before the administration of any anesthetic. A thorough history of the patient's previous pattern of headaches or backaches is essential when faced with the challenge of evaluating similar symptoms in the postoperative period.

To many patients, the risk of paralysis is the most important concern, despite the extreme rarity of any neurologic sequela. The incidence rate of persistent paresthesia and sensory or motor dysfunction is less than 0.1%.[4,28-30] Common patient questions also may include the following:

- "Will the injections hurt?"
- "How long will I be numb?"
- "I am afraid of hearing (or smelling or feeling) the surgery. Can I be asleep?"

Patient perceptions can be corrected with thoughtful explanation and discussion of the clinician's expectations regarding the patient's case. Additional discussion should include the topic of intraoperative risks, such as the inability to obtain adequate anesthesia, paresthesia, hypotension, dyspnea, high or total spinal anesthesia, nausea and vomiting, use of additional sedation, and allergic reactions. Postoperative complications may include backache, postdural puncture headache (PDPH), hearing loss, transient neurologic symptoms, infection, and peridural abscess or hematoma formation.[5,22,31-34]

Before administration of any anesthetic, a thorough preoperative history and physical examination must be conducted. During this part of the preoperative patient visit, any concerns regarding administration of spinal anesthesia can be identified. Often the terms *absolute* and *relative contraindications* are used; the definition of these categories varies, and their use is therefore controversial. It is more important to think of the anesthetic risks and associated complications relative to the possible benefits of the proposed anesthetic technique. An obvious example is patient refusal or lack of cooperation. Other preoperative concerns include increased intracranial pressure, significant preexisting or therapeutic coagulopathy, skin infection at the site of injection, hypovolemia, spinal cord disease, patients with a fixed-volume cardiac state such as hypertrophic cardiomyopathy or severe atrial stenosis, and an anticipated lengthy surgical time. Finally, if a difficult airway is anticipated, the plan of care must be discussed with both patient and surgeon.

Neurologic diseases are often listed as potential, absolute, or relative contraindications for neuraxial anesthesia, but data are often mixed. A dural puncture by a spinal needle or a larger epidural needle creates a rent in dural tissue that may or may not leak CSF. In patients with a preexisting increase in intracranial pressure, the risk of brain herniation is increased. In the case of epidural catheter placement or epidural blood patch, the addition of large volumes of fluid into the epidural or subarachnoid spaces could increase already elevated intracranial pressures.[4,8]

Musculoskeletal deformities such as severe kyphoscoliosis, arthritis, osteoporosis, and fusion and scarring of the vertebrae are considered relative contraindications to neuraxial anesthesia. The location of the epidural or subarachnoid spaces by needle tip may be technically difficult, and spread of anesthetic agents may be limited by anatomic alterations.[28] However, a large retrospective study surmises that osteoporosis may be an important risk factor for CNB complications.[35]

Peripheral neuropathies can be the result of metabolic, autoimmune, infectious, or hereditary etiologies. A presumption is that patients with preexisting neural compromise are more susceptible to and less able to recover from injury when exposed to a secondary insult, compared with patients with healthy tissues. Also, abnormal tissues may not respond to pharmacologic agents in predictable ways. Secondary insults might stem from needle or catheter trauma, ischemic injury from the use of vasoconstrictors, or direct local anesthetic neurotoxicity. For example, diabetes mellitus (DM) is the most prevalent cause of peripheral polyneuropathy, with most patients having some abnormalities in nerve conduction. A study by Hebl et al.[36] supports the increased risk of the "double-crush" phenomenon, finding that 0.4% of patients with diabetic polyneuropathy experience new or progressive changes in their neurologic deficits. This suggests that spinal or epidural anesthesia may worsen or exacerbate conditions such as a gradually progressive diabetic neuropathy. However, the same group of investigators also took a retrospective look at central nervous system (CNS) diagnoses such as post-poliomyelitis, multiple sclerosis, traumatic spinal cord injury, and amyotrophic lateral sclerosis. The nature of their study did not permit definitive recommendations, yet they found no patients with exacerbations or deterioration of symptoms. Additionally, they note that their results suggest the safety of CNB in these patients and that their

findings were supported by other studies. Until further prospective study can support definitive conclusions, the decision to perform a CNB technique must be made by weighing the relative risks to the individual patient's neurologic disease against the potential benefits of minimizing the anesthetic effects on their coexisting diseases.[36] Because few objective data are available, use of CNB in such patients becomes a medicolegal risk, especially if blame is incorrectly placed on the anesthetic. If a neuraxial block is the appropriate anesthetic choice, then precise documentation of the patient's preexisting disease state and existing neurologic compromise is a mandatory precaution, as is attentive follow-up care.[4,8,28,31,37]

The existence of a significant preexisting or therapeutic coagulopathy increases the risk of spinal or epidural hematoma formation in a patient receiving a CNB. Spinal or epidural hematoma is a rare but devastating complication, possibly resulting in permanent neurologic injury. Therefore, central neuraxial anesthesia should be avoided in any patient with a known coagulopathy. Insufficient data are available to quiet the controversy surrounding absolute laboratory values below which the practitioner should avoid CNB. To determine whether a CNB technique should be avoided, it has been suggested that the following arbitrary values be used as a guide: platelet counts of less than 100,000 and prothrombin time (PT), activated partial thromboplastin time (aPTT), and bleeding times that are greater than two times normal values. For a spinal anesthetic, this is perhaps an overly conservative guide.[38] However, severe bleeding with or without symptomatic hypovolemia or the potential for severe bleeding is a possible contraindication to the administration of a regional anesthetic because the sympathectomy caused by CNB further aggravates severely contracted volume states.

Much discussion has arisen regarding the use of spinal and epidural anesthesia when coagulopathy for thromboprophylaxis or for therapeutic treatment of coexisting disease has been initiated, planned, or is ongoing because the therapies, timing, and the effects on coagulation are highly varied. For example, the use of platelet inhibitors, such as aspirin or nonsteroidal antiinflammatory drugs (NSAIDs), is not a contraindication to spinal and epidural anesthesia. Even planned intraoperative anticoagulation with heparin is reasonably safe after atraumatic dural puncture if the patient presents with a normal coagulation profile. Traditionally, a patient's bleeding time was obtained prior to administration of neuraxial anesthesia, but the predictive value of bleeding time has not been established in patients taking aspirin and NSAIDs.[39,40] Also, with the increased use of natural and herbal medicines, anesthetists must be alert to the possibility of drug interactions. Alone, herbal supplements appear not to increase the risk of spinal hematoma; however, data on combinations of herbal and other anticoagulants are not available. Herbal medications that effect hemostasis and some perioperative concerns are listed in Table 44-2. If basic precautions are followed, many thromboprophylaxis strategies have had an extensive safety record when co-administered with neuraxial anesthetics. The surgeon and anesthesia practitioner should consider the potential benefit versus risk before neuraxial intervention for patients who have been or will be anticoagulated for thromboprophylaxis. The number, variety, and indications for the use of anticoagulants and thrombolytics continue to increase.

The incidence of neurologic dysfunction resulting from hemorrhagic complications resulting from neuraxial blockade is unknown. Although the incidence cited in the literature is estimated to be less than 1 in 150,000 epidural and less than 1 in 220,000 spinal anesthetics, recent epidemiologic surveys suggest that the frequency is increasing and may be as high as 1 in 3000 in some patient populations. Overall, the risk of clinically significant bleeding increases with age, associated abnormalities of the spinal cord or vertebral column, the presence of an underlying coagulopathy, difficulty during needle placement, and an indwelling neuraxial catheter during sustained anticoagulation, particularly with standard heparin or low-molecular-weight heparin. The American Society of Regional Anesthesia and Pain Medicine (ASRA) convened its Third Consensus Conference on Regional Anesthesia and Anticoagulation. Practice guidelines were formulated. Many international anesthesia societies have also issued guidelines.[41-43] Guidelines for the use of regional blocks in patients receiving thromboprophylaxis are given in Table 44-3.

By following evidence and consensus-based precautions, the low incidence of permanent neurologic complications can be decreased. A meta-analysis by Brull et al.[44] identified the risk of permanent neurologic injury after spinal anesthesia at 1 to 4.2:10,000 and after epidural anesthesia at 0 to 7.6:10,000. Because complications are very infrequent, risk factor identification is difficult, and vigilant care must be maintained for all patients.

TABLE 44-2 Herbal Medications Affecting Hemostasis*

Herb	Important Effects	Perioperative Concerns	Time to Normal Hemostasis After Discontinuation
Garlic	Inhibition of platelet aggregation (may be irreversible) Increased fibrinolysis Equivocal antihypertensive activity	Potential to increase bleeding, especially when combined with other medications that inhibit platelet aggregation	7 days
Ginkgo	Inhibition of platelet-activating factor	Potential to increase bleeding, especially when combined with other medications that inhibit platelet aggregation	36 hrs
Ginseng	Lowers blood glucose Increased prothrombin (PT) and activated partial PTs in animals Other diverse effects	Hypoglycemia Potential to increase risk of bleeding Potential to decrease anticoagulant effect of warfarin	34 hrs

Adapted from Horlocker TT, et al. Regional anesthesia in the anticoagulated patient: defining the risks (the second ASRA Consensus Conference on Neuraxial Anesthesia and Anticoagulation). *Reg Anesth Pain Med.* 2003;28:172-197.
*At this time, it is not deemed necessary to discontinue herbal medications and allow resolution of their effects on hemostasis before surgery or anesthesia.

Analysis of known case reports found the median time to onset of neurologic dysfunction after initiation of low-molecular-weight heparin (LMWH) therapy to be 3 days. Scrupulous postoperative nursing surveillance is also required to support patient safety. The initial complaint may be of new-onset weakness to the lower limbs and sensory deficit, although bowel and bladder dysfunction and new-onset back pain may occur. If emergent neurosurgical care is required, recovery is unlikely if surgical decompression of the hematoma is delayed more than 8 hours.[30,35,44]

The etiology of neuraxial infection is based on the theory that needle placement disrupts the body's physiologic protective mechanisms and deposits infectious or noxious agents beyond the skin into underlying tissues and the peridural space and past the blood-brain barrier into subarachnoid spaces. Indeed, skin infection at the site of injection increases the risk of meningitis or epidural abscess formation. Infectious complications include, but are not limited to, epidural, spinal, or subdural abscess; paravertebral, paraspinous, or psoas abscess; meningitis; encephalitis; sepsis; bacteremia; viremia; fungemia; osteomyelitis; or discitis. Although colonization of the catheter may be considered a precursor to infection, colonization per se is not considered an infection. A recent advisory committee published guidelines noting several factors to consider to minimize infections. They included conducting a history, physical examination, and preprocedure laboratory evaluations, use of prophylactic antibiotic therapy as indicated, and use of strict aseptic techniques including the use of proper antiseptic solution. The use of sterile occlusive dressings at the catheter insertion site, a bacterial filter during continuous epidural infusion, limiting disconnection and reconnection of neuraxial delivery systems, and limiting the duration of catheterization were also encouraged.[34]

Although infectious complications of CNB are rare, the practitioner must maintain aseptic technique during the preparation and administration of any regional anesthetic to minimize the potential for infection. Septic meningitis or epidural abscess due to bacterial contamination, and the consequences of persistent neurologic deficits such as loss of bowel and bladder control, chronic pain, and lower extremity weakness or paraplegia, can be devastating. Other factors that increase the risk of infection include dermatologic conditions such as psoriasis that prevent aseptic skin preparation, underlying sepsis, diabetes, immunologic compromise, steroid therapy, and the preexistence of chronic infections such as human immunodeficiency virus (HIV) or herpes simplex virus (HSV). Because meningitis after spinal or epidural anesthesia is so rare, it has been difficult to directly attribute causality to the anesthetic or to identify significant risk factors. In fact, based on the limited data available, it would appear that regional anesthesia is safe in cases of secondary HSV infection and reasonable for patients in the early stages of HIV infection. Again, vigilance must be emphasized. Known predisposing factors include advanced age, diabetes, alcoholism, cancer, and AIDS. Patients are monitored for signs of meningeal irritation, fever, increasing back pain, neurologic changes, and local tenderness to injection sites. Although classic symptoms such as high fever, nuchal rigidity, and severe headache may be present, less alarming symptoms can occur, resulting in misdiagnosis. Although α-hemolytic streptococci is commonly seen in spinal block meningitis, *Staphylococcus aureus* is the most common causative organism in epidural abscesses, and

TABLE 44-3 Regional Anesthesia in the Patient Receiving Thromboprophylaxis

Medication	Clinical Management
Antiplatelet medications	No contraindication with aspirin or NSAIDs; discontinue ticlopidine (generic) 14 days, clopidogrel (Plavix) and prasugrel (Effient) 7 days prior to block; GP 11b/111a inhibitors tirofiban (Aggrastat) and eptifibatide (Integrilin) 8 hours, abciximab (ReoPro) 24-48 hours to allow return of normal platelet function
Unfractionated heparin	
Subcutaneous	No contraindication with twice daily dosing of less than 10,000 units; consider delay until after block if technical difficulty anticipated Safety of doses greater than 10,000 units or more than twice daily dosing has not been established
Intravenous	Heparinize 1 hour after block; remove catheter 2-4 hours after last heparin dose; document normal aPTT; sustained heparinization with an indwelling catheter associated with an increased risk; monitor neurologic status aggressively
LMWH	Delay procedures at least 12-24 hours after last dose of LMWH; regardless of technique, remove all catheters 2 hours before first LMWH dose; no additional hemostasis-altering drugs to be administered
Warfarin	Normal INR before neuraxial technique (usually requires 4-5 days); remove catheter when INR is 1.5 or less
Thrombolytics	Absolute contraindication
Thrombin inhibitors	Bivalirudin (Angiomax); desirudin (Iprivask) Avoid regional block, insufficient information
Fondaparinux (Arixtra)	Until additional clinical information is obtained, neuraxial techniques should involve only single needle pass, atraumatic needle placement, no indwelling catheters; if this is not feasible, an alternate method of prophylaxis should be used
Dabigatran (Pradaxa)	Discontinue 7 days prior to regional block; for shorter time periods, document normal thrombin time (TT) or ecarin clotting time (ECT); first postoperative dose 24 hours after needle placement and 6 hours post catheter removal, whichever is later
Herbal medicine	No evidence for discontinuation; be aware of potential drug interactions

Adapted from Horlocker TT, et al. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence Based Guidelines. 3rd ed. *Reg Anesth Pain Med.* 2010;35(1):64-101; Horlocker TT. Regional anaesthesia in the patient receiving antithrombotic and antiplatelet therapy. *Br J Anaesth.* 2011;107(suppl 1):i96-i106; Chelly JE. Thromboprophylaxis and regional anesthesia in the ambulatory setting. *Int Anesthesiol Clin.* 2011;49(4):166-173.
NSAIDs, Nonsteroidal antiinflammatory drugs; *aPTT*, activated partial thromboplastin time; *INR*, international normalized ratio; *LMWH*, low-molecular-weight heparin.

iatrogenic methicillin-resistant. *S. aureus* is a growing concern. Epidural abscess, like epidural hematomas with evidence of neurologic deficit, can best be diagnosed by MRI. Early, aggressive surgical intervention and antibiotic administration are vital.[4,28,35,45-47]

Arachnoiditis and aseptic meningitis are rare but can occur when foreign substances irritate the meninges. As the needle is inserted, precautions must be taken to avoid introduction of glass or metal particles, highly concentrated local anesthetics or dextrose solutions, detergents or antiseptics, and a core of epidermis. Indwelling catheters, previous myelography, and hemorrhages into the subarachnoid or epidural space also have been associated with meningeal irritation and scarring. Modern technology and techniques incorporate the use of disposable equipment, needles with matched stylets, filter needles, and improved pharmacologic agents that make this complication rare.[48]

Shock and severe uncorrected hypovolemia are contraindications to spinal or epidural anesthesia, because both techniques cause sympathetic blockade. The resulting vasodilation prevents physiologic compensation and may worsen hypotension. In addition, management of shock and hypovolemia often requires aggressive fluid therapy and multisystem treatments that are often physiologically and psychologically uncomfortable for the aware patient.[4,8,28]

Patients with a fixed-volume cardiac state such as hypertrophic cardiomyopathy or severe atrial stenosis do not tolerate bradycardia, decreases in systemic vascular resistance, or decreases in venous return and left ventricular filling—all physiologic changes that can be anticipated with neuraxial block by local anesthetics. In these patients, even transient episodes of hypotension can cause serious coronary hypoperfusion and cardiac arrest. Therefore spinal, and usually epidural, anesthesia, are avoided; however, few things in anesthesia are truly absolute. For example, epidural administration of opioids has been used to provide obstetric analgesia and may provide cardiac benefit for these patients. Precautions in such a scenario might include close hemodynamic monitoring with an arterial line and pulmonary artery catheter, careful titration of the anesthetic, intravascular volume expansion, and use of ephedrine or phenylephrine to treat hypotension.[30]

Spinal anesthesia is typically a singular deposit of local anesthetic and therefore provides anesthesia for a fixed duration. If uncertainty exists about the anticipated length of surgery, epidural catheter placement is more appropriate to allow for the additional administration, or continuous infusions, of anesthetic agents. If the extent of the surgery is unknown, a neuraxial anesthetic may be initiated only to be converted at a later time to a general anesthetic when the surgeon exceeds the limits of the anesthetic block. This is rarely an ideal situation; the patient may experience discomfort, albeit brief, and the anesthesia practitioner must contend with less-than-ideal intubating conditions. Despite the advantages of neuraxial anesthesia, many patients such as the elderly and those with arthritis or musculoskeletal limitations of the neck and upper extremities poorly tolerate prolonged immobility. The judicious use of conscious sedation can quickly devolve into a "room air general," placing the patient at risk for hypoventilation, hypoxia, and hypercarbia. To avoid such circumstances, combined neuraxial and general anesthetic techniques are advocated and offer advantages by minimizing the total dose of general anesthetic used. Such techniques lower the risk of secondary effects of general anesthesia (e.g., nausea and vomiting) while gaining the advantages associated with neuraxial anesthesia, such as attenuation of the stress hormone response and improved postoperative pain relief.[8]

The administration of spinal or any regional anesthesia to patients with a difficult airway or full stomach requires careful consideration. The use of spinal anesthesia permits the patient to retain upper airway and pharyngeal reflexes that block the sympathetic nervous system. This theoretically results in increased gastric and intestinal motility, causing the stomach to empty. However, such benefits may be negated by the perception of pain and anxiety that accompanies illness or injury. If sedation is used to counter such perceptions, the airway may again become compromised. Furthermore, if hypotension develops from the resulting sympathectomy, the patient may experience nausea and vomiting. When an injury has occurred after the ingestion of alcohol or if the patient received opioid analgesics, the pain caused by the injury may be the only stimulus for consciousness.

When spinal or other regional anesthesia is instituted, the reticular activating centers in the brain receive less input. This often results in somnolence in a normal patient but can result in unconsciousness in the overly sedated or inebriated patient. In addition, spinal or epidural anesthesia may reach an undesirably high level that is physically and psychologically intolerable for the patient and can even become a "total spinal." A total spinal is characterized by unresponsiveness accompanied by cardiac and respiratory compromise. In such situations, airway support is required, and the emergent management of any airway can severely compromise patient safety. Therefore, regional anesthesia is not an alternative to a secure airway. For patients identified as potentially difficult to intubate, equipment should be immediately available to secure the airway in a safe manner. Advances in airway management such as the laryngeal mask airway, improved fiberoptics, laryngoscopes, and adjunct airway equipment may tip the risk-benefit scale in favor of regional anesthesia.[8,11,48]

SPINAL ANESTHESIA

Spinal anesthesia became popular after the discovery of the local anesthetic properties of cocaine, the invention of the hollow needle and syringe, and the written descriptions of the first lumbar puncture. The first clinical application of the technique was reportedly performed in the late 1890s. However, spinal anesthesia's prominence was short lived. The introduction of specific, reversible, neuromuscular blocking drugs and concurrent improvements in inhalation agents for general anesthesia soon displaced its popularity. It has regained popularity, in large part because of the introduction of newer agents, equipment, and techniques to employ it safely in the ambulatory setting.

Equipment and Techniques

Preparation for spinal anesthetic procedures, like that for any other regional technique, requires the immediate availability of emergency equipment and supplies should emergent resuscitation be required. Usually spinal anesthetics are administered in the operating room where the minimal requirements—functional laryngoscopes, endotracheal tubes, induction agents, cardiovascular drugs including atropine and ephedrine or phenylephrine, suction, oxygen and ventilation equipment, a noninvasive blood pressure monitor, and pulse oximetry and electrocardiographic monitoring equipment—are readily available.

The original spinal technique, performed by August Bier in 1898, has been continually examined and modified in hope of reducing the incidence of complications—primarily that of PDPH. The goal of needle design has been to create a needle that minimally rends, tears, or cuts dural tissues. As technology has improved, the use of sterile, disposable procedure trays containing needles, syringes, catheters, and drugs has virtually eliminated problems previously associated with dull needles or contaminated equipment and has allowed for the development of innovative needles. Currently, two

main types of needles are available for use in spinal anesthesia. Needles such as the Quincke-Babcock or Pitkin have a *cutting bevel tip*. These needles have matching stylets, which minimizes tissue coring, and the tip's cutting angle is blunter than that of a standard needle. The newer *noncutting-tip needles* are either pencil-point shaped with lateral openings (e.g., Sprotte, Whitacre, or Pencan needles) or have the rounded bevel tip of the Greene-type needle and an opening at the needle's end. Several of the more popular types of spinal needles are shown in Figure 44-7. Spinal needles also have matched stylets and are marketed for spinal anesthesia use in sizes ranging from 22- to 29-gauge and in lengths of approximately 3.5 inches (88 mm) and 5 inches (120 mm). Most blocks are performed using 25- to 27-gauge, 3.5-inch (88-mm) needles.[28,48]

Recent data support the use of noncutting-tip needles over cutting needles for several reasons. Cadaver lumbar punctures performed with sharp cutting needles show piercing of the cauda equina roots without resistance appreciated by the practitioner. This does not occur with pencil-point needles. The bevel of cutting-tip needles encourages tip deviation on insertion, whereas symmetric noncutting needles stay midline. The use of a beveled needle requires holding the bevel direction parallel to longitudinal dural tissue fibers to minimize the risk of PDPH. Noncutting needles may drag fewer skin contaminants into subdermal tissue than cutting needles. Pencil-point needles pierce the dura with a clearly perceptible "click" or "pop" not as easily noticed with cutting needles. Newer, thin-walled noncutting needles have improved CSF flow rates without compromise to strength. This allows for their use for CSF diagnostic procedures and helps simplify the identification of the intrathecal space by permitting quick return of CSF after stylet removal. Finally, unless prohibitively small cutting needles are used, the incidence of PDPH is clearly reduced with the use of noncutting needles. Pencil-point needles are associated with less than a 1% risk of PDPH and a failure rate of approximately 5%.[8,28,49,50]

After the patient arrives in the surgical or obstetric preoperative area, the consents for surgery and anesthesia should be checked, and any further patient questions or concerns should be addressed.

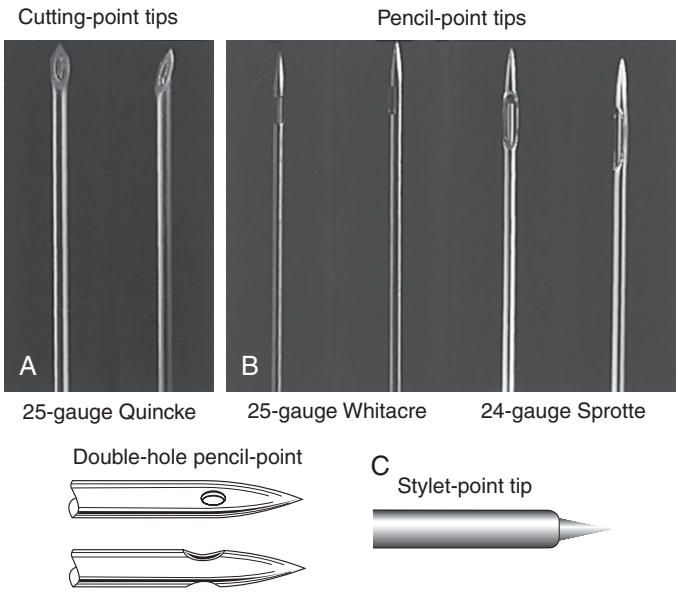

FIGURE **44-7** Graphic representations of spinal needle design features. **A,** Cutting-point tips. **B,** Pencil-point tips. **C,** Stylet-point tip. (**A** and **B,** Chestnut DH. *Obstetric Anesthesia: Principles and Practice*. 4th ed. Philadelphia: Mosby, 2009; **C,** CSEN International. *Eldor Spinal Needle*. Available at: http://www.csen.com.)

Review of the anesthetic preoperative history and physical examination should include the addition of any last-minute changes in patient status and notation of recently obtained diagnostic results. Intravenous access is achieved, and a continuous crystalloid infusion is begun. Preoperatively, most patients benefit from low-dose anxiolysis. With the increased emphasis on same-day admission, surgery, and discharge, long-acting agents are avoided. A rapid-acting benzodiazepine with a relatively short duration, such as midazolam, is highly titratable in 0.5- to 1-mg increments given intravenously and minimally alters the patient's hemodynamic status when used in low doses. The drug's effects can be reversed with flumazenil.

Monitors appropriate to the patient's physical status should be applied and at minimum include blood pressure monitoring, a continuous electrocardiogram, and pulse oximetry. For the purpose of baseline comparisons, vital signs must be assessed with the patient in both the supine position and the position in which the block will be administered.

The surgical or obstetric procedure to be performed helps determine the patient's position for the administration of the block. For example, if vaginal or urologic surgery is planned, a "saddle" block with the patient in a sitting position may be indicated. The prone position is useful for rectal surgery, because the patient can be placed in position before the block is implemented. This reduces the time required for positioning by permitting the patient to move with minimal assistance and to personally verify comfort and adequacy of padding. A lateral position favors spinal drug spread for right- or left-sided extremity or abdominal procedures. When the patient is in the lateral position, a pillow placed under the head and perhaps shoulders helps maintain neutral alignment of the spinal column. Surgical table height or patient position may need to be adjusted to compensate for variations in anatomic structure or physiologic limitations and to maximize anesthetist ergonomics. To maximize the space between spinous processes, the patient should arch the back (with assistance from the clinician) into a C shape or "like a Halloween cat." Once the patient is positioned, anatomic surface landmarks are used to identify the lumbar region of the back to be used for dural puncture, a point below the end of the spinal cord (L2). The line formed between the tops of the iliac crests, called the *intercristal line* or *Tuffier's line*, crosses the vertebral column as high as the L3 to L4 disk or as low as the L5 to S1 disk (Figure 44-8). The accuracy of predicting the precise

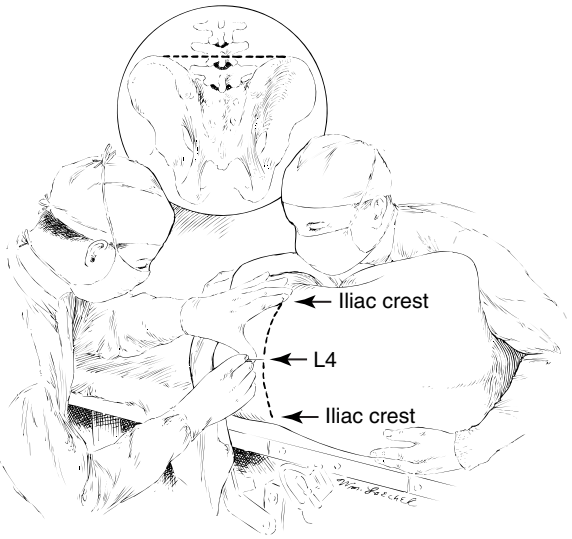

FIGURE **44-8** Patient positioning and identification of landmarks in the lumbar region of the back.

level of needle insertion is at best 50%. This fact may account for variability in the spinal anesthesia level ultimately achieved, yet this landmark has been clinically useful since the advent of spinal anesthesia.[7] The skin overlying a prominent spinous process at this level is marked for easy identification after the skin is prepared and draped. A surgical skin-marking pen is useful for this purpose, with caution exercised to avoid scratching the skin surface and predisposing the patient to infection.

Next, the spinal anesthesia tray is opened, and sterile gloves are donned. The patient is prepared with an antiseptic solution such as Betadine, a povidone-iodine solution that releases a concentration of 1% free iodine as it dries on a surface. The solution must remain in contact with the skin for at least 1 minute to be effective, and then the dry residue can be wiped away with sterile gauze to help prevent a chemical arachnoiditis. Do not use alcohol to remove residue because alcohol neutralizes the iodine solution and minimizes its antiseptic effect. Maintain aseptic technique, and apply the sterile drape to the back. Many spinal and epidural drapes have a circular window that is placed over the area of anticipated injection and adhesive strips to simplify application to the patient's back. Avoid touching the adhesive, because this has been shown to create small holes in gloves, which increases the risk of infection in both the patient and anesthesia practitioner.[51]

A rapid-acting local anesthetic such as 1% lidocaine is used for local infiltration of the area just caudad to the identified spinous process. Approach the skin of the back with the bevel of the needle facing away from the skin and at a 15- to 30-degree angle from the skin. Start injecting before the bevel of the needle is completely through the skin, and raise a skin wheal to place local anesthetic into subdermal tissues most likely to contain nociceptors. Deep tissues, including the supraspinous ligament, can be anesthetized by spreading 3 to 5 mL of local anesthetic through the tissues in a fan pattern.[8,28]

Larger 22- to 25-gauge spinal needles and epidural needles (used for continuous spinal anesthetic techniques) have tensile strength sufficient to permit introduction of the needle without additional support. However, spinal needles smaller than 25 gauge often require an "introducer" needle to help stabilize the needle during insertion and minimize infection in the surrounding dermis. The introducer is typically an 18- or 20-gauge needle with a "B" or blunt bevel. Introducer needles are approximately 3.8 cm long and matched to the spinal needles. The introducer is inserted through the skin and supraspinous ligament and into the interspinous ligament. Care must be taken, especially in thin individuals, not to enter the subarachnoid space with the introducer needle; the dura may be only 2.5 cm beneath the skin. Depth to the epidural space and the nearby dura correlates with weight but typically averages approximately 4 to 5 cm and rarely exceeds 9 cm. An introducer needle placed into the subarachnoid space would be likely to cause a PDPH.[4,8,15,28]

Several common spinal anesthesia techniques can be used, including a straight midline approach. With this easy-to-learn technique, the anesthesia practitioner inserts the needle directly midline between the spinous processes and toward the umbilicus perpendicularly to all planes or at the lumbar level with a slight cephalad angle (Figures 44-9 and 44-10). If bone is encountered early, the needle is withdrawn into the introducer and subcutaneous tissue. The introducer is then redirected in small angular increments in a cephalad direction. If bone is encountered when the needle is deeply inserted, the needle should be withdrawn and redirected caudad. As the tip of the spinal needle passes through the ligamenta flava, the sensation is similar to that felt when a needle is passed through a pencil eraser. As the needle tip passes through the dura, the anesthesia practitioner may sense a "pop" or "click." The stylet is removed, and several seconds are given for CSF to return through the small-gauge needle. Once CSF return is confirmed, some authors recommend rotating the needle 360 degrees in 90-degree increments to ensure that the needle tip is seated well within the subarachnoid space (see Figure 44-10). Other authors suggest that such needle manipulation risks a larger dural rent or needle dislodgement. Whichever method is used, secure needle handling is important. As shown in Figure 44-11, firmly place the dorsum of one's nondominant hand against the patient's back and below the spinal needle. Grasp the needle hub between the thumb and index finger. With this *Bromage* type of grip, the patient's body then acts as a firm support for the needle-stabilizing hand and helps prevent advancement or withdrawal of the needle tip from the subarachnoid space when the syringe is applied to inject the anesthetic agent.

A second technique is called the *paramedian approach*. With this technique, the needle is inserted 1 cm or approximately one fingerbreadth lateral to the caudad aspect of the interspace. The needle is directed toward the spinal canal and angled slightly cephalad and then medially approximately 10 to 15 degrees (see Figure 44-10). Elderly and arthritic patients may have decreased back flexibility and degenerating, calcified ligaments. For such

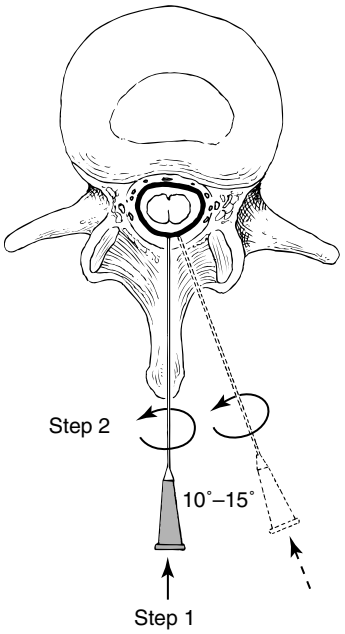

FIGURE **44-9** Insertion of the needle between the spinous processes and toward the umbilicus.

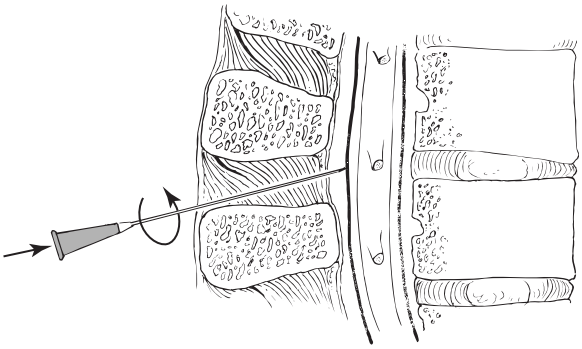

FIGURE **44-10** Spinal needle rotated 360 degrees to aid evaluation of tip location within the subarachnoid space.

patients, this approach may be the only possible means of entering the subarachnoid space because it aims for the largest area between processes and avoids calcified interspinous ligaments. A third approach to the subarachnoid space, known as the *Taylor approach*, takes advantage of the L5 interspace, which is the largest interlaminar space. A point 1 cm medial and 1 cm caudad to the posterior superior iliac spine is located, and the needle is angled medially and cephalad at a 55-degree angle toward the fifth lumbar interspace. The Taylor approach is best used for pelvic and perineal surgical procedures.[4,7,8,15,28]

Intrathecal Drugs, Spread, and Block Levels

Once the anesthetic solution is delivered into the CSF, the distribution of its active molecules through the subarachnoid space is dependent on the chemical and physical characteristics of the solution in relation to the chemical and physical characteristics of the patient's CSF and the subarachnoid space. In adults, approximately 500 mL of CSF is produced each day, predominantly by the choroid plexuses of the cerebral ventricles. Much of the CSF is reabsorbed by arachnoid granulations along the sagittal sinus to regulate CSF pressure to 10 to 20 cm H_2O. At any given time, a total of approximately 140 mL of CSF flows by bulk flow through the subarachnoid spaces, the central canal of the cord, and the ventricles of the brain. It is estimated that only 30 to 80 mL of the total CSF is present in the spinal canal. However, this quantity is difficult to measure, variable among individuals, and uncontrollable by the clinical anesthetist.[3,4,52]

The density of a substance compared with the density of water is a ratio known as *specific gravity*. The specific gravity of CSF is 1.004 to 1.009 and can vary depending on variations in temperature and location of the fluid within the subarachnoid space. For example, the specific gravity of CSF sampled from the lumbar area is slightly greater than that of CSF from the ventricles. This difference is directly dependent on the protein in the CSF, as well as on the effects of gravity and the position of the patient. The specific gravity of CSF also tends to increase as patient age increases, correlating to increases in glucose and protein. Hyperglycemia and uremia increase specific gravity of CSF, whereas jaundice and related liver problems may decrease specific gravity. The change in specific gravity is related to the presence of bilirubin within the CSF. An increase in a solution's temperature decreases its specific gravity. This decrease averages 0.001 point for each degree rise in Celsius temperature. Although all of these factors have been thought to influence the distribution of an anesthetic solution injected into the CSF, they are usually beyond the control of the anesthetist.[4,8,15,28,52]

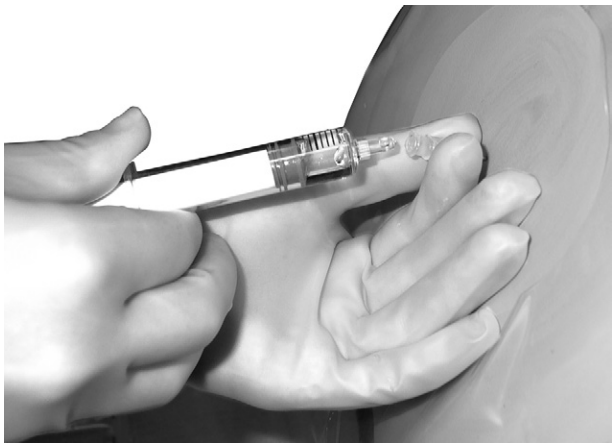

FIGURE **44-11** The Bromage grip, showing needle control and syringe connection.

A closely related concept, *baricity*, refers to the resting position of two fluids with differing specific gravities when the fluids are mixed in a single container, such as CSF and an anesthetic agent in the subarachnoid space. The baricity of the injected solution is compared with that of the CSF. Knowledge about the baricity of an injected solution provides the practitioner with information that helps determine the potential spread of the anesthetic mixture in the subarachnoid space. Therefore, when several medications are combined, the specific gravity of the combined solution at body temperature should be considered when the spread of the medication is anticipated. Unfortunately these bedside mixtures are rarely controlled or measured, and use becomes reliant on practical experience. When baricity (i.e., the ratio of specific gravity of local anesthetic to patient CSF) equals 1, the solution is referred to as being *isobaric*. Because the specific gravity of CSF is variable, it is not possible to prepare a solution that is precisely isobaric. Near-isobaric solutions remain and act in approximately the same location in which they are injected. A *hyperbaric* solution has a specific gravity that is greater than that of CSF. The solution would fall, or sink to the lowest anatomic point at which CSF is contained within the subarachnoid space in relation to gravity and the patient's position (presuming that, as previously mentioned, drug preparations are corrected for body temperature). *Hypobaric* solutions that are less dense than CSF rise or float to the highest anatomic position possible when injected into the subarachnoid space.

Because the normal range for the specific gravity of CSF is variable, local anesthetics, opioids, or other solutions injected into the CSF must be predictably hypobaric or hyperbaric. By tradition, hypobaric solutions are defined as having a baricity of less than 0.999, and hyperbaric solutions have a baricity of greater than 1.0015. Clinically this is accomplished by dissolving the drug in either sterile water to create a hypobaric solution or 5% to 8% dextrose solutions to create a hyperbaric solution. If CSF or normal saline is added to the medications, the specific gravity of the solution is similar to that of CSF, and the drugs remain approximately where injected.[4,8,15,28,52]

More than 23 factors, including CSF density and local anesthetic baricity, have been thought to affect the spread of local anesthetics in CSF and therefore affect the level and quality of the anesthesia achieved. Less than half of these factors have been found to have clinical significance, and an even smaller number are controllable by the anesthetist performing the anesthetic procedure.[28] Clinically the most important factors are those that can be manipulated by the anesthesia practitioner. These are the total dose of the local anesthetic, the site of injection, the baricity of the drug (drug choice), and (when nonisobaric solutions are used) the position or posture of the patient during and after injection.[52]

The duration of a spinal anesthetic is based primarily on local anesthetic choice and total dose. Highly protein-bound drugs, such as tetracaine, bupivacaine, and ropivacaine, have long durations of action compared with less protein-bound drugs such as lidocaine and mepivacaine. Vasoconstrictors such as 0.1 to 0.2 mL of 1:1000 (1 mg/mL) epinephrine solution are sometimes added to the local anesthetic solution to prolong the duration of action. Epinephrine is thought to prolong the duration of spinal anesthesia by causing vasoconstriction, thereby delaying normal uptake of local anesthetics, by direct antinociceptor action, or by a combination of these effects. The effect of added epinephrine on the prolongation of anesthesia is greatest with tetracaine, less with lidocaine, and minimal with bupivacaine. In addition, local

TABLE 44-4 Choice of Medication for Spinal Anesthesia Used for Surgical Procedures

Procedure	Medication*	Dosage	Duration Without Epinephrine	Duration With Epinephrine
Vaginal delivery	Tetracaine	5 mg	1-1.5 hr	2.5-3 hr
	Bupivacaine	5-7 mg	1 hr	1.5 hr
	Lidocaine	25 mg	15-25 min	45 min-1 hr
Cesarean section	Tetracaine	8 mg	1-1.5 hr	2.5-3 hr
	Bupivacaine	10 mg	1-1.25 hr	1.5-2 hr
	Lidocaine	50-75 mg	30-45 min	1-1.25 hr
Anorectal surgery	Tetracaine (hyperbaric)	6 mg	1-1.5 hr	3 hr
	Tetracaine (hypobaric)	6 mg	1 hr	3 hr
	Bupivacaine	8 mg	1 hr	1.5-2 hr
	Lidocaine	25-50 mg	15-30 min	45 min
Genital or lower-extremity procedure	Tetracaine	6-10 mg	1.5 hr	2-3 hr
	Bupivacaine	8-12 mg	1.5 hr	2 hr
	Lidocaine	75-100 mg	45-60 min	1.25-1.5 hr
Hernia, pelvic procedure	Tetracaine	10-12 mg	1.5 hr	2-3 hr
	Bupivacaine	12-15 mg	1.5 hr	2 hr
	Lidocaine	100 mg	45-60 min	1.25-1.5 hr
Intraabdominal surgery	Tetracaine (by patient height)	5 ft to 5 ft, 5 in = 12 mg 5 ft, 6 in to 6 ft = 15 mg >6 ft = 18 mg	1.5 hr	2-3 hr
	Bupivacaine (by patient height)	5 ft to 5 ft, 5 in = 15 mg 5 ft, 6 in to 6 ft = 18 mg >6 ft = 20 mg	1.5 hr	2 hr
Back and spine surgery	Tetracaine	10-15 mg	1-1.5 hr	2-2.5 hr
	Bupivacaine	15-20 mg	1-1.5 hr	1.5-2 hr

*Local anesthetic solutions administered to intrathecal or epidural spaces must be sterile and preservative free.

anesthetic solutions may include opioids (10 to 25 mcg fentanyl, 2.5 to 10 mcg sufentanil, or 250 mcg preservative-free morphine) or the α-agonist clonidine, 150 mcg, to prolong duration. These agents act at opioid and α_2-adrenergic receptors, respectively. The exact nature of the synergistic effect among opioids, α_2-agonists, and the local anesthetics is not clear, but the result is again prolonged spinal anesthesia. Volume in the tested range of 1 to 14 mL, and therefore concentration, minimally affects the duration of anesthesia or the final sensory level achieved. Increasing the total dose of a spinal local anesthetic will increase its duration of action and affect the sensory level achieved. Duration of sensory and motor blockade for local anesthetics has been shown to be predictable. For example, increasing the dose of hyperbaric bupivacaine from 10 mg to 15 mg prolongs the duration of sensory block by 50% and increases the maximum sensory level achieved. Based on these principles, Table 44-4 offers medication administration suggestions to achieve an approximate sensory level and duration of spinal anesthesia in a typical clinical setting.[52,53]

Selecting the precise site of injection, as mentioned, is technically inaccurate at the clinical level.[7] The higher the site of injection, obviously, the higher the level of sensory block, but this is limited by the anatomy of the spinal cord and the anesthetist's desire to approach the subarachnoid space below the termination of the spinal cord. Theoretically, if a patient is administered a hyperbaric solution at the L3 level and placed supine, the local anesthetic would flow both cephalad and caudad from the relative peak of the lumbar lordosis to the troughs of the thoracic kyphosis and sacral regions. If a hyperbaric drug is placed below L3 with the patient in a sitting position, and the patient is left sitting for 5 minutes, a lumbar and sacral-root anesthetic known as a *saddle block* will occur. However, even under experimental conditions using the second to fifth lumbar interspace, the data on the ability to control the maximum sensory block level achieved are inconsistent. Therefore, the site of injection can be a poor predictor of the final level of sensory anesthesia achieved.[52]

Several authors suggest that the level of the anesthetic can be adjusted or modified by use of position changes within the first few minutes after injection or until the medication becomes fixed on the nerve roots and the spinal cord. Some have even found that changes in position as late as 60 minutes after injection can alter the level of block achieved. For example, one of the suggested methods used to modify the level of the anesthetic is to raise a supine patient's legs 45 degrees. This position is thought to increase blood flow through the epidural venous plexus, indirectly altering CSF pressures. Such a position also flattens the lumbar lordosis, altering flow of hyperbaric local anesthetic within the subarachnoid space. The combined effects result in further cephalad spread of local anesthetic solutions. If one uses a similar line of thought, morbid obesity and third-trimester pregnancy also are associated with epidural venous engorgement when the patient is supine, and a slightly higher level of spinal anesthesia is found when compared with controls. With traditional hyperbaric solutions, the block achieved may range from T3 to T6. Therefore, the anesthetist's ability to precisely control the level of sensory anesthesia through baricity and changes in posture is associated with great variability and low predictability from patient to patient.[28,52,54] Once achieved, the final level of sensory blockade should be determined as discussed previously, then documented.

Continuous spinal anesthetics are administered with the same techniques used to establish a spinal or epidural anesthetic. A

small epidural needle is used for the procedure, with the bevel turned parallel to dural fibers to help minimize the risk of PDPH. After the needle is inserted into the subarachnoid space, the bevel of the needle is turned either caudad or cephalad to facilitate passage of an epidural catheter into the subarachnoid space. The catheter is inserted only 2 to 3 cm into the subarachnoid space. Further insertion could result in advancement of the catheter along a nerve root or in curling of the catheter. The incidence of headache is minimal in elderly patients or when the catheter can remain in the subarachnoid space for at least 40 hours. Because of reports of cauda equina syndrome, in 1992 the Food and Drug Administration (FDA) removed from the U.S. market small needles and microcatheters designed to further reduce the risk of PDPH. *Cauda equina syndrome*, or persistent paralysis of the nerves of the cauda equina with resultant lower extremity weakness and bowel and bladder dysfunction, has subsequently been attributed to the deposition pooling and possibly repeat dosing of neurotoxic concentrations of hyperbaric local anesthetics, particularly 5% lidocaine.[4,8,148,53,55]

This same solution of lidocaine in varying concentrations has been associated with *transient neurologic symptoms* (TNS). Symptoms are usually described as pain originating in the gluteal region that radiates to both lower extremities. Symptoms appear within a few hours up to 24 hours after recovery and spontaneously disappear in virtually all cases in 10 days. The symptoms range from mild to severe radicular back pain in up to 30% of patients, and although NSAIDs are the usual treatment, opioids may be required. No permanent problems occur. Symptoms include a burning, aching, cramplike, and radiating pain in the anterior and posterior aspect of the thighs. Pain radiates to the lower extremities, and lower back pain is common. Other anesthetics have been implicated, but it is much more prevalent after spinal lidocaine.[56] Surgical positioning may be a factor as well.[57] The exact mechanism is unclear. Newer techniques and agents other than lidocaine are being used now, and that has diminished this problem as a clinical issue. Treatment is supportive and should include NSAID agents when possible.[58,59]

Physiologic Alterations and Their Management

Spinal anesthesia causes several physiologic changes that are predictable and can usually be readily managed through anticipation and prevention or with minimal intervention. Physiologic changes include effects on the central nervous system, cardiovascular system, respiratory system, and gastrointestinal (GI) system. In addition, physiologic alterations caused by central neural blockade affecting neuroendocrine, renal, and hepatic function are mentioned.

The obvious central nervous system effect of spinal anesthesia is the inhibition of nerve impulse conduction, resulting in spinal anesthesia. This occurs when the local anesthetic concentration exceeds the minimal blocking concentration of the particular nerve exposed to the drug. Neurons have different levels of susceptibility to local anesthetics, and this partially explains the differential block seen with spinal and epidural anesthesia. As a local anesthetic spreads from the epicenter of its injection site, the concentration of molecules decreases. As the local anesthetic spreads rostral and the concentration gradient lessens, only the most susceptible neurons will be blocked, and a differential block occurs. With spinal anesthesia, typically kinesthetic sense is inhibited at a dermatomal level higher than light touch or cold sensation, which in turn is inhibited at a more rostral dermatomal level than pinprick anesthesia. Therefore, a differential blockade among the levels of sympathetic, somatic sensory, and somatic motor fibers can be identified. Attempts to demonstrate the numbers of segments between areas of differential blockade have found that sympathetic fibers are blocked a mean of six or seven segments higher than somatic sensory fibers.[10,11]

The reticular excitatory area in the brainstem is responsible for the brain's overall state of alertness or arousal. The primary determinant of the activity of the reticular excitatory area is the amount of sensory input from the body. Because spinal anesthesia greatly decreases the number of sensory impulses to the reticular excitatory area, normal patients often experience somnolence. Caution must be taken during administration of spinal anesthesia to a patient in pain and already under the influence of central depressants such as alcohol or opioids. The pain caused by the injury may be the only stimulus for consciousness, and when spinal or other regional anesthesia is instituted, unconsciousness may ensue.[11]

Spinal or epidural techniques using local anesthetics block sympathetic nerve transmission in addition to blocking sensory and motor fibers. Therefore, the sum effect of neuraxial anesthesia on the cardiovascular system depends primarily on the overall degree of sympathetic blockade in terms of the rostral spread of the anesthetic and partially on the degree of patient sedation and central sympathetic inhibition. Blockade of the sympathetic nervous system causes arterial vasodilation, decreased systemic vascular resistance, venous pooling, and a reduction in venous return. These changes cause a redistribution of blood that often results in hypotension. If the block is high enough, the sympathetic nerve fibers that innervate the heart, known as the *cardiac accelerators* (T1 to T4), become anesthetized. An imbalance occurs between vagal fibers, and the heart rate often slows, further contributing to hypotension. Baroreceptor reflexes, volume receptor reflexes, and decreased central sympathetic outflow all contribute to the complexity of the cardiovascular response to neuraxial anesthesia. The overall result is loss of normal cardiovascular homeostatic reflexes and the ability to compensate for minor cardiovascular stresses.[60,61] Rapid changes in position, changes in skeletal muscle tone caused by relaxation, decreased venous return, low preoperative volume status, reflex surgical stimulation, preoperative medications (especially opioid- and sedative-hypnotics), and concurrent conditions such as pulmonary embolism, pregnancy, and systemic reactions to medications have all been implicated in increased severity of perioperative hypotension.[11,60]

Hypotension is immediately relevant to the perfusion of critical organs such as the heart and brain and is important to all organs in maintaining near homeostasis. Although normotensive patients have been shown to maintain cerebral blood flow despite a moderate decrease in blood pressure, hypertensive subjects may have altered cerebral blood flow autoregulation and are less tolerant of changes in mean arterial pressures.[11] A similar situation exists with elderly patients and patients with known coronary disease. With these caveats in mind, most clinicians allow a decrease in blood pressure of 20% from a patient's baseline before initiating treatment.

Clinicians continue to debate the optimal treatment of spinal anesthesia–induced hypotension and bradycardia. The treatment is often dependent on coexisting disease, but some general recommendations can be made. Preventive management of hypotension includes the administration of glucose-free crystalloid or colloid solutions in volumes of approximately 15 mL/kg, 15 minutes before the start of the anesthetic procedure to maintain preload to the heart. This initial infusion should include replacement of any fluid deficit caused by restricted oral intake and has been shown to help prevent immediate cardiovascular side effects. Infusions of

α-adrenergic vasoconstrictors and sympathomimetic agents have been shown to help reduce the incidence of cardiovascular side effects requiring treatment. Should the treatment of hypotension become necessary, the ongoing administration of intravenous solution is often the first response; however, excessive fluid therapy can lead to fluid overload and urinary retention, especially in the elderly.[60]

Continued treatment is guided by the patient's presenting symptoms and coexisting disease. The heart rate can be used to help guide pharmacologic intervention. Ephedrine (a mixed α- and β-agonist) in 5 to 10 mg intravenous boluses is the agent of choice in patients with symptomatic bradycardia. Ephedrine's indirect effects cause an increase in peripheral vascular resistance and heart rate. If the heart rate is normal or elevated, incremental injections of an α-agonist, such as 50 to 100 mcg of intravenous phenylephrine, causes increased systemic vascular resistance without further increasing the heart rate. The use of phenylephrine may therefore be more efficacious in the elderly. Bradycardia is treated with intravenous atropine 0.4 to 0.8 mg.

Severe hypotensive events should be treated vigorously with medication and fluids, because mortality from rare cardiac arrests increases when treatment is delayed.[4,10,15,60]

Most studies demonstrate that midthoracic levels of either spinal or epidural anesthesia have minimal effects on tidal volume, respiratory rate, minute ventilation, and arterial blood gas tensions in otherwise healthy individuals. The phrenic nerve is rarely paralyzed, even when sensory levels reach the cervical dermatomes. However, the accessory abdominal and intercostal muscles for ventilation are impaired, and the ability to cough and clear secretions is inhibited. With the loss of perception of intercostal and abdominal wall muscle movement and the inability to cough, the patient may begin to feel dyspneic. Caution must be exercised if the accompanying anxiety is treated with large doses of sedatives or opioids. They may worsen ventilation and result in hypoxia. Although regional techniques have been shown to have minimal effects, adequate ventilatory ability during surgery is dependent on multiple factors, and improved pulmonary outcomes have not been clearly demonstrated. Some of the factors that affect ventilatory ability under spinal or epidural anesthesia include the presence of coexisting disease, depressant medications, patient position, type and location of the surgery and incision, and presence of hypotension and hemorrhage. The anesthetic plan must be adapted to the patient and the operation.[10,11]

The GI tract is regulated by the parasympathetic and sympathetic nervous systems. The parasympathetic innervation of the GI tract is primarily via the vagus nerves and is composed of both afferent and efferent fibers. Parasympathetic afferent nerves transmit sensations of satiety, distention, and nausea, whereas efferent outflow generally increases GI activities such as tonic contractions, sphincter relaxation, peristalsis, and secretion. Sympathetic innervation of the GI tract stems from the T5 to L2 spinal cord segments and via prevertebral ganglia. Sympathetic afferent nerves are responsible for transmitting pain information; efferent nerves inhibit peristalsis and gastric secretion and cause sphincter contraction and vasoconstriction. When spinal and epidural anesthesia cause a sympathetic blockade, the result is unopposed or dominant parasympathetic activity. The neuraxial sympatholysis results in a generalized constriction of the bowel, normal to increased peristalsis, increased intraluminal pressure, and increased GI blood flow.[10,11,15] The combination of abdominal muscle relaxation and a contracted bowel offers improved operating conditions for intraabdominal procedures, but because gastric motility can be increased, some clinicians have questioned the risk of wound disruption. Several studies have reported that the intraoperative and postoperative use of neuraxial anesthesia does not increase the risk of wound breakdown. Steinbrook[62] and other researchers suggest that continued postoperative analgesia, especially with a thoracic epidural and local anesthetic infusion, has beneficial effects on the recovery of bowel function after major abdominal surgery.[10,11]

Nausea and vomiting are associated with neuraxial block in up to 20% of patients. Nausea and vomiting are primarily related to the GI hyperperistalsis of parasympathetic dominance, although other contributing factors may include hypoxemia, hypotension, systemic medications (opioids or rapidly infused antibiotics), and psychological stimuli. A cardiac mechanism associated with spinal anesthesia, as proposed by some authors, also may lead to nausea and vomiting. Theoretically, cardiac vagal afferent nerves can be activated in response to a decrease in venous return via ventricular mechanoreceptors, especially with high block levels. Therefore, the vagolytic properties of atropine provide indirect-acting antiemetic effects in the treatment of the nausea and vomiting associated with high spinal anesthesia.[11,15]

The neuroendocrine stress response is a combination of responses of the body to tissue trauma (such as surgery) or critical illness. The response includes components of neural, immune, endocrine, metabolic, and inflammatory systems that are closely integrated through a complex mechanism of hormones, neurotransmitters, and receptors that affect cells throughout the body. These systems are activated in proportion to the level of critical illness or tissue injury experienced by the body.[11] The stress response is usually associated with increases in blood concentrations of adrenocorticotropins, cortisol, insulin, growth hormone, aldosterone, and glucose. Initially a protective response—the stress response—can lead to tachycardia, hypertension, catabolism, immunosuppression, and hypercoagulability.[10] Regional blocks such as spinal and epidural techniques moderate the stress response to surgery. Although spinal anesthesia blocks this response only for the duration of the anesthetic administration, the use of continuous epidural analgesia well into the postoperative period has the potential to improve perioperative outcome.

Renal blood flow and function are well preserved during spinal anesthesia when blood pressure is maintained. Hepatic blood flow is directly proportional to the mean arterial pressure and therefore depends on the treatment of any hypotension associated with the spinal or epidural anesthetic.[10] Spinal and epidural anesthetics block sympathetic fibers, thereby increasing the tone of the internal urethral sphincter; in addition, neuraxial opioids cause a decrease in detrusor contraction and an increase in bladder capacity. These changes in the genitourinary system can result in the rare complication of urinary retention.

Complications of Spinal Anesthesia

Postdural Puncture Headache

PDPH is perhaps the most commonly discussed and managed complication of neuraxial anesthesia, with a documented incidence that has varied over the years from 0.2% to 24%. Theoretically PDPH is caused by a decrease in the CSF available in the subarachnoid space through a leak created by the dural puncture with an intruding needle. The medulla and brainstem, having lost their hydraulic support, drop into the foramen magnum, stretch the meninges and pull on the tentorium. This pulling, further irritated by movement and the upright position, causes a characteristic headache.[4,22,28,63] A contributing theory suggests that cerebrovasodilation may result from low CSF pressure. This theory is supported by the beneficial effects of vasoconstrictor drugs such as caffeine and theophylline.[63]

Several factors are known to increase the incidence of PDPH. The use of large, non–pencil-point needles or a cutting-needle bevel direction that is perpendicular to the long axis of the body will make larger holes in the dural fibers and create larger CSF leaks. Multiple punctures also increase CSF leak and the risk of headache. In addition, female patients are more likely than male patients to get a PDPH, and the young are more likely than the elderly to experience this complication. Most studies also demonstrate a higher incidence of PDPH in the pregnant population. Postpartum women in their 30s are most often affected. Patients with a history of PDPHs are predisposed to another headache after a subsequent spinal anesthetic procedure. However, one should keep in mind that not all headaches that follow spinal anesthetic procedures are PDPHs. It is common for patients to experience headaches after surgery and even after general anesthetics. Factors that contribute to headaches may include anxiety, interrupted sleep, dehydration, hypoglycemia, and even simply the lack of normal morning caffeine intake. A differential-diagnosis approach should be taken to identify serious complications such as subdural hematoma, subarachnoid hemorrhage, meningitis, sinusitis, or subarachnoid hemorrhage.[15,22,28,50,63]

Fortunately, PDPHs have several characteristic features that aid in diagnosis. Usually PDPHs occur within several hours to the first or second postoperative day. Historically, bed rest was thought to help prevent PDPH, but subsequent studies found that avoiding early ambulation simply postponed the onset of PDPH. The headache is typically described as a mild to incapacitating bilateral frontal headache that radiates from behind the eyes and across the head toward the occiput and often into the neck and shoulders. The headache is considered positional, because it subsides when the patient is lying down. The only other form of headache that has this positional component is caused by pneumocephalus. Other symptoms that may be associated with PDPH include nausea and vomiting, appetite loss, blurred vision or photophobia, a sensation of a plugging of the ears and loss of hearing acuity, tinnitus, vertigo, and depression.[8,22,28,63]

Although PDPHs are self-limiting and often resolve in less than 10 days, early identification and prompt treatment are essential if complications of immobility, depression, and patient dissatisfaction (a potential reason for litigation) are to be avoided. Conservative management includes a horizontal position, adequate hydration, oral analgesics, and the administration of 500 mg intravenous caffeine benzoate, 300 mg of oral caffeine, or theophylline. Caffeine has shown effectiveness for treating PDPH, decreasing the proportion of participants with PDPH persistence and those requiring supplementary interventions. Gabapentin, theophylline, and hydrocortisone also have shown a decrease in pain severity scores when compared with placebo or conventional care. There is a lack of conclusive evidence for the other drugs such as sumatriptan.[64,65] The horizontal position is impractical for most patients, especially mothers of newborns, and encourages further complications of immobility.[63] Abdominal binders, thought to increase epidural venous plexus blood flow and therefore CSF pressure, are also uncomfortable and often impractical. Increasing fluids during the evaluation and early management period was thought to increase the central volume and increase the secretion of CSF from the choroid plexus, but this is not well supported in the literature. However, adequate hydration should be maintained in all patients.[28] Caffeine and theophylline are both methylxanthine derivatives that cause cerebral vasoconstriction and central nervous system stimulation. Caffeine therapy, both oral and parenteral, is the most commonly used pharmacologic treatment modality. Caffeine has been shown to eliminate headache in up to 70% of patients, but this effect may be transient. Still, Baysinger et al.[66] suggested that prophylactic intravenous caffeine administration may safely minimize PDPHs.

An epidural blood patch is considered the definitive treatment for PDPH. Thought to work via clot formation that seals the dural rent and increases CSF pressure, the epidural blood patch is associated with a greater than 90% cure rate. Clinically an epidural blood patch is performed in a manner similar to that of placing an epidural catheter. First, the availability of intravenous access is identified, usually in the antecubital fossa, and informed consent is obtained. Both the patient's back and intravenous access site are prepared and draped in an aseptic manner. An insertion site at or below the level of the lowest initial needle insertion is chosen, because blood has been shown to spread in a predominantly cephalad direction within the epidural space. The epidural space is identified by use of either loss-of-resistance or hanging-drop technique (discussed in the section on epidural anesthesia). Autologous venous blood (approximately 20 mL) is withdrawn from the vein and then slowly injected through the epidural needle into the epidural space. The injection proceeds until the patient senses pressure in the back, buttocks, or legs. Typically, this occurs at a volume of 12 to 15 mL, which is sufficient blood to patch most patients. A supine position should be maintained for $^1/_2$ to 1 hour before the patient ambulates. Relief of the headache is often instantaneous. In the rare case in which an epidural blood patch fails, a repeat blood patch may be attempted in 24 hours, with a similar success rate.[22,28,63]

The success rate and excellent safety record of the epidural blood patch encourages the use of this therapeutic option early in the treatment of PDPH. However, some risks, although minor or rare, are associated with this more invasive procedure. Backache, often associated with the administration of general, spinal, or epidural anesthetic techniques, occurs in up to 35% of patients after an epidural blood patch. Although rarely as debilitating as a PDPH, backache risk should be explained to the patient. The most common cause of backache is relaxation of the muscles of the back and flattening of the normal lordotic curve. As the muscles stretch, injury to tendons and ligaments can occur. The position of the patient might increase the severity of the problem. An exaggerated lithotomy position or a completely supine position can further increase tension on tendons, resulting in increased trauma to both the muscles and the tendons. Trauma from multiple punctures; hemorrhage; infections; use of large needles, retractors, and forceps; extremes of positions; preexisting diseases such as arthritis and osteoporosis; and prolonged labor can contribute to backaches that may persist well into the postoperative period.[28,63]

Management of backache includes the use of antispasmodics and NSAIDs to reduce discomfort, permit ambulation, and promote a more rapid recovery. In addition, authors have reported a 5% incidence of transient (24- to 48-hour) temperature elevation, a 1% incidence of neck ache, radicular pain, nerve root irritation, cranial nerve palsy, and meningitis, although the cause of meningitis was unproven.[23,28,63]

Several caveats regarding the treatment of PDPH are worth mentioning. Systemic infection, perhaps indicated by fever, presents a relative contraindication to epidural blood patch and warrants a trial of pharmacologic intervention. The risk of neurologic sequelae after epidural blood patch in the presence of HIV infection or sepsis is controversial, because few data are available, leading some authors to suggest alternative therapies such as epidural 0.9% sodium chloride or dextran.[15,46,63] Prophylactic epidural blood patch placement has not been shown to be consistently successful.[22] In light of the relatively low incidence of PDPH and the

effectiveness of the epidural blood patch, treatment should not begin until the problem exists. Finally, an alternative diagnosis should be sought if two epidural blood patches fail to resolve the patient's symptoms.[28,63]

Nausea

As with general anesthesia, intraoperative and postoperative nausea and vomiting (PONV) associated with CNB is a complex issue. Although it is believed that PONV is less common with regional anesthesia techniques than general anesthesia techniques, agents such as propofol have considerably narrowed the incidence gap. Although not life threatening, PONV remains a significant concern for patients and clinicians. General strategies can be implemented to help reduce the incidence of this unpleasantness.

Nausea immediately after the initiation of CNB is often considered a sign of significant hypotension and a climbing block level. Resulting cerebral ischemia affects the vomiting centers of the medulla, possibly triggering nausea. Others posit that gut ischemia leads to the release of emetogenic substances such as serotonin. Fluid and sympathomimetic administration treats the hypotension, and the nausea resolves. Another contributing element may result from the sympathectomy caused by the onset of CNB. The resulting unopposed parasympathetic activity in the gastrointestinal tract results in hyperactivity, possibly contributing to nausea. Evidence that this may be the case is that vagolytic agents such as atropine are efficacious in treating this nausea.[67]

Avoiding hypotension, providing adequate hydration, and supporting perfusion with supplemental oxygen are the basis of an antiemetic plan for CNB. Premedication and intraoperative sedation can significantly affect the incidence of intraoperative nausea and PONV. Clonidine does not influence the incidence of PONV, and evidence supports that propofol has antiemetic effects. The addition of epinephrine to local anesthetics administered intrathecally for spinal anesthesia increases the incidence of nausea. Also, a dose-dependent increase in PONV occurs when intrathecal morphine is used. However, the addition of 20 mcg fentanyl or 2.5 to 5 mcg of sufentanil to spinal bupivacaine results in less intraoperative nausea compared with placebo. Similar strategies apply to epidural anesthesia, although opioid use must be matched to patient and case type to maximize analgesia while minimizing secondary effects.[67] Multimodal approaches that have been widely adapted should be applied to PONV after regional anesthesia as well.[68]

Urinary Retention

Urinary retention is common after anesthesia and surgery with a reported incidence of between 5% and 70%. Spinal or epidural anesthetics block sympathetic fibers and increase the tone of the internal urethral sphincter. However, other factors often contribute to the risk of urinary retention after surgery and anesthesia. These include the type of surgical procedure, bladder distention from the administration of large volumes of intravenous fluids, bladder trauma, prolonged hypotension, incision pain, urethral edema caused by prolonged labor, benign prostatic hypertrophy, and the use of neuraxial or intraoperative opioids, anticholinergics, sympatholytics, and other drugs. Comorbidities, type of surgery, and type of anesthesia influence the development of postoperative urinary retention (POUR). The risk of retention is especially high after anorectal surgery, hernia repair, and orthopedic surgery and increases with advancing age. Certain anesthetic and analgesic modalities, particularly spinal anesthesia with long-acting local anesthetics, adding epinephrine and epidural analgesia, promote the development of urinary retention. Reasonable fluid administration with less than 1000 mL helps avoid bladder overdistention. Portable bladder ultrasound provides rapid and accurate assessment of bladder volume and aids in the diagnosis and management of POUR. Catheterization is recommended when bladder volume exceeds 600 mL to prevent the negative sequelae of prolonged bladder overdistention. Urinary retention and subsequent catheterization can lead to complications such as urinary tract infections and urethral strictures. Low-risk patients with less than 600 mL bladder volume may be sent home with instruction to return if they cannot void.[67-71]

Neurologic Risk

Patients greatly fear the perceived risk of paraplegia resulting from neuraxial anesthetics, and the seriousness of such complications warrants concern. However, several very large series have shown that the incidence of persistent motor paralysis is exceedingly rare (less than 1 per 10,000). Because neurologic sequelae are rare, the knowledge base of complications comes from case studies, and often the cause is not proved but rather inferred by association. Direct needle or catheter nerve injury, drug-related neurotoxicity, anterior spinal artery syndrome, undiagnosed neurologic disease, intraneural or intramedullary injections, the presence of blood in the CSF, patient positioning, hematomas, and abscesses are associated with permanent neurologic deficits. Therefore, good clinical practice depends on (1) the use of appropriate anesthetic techniques that minimize risk and (2) the conduct of postoperative assessments in a manner that promotes early detection, diagnosis, and treatment—especially because reversibility of complications is often time dependent.[15,28,30,72,73] Transient neurologic symptoms are discussed in Chapter 10.

Unexpected Cardiac Arrest

Cardiac arrest associated with neuraxial anesthesia is often sudden and unexpected and can result in severe neurologic injury and death. Additionally, this undesired complication occurs in a significant number of young, previously healthy patients. Estimates of occurrence have ranged from 7:10,000 for spinal anesthesia and 1:10,000 for epidural anesthesia. This suggests that cardiac arrest is not such a rare event in neuraxial anesthesia. How then might it be differentiated from arrests under general anesthesia (3:10,000)?[74]

Because unexpected cardiac arrest with spinal anesthesia has been reported in previously healthy patients, some authors consider this a physiologic response to neuraxial blocks. Other authors suggest a pattern of presentation with a gradual downward trend in heart rate followed by an abrupt onset of severe bradycardia or asystole.[11] Spinal anesthesia cardiac arrest can occur well after the onset of spinal blockade. Large and recent retrospective studies note that arrests can occur 20 to 60 minutes after the onset of spinal blockade and are frequently associated with intraoperative events such as significant blood loss and orthopedic cement placement.

The etiology of cardiac arrest during spinal block anesthesia is related to cardiocirculatory factors, mainly a reduction of preload resulting from sympathetic blockade. These decreases in preload may initiate reflexes that cause severe bradycardia. Three reflex responses have been suggested. The first involves the pacemaker stretch. The rate of firing of these cells within the myocardium is proportional to the degree of stretch. Decreased venous return results in decreased stretch and a slower heart rate. The second reflex may be attributable to the firing of low-pressure baroreceptors in the right atrium and vena cava. The third is a paradoxical Bezold-Jarisch reflex, in which mechanoreceptors in the left ventricle are stimulated and cause bradycardia. Other factors that

increase the risk of developing cardiac arrest include changes in patient positioning and hypovolemia.

Maintaining preload should be a priority, and prophylactic preloading with a bolus of IV fluid should not be omitted before initiating spinal anesthesia. It is important to institute treatment as soon as possible. Standard regimens for volume preloading may not be sufficient to maintain adequate preload, so a low threshold for administering additional fluid boluses, using vasopressors or repositioning the patient to augment venous return, may be appropriate. For patients with bradycardia during spinal anesthesia, the stepwise escalation of treatment of bradycardia with atropine (0.4-0.6 mg), ephedrine (25-50 mg), and, if necessary, epinephrine (0.2-0.3 mg) may be appropriate. For severe bradycardia or cardiac arrest, full resuscitation doses of epinephrine should be promptly administered.[74-77]

Auditory, Ocular, and Facial Complications

Unexpected complications or complications that a patient may not ascribe to anesthesia may be unreported or underreported, especially if they are transient in nature and not life threatening. The complications of transient hypoacusis or hearing loss and retinal hemorrhage are thought to be caused by changes in CSF pressure, either from postdural puncture leaks or increases in pressure from the epidural administration of a large volume of solution. Epidural injection of 8 to 16 mL of fluid can increase CSF pressure by 85 cm H_2O for several minutes before compensation occurs. Horner syndrome (i.e., ptosis, miosis, anhidrosis, and enophthalmos) and trigeminal nerve palsy probably result from a high spread of local anesthetic to the sympathetic fibers of the head and neck and to cranial nerve V, respectively. These problems are usually self-limiting; however, knowledge of their previous occurrence enables the compassionate anesthetist to provide counsel and reassurance to anxious patients.[32,78]

EPIDURAL ANESTHESIA

Epidural anesthesia is a central neuraxial block that can be used for a wide variety of procedures. Unlike spinal anesthesia that results in an all-or-none block, epidural anesthesia can be titrated to deliver either analgesia or anesthesia for a wide variety of surgical and analgesic procedures. Epidural anesthesia allows the anesthesia practitioner better control of the extent of sensory and motor blockade than is offered by spinal anesthesia. The luxury of placing an epidural catheter that can be used before, during, and for an extended period after any surgical procedure is another advantage. The general indications for epidural anesthesia are the same as those outlined for spinal anesthesia, with the distinct difference that epidural anesthesia allows for continuous anesthesia secondary to placement of an epidural catheter. This makes epidural anesthesia more suitable for procedures of long duration and for extended use in the postoperative period to deliver long-term, titratable analgesia.

Local anesthetics or other analgesic solutions injected into the epidural space spread anatomically. Horizontally, medication spreads to the regions of the dural cuffs, where it is able to diffuse into the CSF and leak into the intravertebral foramen and paravertebral spaces to achieve analgesia/anesthesia. Longitudinally, medication spreads in a cephalad direction, with possible sites of anesthetic action along the paravertebral nerve trunks, intradural spinal roots, dorsal and ventral spinal roots, the dorsal root ganglia, the spinal cord, and the brain. Initial blockade is probably a result of anesthetic blockade at the spinal roots within the dural sleeves.[4] The dural cuffs or sleeves have a proliferation of arachnoid villi and granulations that effectively reduce the thickness of the dura mater, permitting rapid diffusion of anesthetics from the epidural space through the dura and into the CSF. Differences in physicochemical properties of anesthetics (e.g., lipid solubility) may account for the differences in diffusion rates across the dura, which contributes to the variances seen in sensory, motor, and sympathetic blockade.[5] Because epidural anesthesia is diffusion dependent, relatively large volumes (20 mL) of local anesthetics must be used to achieve anesthesia as compared with spinal anesthesia, which routinely only requires 1 to 2 mL. In addition, because epidural anesthesia requires that the medication be delivered to the subarachnoid space by the process of diffusion and spread, anesthesia takes significantly longer to achieve than spinal anesthesia. Given these caveats, any procedure that can be done with the patient under spinal anesthesia can also be done under epidural anesthesia.[4] However, epidural techniques allow for the placement of a continuous catheter, which is especially useful in cases of unpredictable duration, for prolonged postoperative analgesia, and for chronic pain control. In addition, labor epidural analgesia is the only method currently available that can relieve most of the discomfort of labor while minimally affecting maternal or fetal physiology. Labor epidural analgesia is highly satisfactory in these patients because it permits their participation in a comfortable delivery and allows maternal-infant bonding after delivery. Labor analgesia also satisfies obstetricians and anesthesia practitioners in that its flexibility allows quick conversion from an analgesic technique to a surgical anesthetic technique for cesarean section.

Equipment and Techniques

Patient preparation and positioning and the availability of emergency equipment and monitors are similar to the preparation for a spinal anesthetic. With a spinal anesthetic, the practitioner seeks CSF by piercing the dura, while the tip of the epidural needle seeks the fat-filled space deep to the ligamentum flavum and shallow to the dura. The standard epidural needle is typically 16 to 18 gauge and 3 inches long, with a blunted bevel and gentle curve of 15 to 30 degrees at the tip. This blunt bevel and curve allow the needle to pass through the skin and ligamentum flavum and abut against the dura, rather than penetrate through the dura. The two most common epidural needles used in clinical practice with a curvature at the blunt bevel are the Tuohy and Hustead needle designs. The Tuohy needle has the most pronounced curvature (30 degrees) at the tip and is often cited as the easiest for beginning practitioners to place because it allows directional placement of the epidural catheter into the space and the curved, blunt tip is less likely to penetrate into the subarachnoid space. However, it also has been noted that placement of the Tuohy needle can be more difficult because the tip's exaggerated curvature is too blunt, inhibiting penetration through the skin and ligamentum flavum as compared with other needle tips. The Hustead needle is an intermediate needle with a less-pronounced 15-degree curvature that can more easily pass though skin and ligamentum flavum.

A third epidural needle is the Crawford needle. It is a thin-walled epidural needle that does not have the curvature of the Tuohy or Hustead needle. The straight tip may allow easier access through the skin into the epidural space. The Crawford needle is preferred by practitioners when catheter advancement into the epidural space is difficult or the angle of approach is steep, as encountered with thoracic epidural catheter placement. Because the Crawford needle lacks the curvature at the bevel end, it also has been implicated in a higher ratio of accidental dural punctures and is typically not used by beginning practitioners. These three common epidural needles are shown in Figure 44-12.

Smaller-gauge (20- to 22-gauge) epidural needles are available in each needle design for pediatric catheter techniques, regional blocks, and specialty use. Many needle designs incorporate wings near the base or hub. The wings provide a grip for the practitioner that permits distribution of pressure equally over the needle during insertion. The wings and notches in the hub also align with the stylet and needle tip to indicate the direction of the needle tip's bevel and lumen. Needles also may have clear hubs to allow early detection of blood or CSF, plastic stylets to prevent coring, and 0.5- or 1-cm depth markings along the needle shaft.

Epidural catheters also come in a variety of materials and designs. Typically, catheter diameter is 2 gauges smaller than the needle. For example, a 20-gauge catheter would be used with an 18-gauge Tuohy needle. Catheters are constructed of physiologically inert materials designed to resist kinking, compression, and stretching and should be radiopaque. The two most common epidural catheters used in clinical practice are the single-holed, open-ended (uniport) and lateral-holed, closed tip (multiport) epidural catheters. Each catheter design is reported to offer several advantages and disadvantages. Studies that have compared the differences in catheter designs show a significantly lower incidence of inadequate analgesia with multiport catheters but a higher incidence of inadvertent intravenous cannulation.[79] Catheters have markings that identify the tip of the catheter to help verify removal of the catheter and identify when the catheter is at the tip of the needle, with 1-cm markings to measure depth of catheter placement. The depth that a catheter should be threaded beyond the needle tip and into the epidural space is often a controversial topic. Manufacturers of epidural catheters recommend that a catheter should be threaded 1 to 3 cm into the epidural space to avoid possible migration into an epidural vein or through an intravertebral foramen.[15,80] However, in clinical practice practitioners noted that when an epidural catheter was only threaded 1 to 3 cm, a higher incidence of epidural catheter failure could result. Many practitioners reported anecdotally that when the catheter was threaded 3 to 5 cm into the epidural space, a higher success rate without a resultant increase in migration into an epidural vein or intravertebral foramen occurred. This routine clinical practice was validated by Beilin et al.[80] They reported that a catheter insertion of less than 3 cm resulted in a higher incidence of inadequate analgesia, and an insertion depth of more than 5 cm resulted in an increase in inadvertent intravenous cannulation. They recommended that optimal catheter insertion should be 3 to 5 cm into the epidural space.

Proper patient positioning is important to ensure successful catheter placement. Epidural anesthesia is most often instituted with the patient in the sitting or lateral decubitus position and the landmarks, aseptic preparation, draping, and localization are similar to those for a spinal anesthetic. The spine should be in proper alignment, using pillows or pads if necessary, and intervertebral spaces should be identified and marked prior to preparation of the patient's back (see Figure 44-8). In contrast to thin, flexible spinal needles, epidural needles are larger and more rigid. Therefore, placement of the epidural needle does not require an introducer needle and offers better directional control; however, all needle-handling techniques must anticipate patient movement. Whether inserting a spinal or epidural needle into a patient, a similar controlled grip is used to accommodate for potential patient movement. This grip, described earlier as the *Bromage grip* (see Figure 44-11), allows the patient's body to act as a firm support for the needle-stabilizing hand and helps prevent advancement or withdrawal of the needle tip from its position (1) if the patient should move, (2) when the syringe is applied, and (3) as a catheter is passed into the epidural space. The needle is placed bevel tip cephalad through the supraspinous ligament and seated in the interspinous ligament before the stylet is removed. After the stylet is removed, the needle is slowly advanced by use of either the hanging-drop technique or the loss-of-resistance technique into the epidural space.[5]

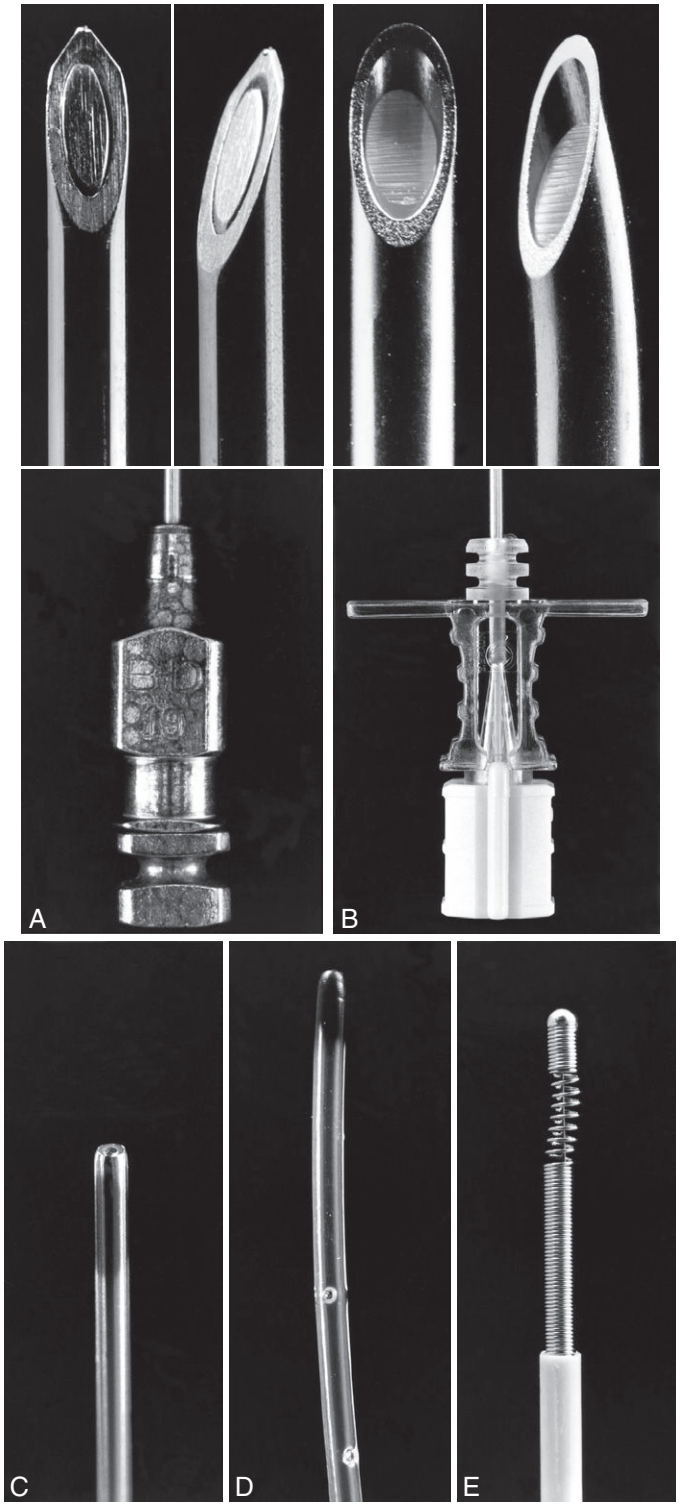

FIGURE **44-12** Epidural needles with catheter assortment. **A,** A 19-gauge, reusable Crawford epidural needle. **B,** A 19-gauge, disposable Tuohy needle. **C,** Single–end-hole epidural catheter. **D,** Closed-tip, multiple–side-hole catheter. **E,** Spring wire–reinforced, polymer-coated epidural catheter. (From Miller RD, et al. *Miller's Anesthesia*. 7th ed. Philadelphia: Churchill Livingstone; 2010;1628-1629.)

After the needle is seated in the interspinous ligament, the hanging-drop technique is accomplished by filling the hub of the needle with saline. The surface tension of the saline creates a droplet hanging on the needle hub. The needle is then advanced slowly in a slight cephalad orientation toward the epidural space. As the needle is advanced through the ligamentous structures, the drop should not move; however, as the tip of the needle enters into the epidural space, the negative pressure within the space will cause the drop of fluid to be drawn into the needle. This aspiration of the hanging drop into the needle signifies that the needle has successfully entered the epidural space. It should be noted that if the needle becomes plugged or the negative pressure in the epidural space is very low, the drop will not be drawn into the hub of the needle and passage into the epidural space will not be recognized. A dural puncture could result. Therefore, the hanging-drop technique is not recommended for the novice practitioner.[5]

The loss-of-resistance technique is the most common method used to enter the epidural space. The epidural needle is placed through the dermis into the interspinous ligament or ligamenta flava, at which time the stylet of the epidural needle is removed. Once the needle has been firmly seated into the ligament, a loss-of-resistance syringe (plastic or glass) containing 2 to 3 mL of normal saline or air and a freely movable plunger is attached. If the needle is properly seated in the ligament, it should be difficult to inject the normal saline or air, and slight pressure on the syringe plunger should result in the plunger springing back to its original position. Some practitioners use a combination of saline and air in the syringe during the loss-of-resistance technique, using approximately 3 mL of normal saline and a small air bubble (0.1 to 0.3 mL). They report that this provides them with a more compressible feel for entry into the ligamentum flavum. If the air bubble cannot be compressed without injecting the normal saline, the needle is most likely not seated into the ligamentum flavum and may still be in the interspinous ligament or off midline into the paraspinous muscles. The needle is advanced toward the epidural space by application of pressure to the needle, not the syringe or syringe plunger. If normal saline is used, constant pressure may be applied to the syringe plunger. Contact with the needle or needle wings is maintained to control needle advancement. As the needle passes through the ligamentum flavum, resistance increases, and it is very difficult to inject either saline or air. Once the bevel of the needle completes the passage through the ligamenta flava and enters the epidural space, an immediate loss of resistance occurs. The contents of the syringe can then be injected gently and without resistance. After the syringe is removed from the needle, an outward rush of a small amount of air or fluid may occur. Penetration of the dura with a large epidural needle usually results in profuse return of CSF; the needle should be removed immediately to minimize CSF loss.

The loss of resistance experienced by a beginning practitioner, or by the experienced practitioner in a patient with difficult anatomy, may not be easily discerned. Sometimes it may be necessary to further evaluate the needle tip's location. For example, several milliliters of air can be injected through the needle while the soft tissue lateral to the spinous process is palpated. If crepitus is felt, the needle is most likely located in the tissues adjacent and shallow to the spinous process. If fluid returns from either the needle or catheter, CSF can be distinguished from normal saline (NS) or local anesthetic. CSF is warm to the forearm, compared with recently administered room-temperature fluids. Glucose test paper will detect the glucose in CSF. Local anesthetics mixed with a similar volume of thiopental will immediately form a precipitate. Multiple tests should be used to achieve the most accurate confirmation of fluid type.

Once the practitioner is reassured of the needle tip's position, an epidural catheter is threaded through the needle and into the epidural space to a depth of 3 to 5 cm. As the catheter is passed into the epidural space, it is important to warn the patient that a "funny bone" sensation may be experienced down one or both legs. This is a paresthesia that may indicate that the catheter has brushed by a nerve root as it was passing into the epidural space or perhaps even lodged into the nerve root. If the paresthesia is persistent prior to or after needle removal, the catheter must be withdrawn and replaced. Injection of medication into a patient complaining of persistent paresthesias can result in nerve-root damage or even nerve-root death and cause long-term morbidities. If the catheter is being replaced secondary to a persistent paresthesia, it is best to move to a new interspace to avoid oversensitized nerve roots. It is important that the needle remain stabilized during catheter advancement. Often if a patient does experience a paresthesia during threading of the catheter, the patient will move reflexively. Unanticipated movement and an uncontrolled needle could result in inadvertent subarachnoid puncture. Once the catheter is threaded approximately 3 to 5 cm, the needle is withdrawn slowly over the catheter. It is common practice to note the depth of the catheter at the level of the skin (by noting the cm-depth mark on the catheter) both prior to and after removal of the epidural needle. Once the epidural needle is removed, the catheter depth should be noted and documented. If the catheter was inadvertently threaded deeper than desired into the epidural space, it should be slightly withdrawn to the desired depth as noted at the level of the skin. If the catheter migrated out of the epidural space, again the depth should be observed and recorded. Finally, if the depth into the epidural space is less than 1 cm, replacement of the catheter should be considered before any attempts are made to inject through the catheter. Never attempt to withdraw the catheter through the needle! This can shear the catheter and embed foreign material in the patient's back. Surgical intervention may be required for catheter remnant removal.

Once a catheter is placed and the needle removed safely, a catheter-to-syringe adapter is placed on the free catheter end. Observe the clear catheter as it enters the back. Look for backflow of CSF or blood. Owing to the greater resistance of a long and narrow catheter compared with a needle, gravity flow alone may not reveal the presence of blood or CSF. Therefore, gentle syringe aspiration is applied to the catheter via the adapter. Because tissue at the catheter tip may create a ball-valve effect, CSF or blood may not flow out; therefore, a negative aspiration test does not guarantee that the catheter tip is in the epidural space. Only if fluids do return does this test confirm that the catheter tip is placed either into an epidural vein or the subarachnoid space. The return of CSF or blood indicates that the catheter should be removed and replaced at a different interspace. To avoid this ball-valve effect or to dislodge any skin or tissue that may have lodged at the catheter tip, some practitioners advocate injection of 1 to 2 mL of normal saline solution through the catheter to confirm catheter patency before injection of medications. After needle removal, the catheter should be taped away from the midline of the back to avoid spinous processes and minimize the risks of catheter displacement from the epidural space or pressure injuries over bony prominences.

Prior to injection of a large amount of medication into an epidural space, a test dose of a small amount of medication is administered to determine whether the catheter or needle has inadvertently entered the subarachnoid space or possibly threaded into an epidural vein. A test dose of 3 mL of a rapid-acting, low-toxicity local anesthetic agent with or without a small

concentration of epinephrine is most typically used. A lidocaine 1.5% with 1:200,000 epinephrine solution provides 45 mg of lidocaine with 15 mcg of epinephrine per 3 mL dose. If the needle or catheter tip is in the subarachnoid space, this dose will result in spinal anesthesia within 3 minutes. If the same test dose is injected into a blood vessel, the 15 mcg of epinephrine will result in a 20% rise in heart rate and systolic blood pressure within 30 seconds. The patient also may experience sensations from the intravascular lidocaine, describing symptoms such as tinnitus, a metallic taste, circumoral numbness, or a rushing sound in the ears. The duration of these test-dose effects is less than 5 minutes. After the test dose is injected, vital signs are reassessed. Additionally, 100 mcg of undiluted fentanyl can be injected as a test dose to avoid potential complications caused by even low doses of epinephrine. If the needle or catheter is intravascular, the patient will experience immediate dizziness and sleepiness from the opioid. Despite all efforts to avoid them, systemic toxic reactions can still occur. Be vigilant, be cautious, and be prepared to handle emergencies.[81-83]

Epidural anesthesia also can be administered by direct injection through the needle once it has been placed into the epidural space. This is called a "single-shot" epidural anesthesia technique, and the same contraindications and safety precautions apply as those already reported for catheter insertion. Once the needle is placed into the epidural space, the end of the open needle is observed for the presence of blood or CSF. Allow a few seconds for gravity flow of fluids to detect blood or CSF when the single-shot technique is used, then attach a syringe for medication administration using needle control techniques previously discussed.

Epidural anesthesia can be performed at any of the four segments of the spine but is most typically performed at the lumbar level. As with spinal anesthesia, there are two approaches, the midline and paramedian approach, that are used to facilitate placement of the epidural needle into the epidural space. The most common approach is the midline approach because it is the easiest to perform and helps place the catheter in the medial region of the epidural space. The paramedian approach is usually selected when surgery or degenerative joint disease contraindicate the midline approach. Using the paramedian approach is more difficult for the beginner because advancement into the interspinous ligament does not occur. The needle advances primarily through paraspinous muscle mass, and resistance is only felt when entering the ligamentum flavum. The technique for paramedian placement involves identification of the desired interspace and the spinous process. The skin surface area approximately 3 cm lateral to the lowest aspect of the spinous process is prepped and anesthetized. The epidural needle is then placed through the anesthetized region and directed toward the midline using a slight cephalad orientation. Once the dermal levels are penetrated and the paraspinous muscle mass encountered, the needle stylet is removed and attached to a syringe containing either air or normal saline (or both) and advanced. The midline of the spine should be encountered approximately 3 to 5 cm from the entry point. The needle is advanced slowly using the incremental approach described earlier through ligamenta flava and then into the epidural space. When a paramedian approach is required by difficult surface anatomy or a steep approach to the thoracic levels is anticipated, the Crawford needle may be preferred. The Crawford needle's straight, blunt bevel allows the catheter to pass directly through the end of the needle, thus facilitating threading of the catheter.

Ultrasound Epidural Placement

The loss of resistance technique using air, normal saline, or a combination of air/normal saline is the gold standard method used by anesthesia practitioners to identify the entry into the epidural space. Traditionally epidural needle placement at a desired interspinous level is determined by palpation of anatomic landmarks; however, appreciating these landmarks can be extremely difficult in some patients. This difficulty could be secondary to obesity and/or scoliosis of the spine, which often require multiple passes with the epidural needle before proper placement or completely abandoning placement attempt secondary to inability to find the epidural space. Despite considerable improvement in the quality of needles and epidural catheters within the last 30 years, the techniques for identification of the epidural space have remained the same, and as described previously, using these techniques to identify the epidural space can be impossible in some individuals.

To facilitate placement of spinal and epidural analgesia/anesthesia, ultrasound has been introduced into clinical anesthesia, and it has been found to be particularly useful in determining the spinous and transverse processes, thereby facilitating easier placement.[84] In addition, ultrasonography also allows the Certified Registered Nurse Anesthetist (CRNA) to adequately determine the distance from the skin to the epidural space, which may result in a lower incidence of accidental dural punctures. There are two useful acoustic windows used to assess lumbar spine anatomy. One of these windows is assessed using a transverse midline approach, whereas the other is assessed using a paramedian longitudinal approach (Figure 44-13). The midline approach allows the anesthetist to adequately identify the midline, whereas the transverse approach allows for assessment of the interspace. In addition, the depth to the epidural space can be determined using ultrasound equipment.

In contrast to the ultrasound machines used for peripheral nerve blocks, which operate using a high-frequency linear probe (10-15 MHz), the ultrasound probe used for spinal and epidural placement needs to be low frequency (2-5 MHz). These low-frequency probes are traditionally curved linear probes of the same type used routinely on pregnant women in labor and delivery to assess fetal function. The ultrasound can be used to identify the epidural space depth and position, or it can be used to facilitate real-time viewing of epidural needle placement into the epidural space. The technique of using one or two operators is well described in the literature.

Technique

An ultrasound (US) machine that is capable of deep scans and equipped with a low-frequency (2-5 MHz) curvilinear probe should be used to facilitate the scan. Two different approaches (longitudinal paramedian and transverse midline) are used to help identify spinous processes, articular processes, ligamentum flavum, anterior dura mater, posterior dura mater, and depth to epidural and subarachnoid space.[85] The patient is placed in a lateral position with flexed knees and hips or in a sitting position with the back curved out to present the spines. After proper positioning of the patient, the low-frequency US probe is placed over the sacral area, 3 cm left of midline and slightly angled toward the center of the spine. The hyperechoic (white) line of the sacrum is identified and then the probe is moved slowly cephalad until hyperechoic sawlike images are seen (see Figure 44-13). These sawlike projections are the articular processes, and between the sawlike images are the vertebral interspaces. Next the ligamentum flavum, posterior dura mater, and vertebral body are identified, and the exact level of each interspace and the spinous process is marked. The probe is then placed horizontal along the midline of the spine at the marked levels of the interspaces and spinous processes. The hyperechoic spinous process is identified using the long triangular

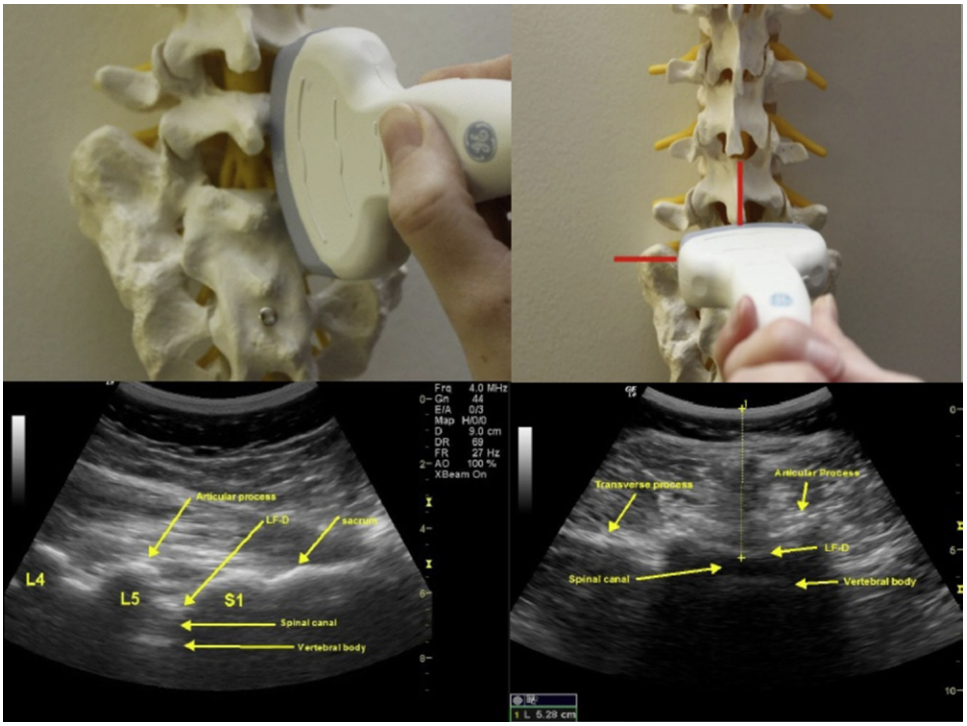

FIGURE **44-13** Orientation of ultrasound probe and identification of underlying structures.

hypoechoic shadow. The probe is moved caudad or cephalad to capture the best view of the interspace, ligamentum flavum, and dorsal dura mater. Once a clear image is obtained, the screen is frozen and the midline is marked along the right lateral surface of the probe. The insertion point is determined by the intersection of the extensions of the two marks on the skin in the vertical and horizontal planes. One mark identifies the midline and the other identifies the interspace (see Figure 44-13). The depth to the epidural or subarachnoid space is obtained from the "frozen screen" of the transverse view using the US machine calipers; one prong of the calipers is placed at the skin and the other at the inner side of the ligamentum flavum.[86]

Epidural Drugs, Spread, and Block Levels

As with any anesthetic technique, the clinical success of epidural anesthesia is often dependent on experience because multiple factors must be managed and balanced to provide safe patient care. Two of these factors, dose and the site of injection, are the most important factors in determining the extent of dermatomal blockade. It should be remembered that the size of the segmental epidural spaces increases down the spinal cord as the spinal cord occupies less and less space. For example, when a very small volume of local anesthetic is injected into the cervical region, it will spread across a larger number of segments as compared with when the same volume is injected into the thoracic region. This is also true when comparing the dermatomal spread between the thoracic and lumbar or caudal regions. The suggested dose of local anesthetic is dependent on the location of the catheter tip as it lies in the epidural space. Common clinical practice is to insert the epidural needle at a vertebral interspace such that the catheter tip falls near the middle of the spinal dermatomes of the proposed surgical incision. For example, an epidural catheter placed for labor or lower abdominal anesthesia would be placed at the L2 or L3 interspace. Placement would be at T8 to T10 for upper abdominal surgery; T4 to T5 for thoracic surgery; and C7 to T1 for chronic pain treatments or surgeries of the arms, shoulders, or upper chest. This has several advantages. The catheter tip, being at the relative center of the spread of the local anesthetic, creates an area of high concentration at the spinal nerves specific to the site of the operation with the least amount of local anesthetic. This high concentration at a specific location results in rapid block onset and greater block density, which often creates a differential blockade that can be controlled by dose.

Dose is described as volume multiplied by concentration. The concentration of the local anesthetic generally affects the density of the block, whereas the volume, within limits, affects the spread from the needle or catheter tip throughout the epidural space. Successful analgesia can be achieved with relatively small volumes and high concentrations of local anesthetics. Clinically useful doses are based on volumes that permit an even filling of the anterior and posterior epidural spaces at the level of insertion. For example, the suggested volumes per segment at the cervical and thoracic levels are 0.7 to 1 mL per segment, remembering that the spread will occur in both a cephalad and caudad fashion. Therefore, an initial total dose, usually less than 10 mL, will achieve a 10- to 14-dermatomal spread of local anesthetic. In contrast, when the local anesthetic is injected at the lumbar level, the volume of local anesthetic required is 1.25 to 1.5 mL per segment. A typical initial volume of 15 to 20 mL is required to ensure adequate anesthesia by blocking a total of 12 to 16 segments (6 to 8 segments above and below the catheter tip). Also, it should be remembered that spread of blockade tends to occur faster in the cephalad direction from the catheter tip, possibly because thoracic nerve roots are smaller in diameter than large lumbar and sacral nerve roots.[4,5,8]

Other factors thought to affect the level of blockade achieved with epidural anesthesia include height, weight, age, patient position during injection, pregnancy, and the speed or mode of injection. However, the clinical significance of these factors has been challenged. Correlations between patient height and weight and the spread of the epidural block are clinically insignificant, except perhaps, in the extremely tall, short, or morbidly obese patient. Studies have examined patients in the sitting and lateral positions

during administration of epidural anesthetics and found small differences in spread and onset that favor the dependent portion of the patient's body. Therefore, provision of anesthesia to the sacral roots might be facilitated by having the patient sit up during the injection. In addition, leaving the patient on the operative side after the solution is injected may speed onset. However, these are clinically small differences and may not always be effective.

Drugs should be injected slowly into the epidural space to avoid rapid increases in CSF pressure, headache, and increased intracranial pressure. A rapid speed of injection has not been shown to increase the spread of anesthetic. Also, incremental or bolus injection modes appear to have no influence on spread. The spread of epidural anesthetics may be three or four dermatomes greater in elderly patients, because age-related tissue changes create a less compliant and less leaky epidural space. Although conflicting data exist, some studies suggest that the epidural spread of anesthetics is greater in pregnant patients.[4,5,8] Therefore, it is recommended that the volume of anesthetic solution administered to pregnant patients and elderly patients should initially be limited to 0.5 to 1 mL per segment when injected at lumbar levels.

The density of block is also more dependent on the concentration of local anesthetic used. The lower the concentration, the lower the effect the local anesthetic will have on the degree of sensory and motor blockade. Routinely a lower concentration of local anesthetic is used to facilitate analgesia (as in laboring analgesia) or to provide a sympathectomy. If the primary purpose of the epidural is to provide complete surgical anesthesia, higher concentrations must be used. Table 44-5 lists recommended volumes of local anesthetic based on the position of the catheter and the location of the intended surgical intervention.

All solutions should be injected in increments of 3 to 5 mL every 3 minutes and titrated to the desired anesthetic level. With loading doses and intermittent injections, aspiration of the catheter should occur before any injection. This gradual administration of the medication slows the rate of onset of the anesthetic level and controls the development of the sympathetic blockade. After a loading dose is given, the anesthetic is maintained with either intermittent dosing or a continuous infusion technique.

Intermittent injections are most often used when high concentrations of local anesthetic (2% lidocaine or 0.5% ropivacaine) are administered. A continuous infusion is more appropriate when the goal of the epidural is to provide a consistent level of analgesia. Continuous infusions typically use a lower concentration of local anesthetic solution (0.0625% to 0.125% bupivacaine or 0.1% to 0.2% ropivacaine), and the level of block is monitored on a regular interval basis. A continuous opioid infusion also may be used either as a sole agent or as an admixture with low concentrations of local anesthetic. Typical infusion rates range from as low as 2 mL/hr for concentrated hydrophilic opioid solutions, such as preservative-free morphine, up to 20 mL/hr for dilute solutions of local anesthesia (0.125% bupivacaine or 0.1% ropivacaine) used for postoperative or labor analgesia. Often continuous infusions will contain a dilute concentration of local anesthetic solution with an admixture of a low-dose lipophilic opioid such as fentanyl, 1 to 5 mcg/mL, or sufentanil, 1 to 1.5 mcg/mL. Epidural infusions of these mixtures augment the quality and duration of analgesia while limiting the side effects of any one drug.

Epidural Opioids

Opioids placed into the epidural space may undergo uptake into the epidural fat, systemic absorption, or diffusion across the dura into the CSF.[87] When administered via the epidural route, opioids produce considerable CSF concentrations of drug. Penetration of the dura from the epidural space into the subarachnoid space is influenced by lipid solubility and molecular weight. The administration of an epidural opioid by either an intermittent or continuous infusion has become common in many anesthesia practices. When an opioid is administered epidurally, it needs to cross from the epidural space through the dura to reach the opioid receptors located in the substantia gelatinosa in the spinal cord. Besides the physical barrier of the dura, epidural opioids also may be deposited in the fat and connective tissues in the epidural space, which may significantly increase the opioid dose required to achieve analgesia. In fact, in order to achieve adequate analgesia from epidurally administered opioids, the dose is increased by approximately 10 times the opioid dose administered intrathecally. Also, the epidural space is highly vascularized, and there is significant absorption of the opioids into the systemic circulation; however, the rate of absorption is dependent on individual pharmacokinetics and lipid solubility of the opioid. For example, epidural administration of fentanyl and sufentanil (highly lipid-soluble opioids) results in a serologic level of opioid similar to that produced when the drugs are administered intravenously. When an opioid is administered by the epidural route, the onset of action and duration are dependent on the type of drug used. A faster onset and analgesic peak effect is achieved when a more lipophilic opioid is used versus an opioid that is more lipophobic. Epidural opioids can be administered by either a single bolus dose or a continuous infusion. A continuous infusion provides easier analgesic titration to patient requirements, which is especially important when a shorter-acting opioid such as fentanyl is used. Epidural opioids also

TABLE 44-5 Recommended Doses for Epidural Analgesia

Procedure	Position of Catheter	Dose (mL)
Chest	T12-L2	8-12
Upper Abdomen		
Cholecystectomy	L2	12-16
Gastric resection	L2	12-16
Incisional pain	L2	7-10
Lower Abdomen		
Colon resection	L2	12-16
Repair of aortic aneurysm	L2	12-16
Retropubic prostatectomy	L3	12-16
Herniorrhaphy	L3	8-12
Incisional pain	L3	8-12
Pancreatic pain	L3	5-7
Hysterectomy	L3	10-14
Lower Extremities		
Anesthesia	L4	10-14
Sympathetic block	L2	5-7
Perineum		
Transurethral resection of prostate	L4	8-12
Vaginal hysterectomy	L4	8-12
Back and Flank		
Nephrectomy	L2	10-14
Vaginal Delivery		
First-stage labor	L3	5-7
Second-, third-stage labor	L3	10-12

can be administered using patient-controlled (assisted) epidural analgesia (PCEA), which is a hybrid of continuous infusion and patient-assisted boluses to titrate analgesic requirements based on individual patient needs. The goal is to establish a continuous or "basal rate" infusion to optimize the analgesic effect. The PCEA bolus component can then be preset by the anesthesia practitioner to meet individual patient requirements and used in the event of breakthrough pain.[87] Table 44-6 lists the opioids and dosages most commonly used to achieve epidural-based analgesia.

Extended-Release Epidural Morphine (DepoDur). A sustained-release formulation of morphine sulfate (DepoDur; SkyPharma, San Diego, Calif) is newly available for use in the treatment of acute postoperative pain. DepoDur consists of microscopic spherical particles with integral aqueous chambers separated by lipid membranes containing an encapsulated dose of morphine. DepoDur is unique in that it delivers standard morphine sulfate using DepoFoam technology. DepoFoam (also from SkyPharma) is a drug-delivery system composed of multivesicular lipid particles containing nonconcentric aqueous chambers that encapsulate the morphine sulfate, allowing the morphine to be released over an extended period of time (up to 48 hours) without a requirement for subsequent dosing.[87,88] The half-life of DepoDur is dose dependent, but the DepoFoam technology allows for larger doses to be administered than could be given when conventional epidural injection is used. For example, a study done by Carvalho et al.[88] compared analgesia and side effects in groups of cesarean section patients receiving either a single epidural injection of 5 mg of preservative-free morphine or 5, 10, or 15 mg of DepoDur. After cord clamp, the authors noted that patients who received the 10- and 15-mg doses of DepoDur had significantly lower pain scores and analgesic requirements for the first 48 hours after cesarean delivery.

DepoDur is intended to be used as a sole agent and cannot be administered concomitantly with a local anesthetic solution. Because DepoDur is encapsulated by DepoFoam technology, studies have shown that administration of any local anesthetic solution may elicit a physicochemical interaction and cause a reduction in the sustainability of the DepoFoam to release the morphine over an extended period of time. This can result in an increase in the quantity of the encapsulated morphine released to the systemic circulation and place the patient at increased risk for respiratory depression and hypotension. The full extent of this interaction is being investigated by the manufacturer. This recommendation for not mixing with local anesthetics does not preclude the anesthetist from testing the epidural catheter for possible subarachnoid or intravascular migration preceding injection, and it is recommended that a routine test dose be performed prior to injection of the DepoDur, with some added precautions. The manufacturer recommends that the test dose be administered using prescribed techniques, then the catheter should be flushed with at least 1 mL of 0.9% NaCl solution a minimum of 15 minutes prior to injection of the DepoDur. It has also been recognized that sustained levels of analgesia from DepoDur require a minimum dose of 10 mg. Current research shows that when a dose of 5 mg of DepoDur is administered, the terminal half-life of the morphine is comparable to a similar 5-mg dose of standard morphine.[88]

Management of Epidural Anesthesia

After epidural administration of local anesthetic, the spread of the dermatomal block will continue and peak in an amount of time dependent on the factors previously mentioned and the local anesthetic solution used. Typically the time to maximal spread is between 10 and 25 minutes, and the level of the block will regress over time; therefore, consistent monitoring of sensory dermatomal level should be performed. When the sensory level of the block has diminished by one or two dermatomes, as detected by the "scratch" or "ice" test used to denote dermatomal level, then another dose, 30% to 50% of the initial dose, is given to reestablish the initial level of anesthesia. It is important to perform consistent monitoring of the anesthetic level because tachyphylaxis, or the need for an increase in the dosage required to maintain an adequate level of blockade, may occur if the regression is allowed beyond two dermatomal segments. The phenomenon of

TABLE 44-6 Recommended Doses of Epidural Opioids

	ANALGESIA				CONTINUOUS INFUSION RATE			
Agent	**Bolus Dose**	**Onset (min)**	**Peak (min)**	**Duration (hours)**	**Range (mL/hr)**	**Basal Rate (mL/hr)**	**PCEA Bolus (mL)**	**Interval (min)**
Morphine	3-5 mg	20-30	30-60	12-24				
Morphine 0.05%-0.1% solution					1-6			
Morphine 0.05%-0.1% + bupivacaine 0.0625%-0.125%					3-6	3-4	1	20
Morphine 0.05%-0.1% + ropivacaine 0.08%-0.2%					2-4	3-4	10	20
Meperidine	25-100 mg	5-10	10-30	4-6				
Meperidine 0.1%-0.25% bupivacaine 0.0625%-0.125%					2-10	5	1	12
Hydromorphone	1 mg	10-15	20-30	8-15				
Hydromorphone 0.05%					0.8			
Fentanyl	50-100 mcg	5-10	20	2-6				
Fentanyl 0.001%-0.002%					4-12			
Fentanyl 0.001% + bupivacaine 0.0625%-0.1%					4-10	5	1	12
Sufentanil	10-60 mcg	5-10	20-30	4-6				
Sufentanil 0.0001%					10			

tachyphylaxis is poorly understood but is more likely to occur with short-acting amides such as lidocaine or mepivacaine. It can be avoided by using longer-acting agents (e.g., bupivacaine, ropivacaine, and tetracaine) or using a continuous infusion device.

One of the most frustrating problems that can occur with epidural anesthesia is the phenomenon of an inadequate block, a one-sided block or single-sensory dermatome segment that fails to achieve adequate anesthesia. A variety of techniques are used to deal with this phenomenon. Some anesthetists will attempt to increase the spread of the local anesthetic to the area of missed dermatomes by repositioning the patient with the unblocked side down (dependent) or by administering more local anesthetic solution. An inadequate block could be secondary to coiling of the epidural catheter or an anatomic abnormality. However, inadequate anesthesia during epidural anesthesia placement may be secondary to the technique used during identification of the epidural space. Studies have shown that using air during the loss-of-resistance technique may be a contributing factor in missed dermatomal spread of the local anesthetic. Studies by Beilin et al.,[89] Valentine et al.,[90] and Shenouda and Cunningham[91] report that when air was used during a loss-of-resistance technique, a significant number of patients experienced "missed" dermatomal spread of the local anesthetic solution. They recommend using normal saline during catheter placement to minimize this complication.

Rarely an epidural catheter passes through dura but without penetrating the arachnoid membrane. This is sometimes thought of as intradural placement. Spread of the injected anesthetic in this situation can be very unpredictable. Anesthesia can range from a patchy, inadequate block to a rapid and high level of anesthesia requiring ventilatory support, similar to the total-spinal anesthetic complication. Fortunately, intradural catheter placement is rare, and complications can be avoided by the careful use of test doses, maintained vigilance, and a high index of suspicion. If an intradural catheter placement is suspected, the catheter needs to be removed and replaced after resolution of any side effects (e.g., hypotension, bradycardia). Additionally, it is recommended that the catheter be replaced at a dermatomal level more cephalad to the interspace previously attempted.[5,14]

Complications of Epidural Anesthesia

As with spinal anesthesia, the hemodynamic changes seen with epidural anesthesia are attributed to sympathetic blockade and subsequent arterial and venous dilation. Use of plain local anesthetic solutions in the epidural space to create a high level of blockade will decrease the mean arterial pressure, cardiac output, stroke volume, heart rate, and peripheral vascular resistance. The addition of epinephrine (usually a 1:200,000 to 1:400,000 solution) to the epidural local anesthetic solution diminishes and slows systemic uptake, resulting in lower plasma levels of the local anesthetic and prolongation of its duration of action. However, the epinephrine is thought to be absorbed systemically in low levels, thereby causing β_2-adrenergic vasodilation. The result is lower arterial pressure and peripheral resistance when compared with spinal anesthesia. Treatments of these hemodynamic alterations are very similar to those used for effects of spinal anesthesia. They include ephedrine 5 to 10 mg, phenylephrine 50 to 100 mcg, or a low- to moderate-rate infusion of dopamine, keeping in mind the caveats for use of these potent vasopressors. Atropine or glycopyrrolate is also useful for the treatment of bradycardia.[4,8]

One complication that is more prevalent with epidural anesthesia than spinal anesthesia is backache. The incidence of back pain after epidural anesthesia is between 30% and 45%, especially in the obstetric patient.[15] There have been several studies that have identified various techniques to use to decrease the incidence and severity of back pain after epidural anesthesia. For example, Todd et al.[92] analyzed what effect the addition of ketorolac to the dermal anesthesia solution would have on the overall incidence and severity of back pain after laboring epidural placement and delivery. These authors reported that the addition of 6 mg ketorolac to 3 mL 1% lidocaine dermal anesthetic solution resulted in a decrease in the incidence and severity of back pain in the postpartum period as compared with a similar group receiving 1% lidocaine solution alone for dermal anesthesia prior to entry of the epidural needle through the skin.[92]

Other complications associated with epidural catheters are similar to those associated with spinal anesthesia and have already been discussed. As with spinals, the overall risk of PDPH is low. For placement of epidural catheters, the PDPH rate is 1% to 2%. However, epidural needles are large in diameter compared with spinal needles. Although the goal of an epidural catheter technique is to avoid puncture of the dura, an inadvertent rent created by a 17-gauge Tuohy is a rather large dural perforation and is referred to as a "wet tap" for the quite brisk free flow of CSF that can escape through the needle. With such a rent in the dura, the incidence of PDPH can be as high as 75% in young patients. Epidural catheters are also more likely to place a patient at risk for neuraxial anesthesia complications than the single passage of a smaller-gauge spinal needle because the catheter acts as a foreign body that remains within the patient. The catheter causes mechanical tissue disruption, acts as a physical irritant, may provide a path for infection, and will cause tissue trauma on removal—perhaps as much trauma as that associated with catheter placement. Therefore, although complications are rare overall, patients must be followed closely in the postoperative period for signs and symptoms of neurologic compromise such as spine ache, root pain, weakness, and bowel or bladder dysfunction.

COMBINED SPINAL AND EPIDURAL ANESTHESIA

First described in 1937, the combined spinal epidural (CSE) anesthesia technique has risen in popularity and is used successfully for orthopedic, urologic, and gynecologic surgeries and for providing postoperative pain relief. It also has gained favor in the obstetric suite for providing anesthesia and analgesia for labor and delivery and for cesarean section.[93-97]

CSE anesthesia and analgesia offers the advantages of both spinal and epidural techniques while reducing or eliminating the associated disadvantages.[5,53] The CSE technique is appropriately used in any setting in which the practitioner plans a spinal or epidural anesthetic and desires to exploit the advantages of each technique—usually the quicker onset of the spinal anesthetic combined with the flexibility of an epidural catheter.

History and Development

In 1937, Soresi described the sequential injection of local anesthetic, first into the epidural space, then into the subarachnoid space, using the same small-gauge spinal needle. Soresi described placing an epidural needle (without a stylet) into the epidural space using a hanging-drop technique and injecting 7 to 8 mL of procaine, then advancing the needle into the subarachnoid space, where he injected 2 additional mL of procaine. He reported the anesthesia lasted between 24 to 48 hours. His experience using this technique in more than 200 patients led him to state that "by combining the two methods many of the disadvantages of both methods are eliminated and their advantages are enhanced to an almost incredible degree."[98]

In 1979, Curelaru reported application of the CSE technique in 150 patients. He used a two-puncture technique; he placed an epidural catheter first, using a standardized epidural needle, followed by a subarachnoid puncture, using a spinal needle one or two interspaces below the level of the epidural puncture. Advantages of the technique included "the possibility of obtaining a high quality conduction anesthesia, virtually unlimited in time, the ability to extend over several anatomic regions the surgical field, minimal toxicity, the absence of postoperative pulmonary complications, and the economy." Disadvantages included "the need for two vertebral punctures, the longer induction time of anesthesia, and some difficulty in finding the subarachnoid space after catheterization of the epidural space."[99]

Finally, in 1982 Coates[95] used a single-space technique in which a long spinal needle was inserted through the epidural needle to provide the spinal component of the CSE technique.[94] Coates stated that the technique was "simple, reliable and quick to perform." He was, however, concerned that "the theoretical hazards of this technique include the possible passage of the epidural catheter through the hole in the dura mater and the possibility of subarachnoid effects from epidurally injected drugs by passage through the hole in the dura." Eldor[96] described finding metallic particles while using the needle-through-needle technique, supposedly formed by abrasion of the inner surface of the epidural needle by the passage of the spinal needle. They were concerned that these particles might be introduced into the epidural space. In addition, they were concerned that uneven distribution of the spinal local anesthetic was possible. The delay, they theorized, inherent in introducing the epidural catheter after intrathecal administration of local anesthetic could affect the spread of the anesthetic. These concerns led to the development of a combined spinal-epidural needle with two separate conduits to allow the epidural catheter to be placed first, followed by the spinal puncture. Because the needle had two conduits, it allowed both techniques to be performed with one puncture at one interspace. This innovation led to the development of several needle types, each of which sought to improve on the others.

Equipment and Techniques

Two-Level Technique

The two-level technique is unique in that each component is performed separately at two different interspaces. An epidural catheter is inserted first, followed by a spinal anesthesia needle placed one or two interspaces lower. The primary advantage of this technique is the ability to insert and test the epidural catheter first, then place the spinal anesthetic needle. Once the spinal needle is placed, no delay occurs in positioning the patient, which may be an important factor when using a hyperbaric spinal anesthetic solution. Prior placement of the epidural catheter is not entirely benign. Potential problems include the inability to distinguish the epidural test dose from the spinal block, inability to differentiate the epidural test dose from CSF, epidural catheter laceration by the spinal needle, misdirection of the spinal needle by the catheter, inability to obtain CSF because of compression of the dural sac by the test dose, and an increased risk of dural puncture by the epidural catheter.[91] Other disadvantages include increased discomfort, tissue trauma, and morbidity associated with multilevel interspinous space penetration (e.g., backache, epidural venous laceration, hematoma, infection, and technical difficulties).[97]

Single-Level Technique: Needle Through Needle

First described in 1982, the needle-through-needle technique involves insertion of an epidural needle at the appropriate interspace and then using the epidural needle as a guide for the spinal needle.[92,93] A small (25-, 27-, or 29-gauge) pencil-point spinal needle is inserted through the epidural needle into the subarachnoid space, and local anesthetic is injected. The spinal needle is removed, and an epidural catheter is threaded into the epidural space. The epidural needle is removed, and the catheter is secured. The main advantages are related to performance of a single interspace insertion (e.g., less tissue trauma, backache, and associated morbidity). Disadvantages include the possibility of inadequate spinal block if catheter placement is delayed, potential for increased nerve-root trauma if paresthesias occur during catheter insertion, and the inability to reliably test the catheter with a preexisting spinal block. Inability to obtain CSF because of inadequate spinal needle length is a risk avoided by the use of the appropriate specialized needles.

Specialized Needles

Eldor[96] was the first to develop and patent a combined spinal-epidural needle with two channels—one for the epidural catheter, the other for the spinal needle. The needle is placed at the selected interspace, the epidural catheter is inserted through its designated conduit, and then the spinal needle is placed through its conduit. Once CSF is obtained, the chosen local anesthetic is injected, and the needle is removed. The catheter is taped in place, and the patient is positioned. Purported advantages and disadvantages are similar to those described for the single-level technique. Although the risk of metallic particle formation may be reduced, the risk of trauma to the interspinous ligaments is increased because of a larger needle diameter.

Several other needles have been developed, all seeking to minimize or eliminate potential problems.[96] To reduce external size, decrease needle abrasion, and allow for a direct angle of approach to the dura, a Tuohy needle was modified with a separate back-eye at the bend of the needle, thereby permitting straight passage of the spinal needle. These needles are subject to their own limitations and failure rates as well. The spinal needle can miss the back-eye hole and exit the epidural needle through the main orifice, as occurs in the needle-through-needle technique.

Sequential Technique

Rawal et al.[94] described a single-level "sequential" technique that was developed to minimize the hypotensive effects of the spinal component of CSE anesthesia for cesarean section. An epidural needle is placed at the selected interspace, and a low-dose (7.5 mg of hyperbaric bupivacaine) spinal anesthetic is placed using the needle-through-needle technique. The spinal needle is removed, the catheter is inserted and taped in place, and the patient is placed in the supine position with a left lateral tilt. After 15 minutes, the block is extended by titrating epidural local anesthetic until the desired level is achieved (1.5 to 2 mL for each unblocked segment). Although this technique takes longer to perform, it has been shown to decrease the frequency and severity of the hypotension seen with spinal anesthesia. This technique has also been applied in other types of surgery.

Agents

As discussed previously, local anesthetic agents and their concentration are chosen depending on the effects desired. Appropriate anesthetics for the spinal component include isobaric or hyperbaric 5% lidocaine with or without epinephrine, hyperbaric 0.75% (spinal) bupivacaine, and isobaric or hyperbaric 1% tetracaine. Appropriate anesthetics for the epidural component include 2% lidocaine with or without epinephrine, 0.5% or 0.75%

bupivacaine, 2% or 3% 2-chloroprocaine, and 1% ropivacaine. The concentration of these agents may be adjusted to provide postoperative analgesia in combination with opioids such as morphine and fentanyl. All agents should be preservative free to reduce or eliminate any neurotoxic effects.

Management of CSE Anesthesia

Although the CSE technique may be used in any type of surgical procedure in which a spinal or epidural would be acceptable, this technique may be particularly well suited to providing analgesia and anesthesia in obstetric patients. The CSE technique offers several potential advantages over conventional epidural anesthesia and analgesia.[93]

- Rapid onset of the intrathecal component for women who are in the later stages of labor and in significant pain and distress
- The use of intrathecal opioids (e.g., fentanyl, sufentanil, morphine, and meperidine) in early labor; the minimal-to-absent motor block associated with intrathecal opioids allows the patient to ambulate while in labor

The CSE technique for the laboring patient usually involves the placement of an epidural needle at the selected (usually lumbar) interspace, followed by the placement of the spinal needle using the needle-through-needle technique. Intrathecal opioids (5 to 15 mcg of sufentanil or 25 to 50 mcg of fentanyl) may be given alone or in combination with a small dose (2.5 mg of bupivacaine) of local anesthetic, saline, or both. The spinal needle is withdrawn, and the epidural catheter is inserted. The epidural needle is removed, and the catheter is taped in place. The catheter can be activated at any time if supplemental analgesia or anesthesia is required. Standard testing of the epidural catheter before use is always recommended.

The CSE technique also can be used to provide anesthesia for cesarean section if required. If the patient already has an epidural catheter in place, a test dose (3 mL 1.5% lidocaine with 1:200,000 epinephrine) is given to rule out intrathecal and intravascular placement. After a negative test dose, incremental administration of 2% lidocaine, 0.5% bupivacaine, or 3% 2-chloroprocaine can be used to establish a level of surgical anesthesia.

If a catheter has yet to be placed, and if time allows, the anesthetist can proceed as with any new patient. After the spinal needle is placed, an intrathecal dose of local anesthetic (12 to 15 mg of 0.75% bupivacaine) with or without opioid (10 to 15 mcg of fentanyl, 0.2 to 0.3 mg of preservative-free morphine, or both) is given. The catheter is inserted and taped in place. The spinal anesthetic will set up quickly and allow for urgent (but maybe not emergent) delivery.

Despite the utility and flexibility of the CSE technique, several concerns related to its use exist. The first of these concerns is related to the use of intrathecal sufentanil and its associated hypotension.[100] Controversy exists with regard to whether intrathecal sufentanil causes clinically significant changes in blood pressure and fetal heart rate (fetal bradycardia). Purported mechanisms include pain relief, mild sympatholysis, and uterine hypertonus.[101-103] Studies show no differences in outcome between CSE using intrathecal sufentanil and epidural anesthesia.[104,105]

A second concern with CSE analgesia is the ability to ambulate after receiving intrathecal narcotics. The concern is related to possible motor weakness if low-dose local anesthetic is added and regarding the effects on blood pressure.[106] Hypotension appears within the first 30 minutes after intrathecal fentanyl but remains stable through ambulation and follow-up doses of epidural local anesthetic. Studies demonstrate the safety of allowing ambulation with no apparent deleterious effects.[107]

A third concern with CSE technique in laboring patients is related to complications. Overall, the complications of itching and hypotension, although bothersome, do not appear to significantly affect outcome or patient satisfaction.[89] CSE anesthesia is associated with faster onset, denser motor block, lower anxiety, lower preoperative and intraoperative pain scores, and greater patient satisfaction preoperatively. There were no significant differences in the incidence or severity of hypotension or nausea, the need for supplemental analgesics, or the postoperative assessments of intraoperative pain, anxiety, and satisfaction.[108,109]

Complications of CSE Anesthesia

Spinal and epidural anesthesia both have their own associated complications as discussed. The CSE technique has the same complications and some additional unique complications. Therefore, as always, vigilance is prudent.

Failure to Obtain a Subarachnoid Block

The failure rate for subarachnoid block alone ranges from 3.1% to 17%. With the single-level CSE technique for anesthesia, the range is 0% to 24.5%, and for the two-level technique, the range is 1.6% to 4%.[110-112] Failure with the single-level CSE technique may occur because the epidural needle is not in the epidural space, because the epidural needle is off midline, because the spinal needle is too short (or dull) and does not penetrate the dura, or because the angle of approach of the spinal needle is too oblique to puncture the dura.

One of the most important considerations is the length of the spinal needle—specifically, the length of needle that extends beyond the tip of the epidural needle.[97] Studies have shown an increased success rate when the tip of the spinal needle extends 7 to 15 mm beyond the tip of the epidural needle.[112,113] The angle at which the spinal needle approaches the dura also may be important. As the spinal needle exits a standard epidural needle tip, the angle caused by the epidural needle's curve may be 4 to 5 degrees or more.[114] This factor, combined with inadequate needle length, may result in failure to obtain CSF. This situation has led to the development of a modified Tuohy needle that has a separate backeye at the bend of the needle to allow for a straight-on approach to the dura. Pan[115] determined that the success rate for the needles exiting the correct hole ranged from 50% to 67%. The success rate can be improved to 81% to 94% by bending the spinal needle slightly in the direction of the epidural needle bevel and to 91% to 96% by orientating the epidural needle bevel upward.

Failure rates also may be directly related to level of experience with the technique and are not easily correctable. The problem of spinal needle displacement during connection of the syringe, aspiration, or injection of the local anesthetic has led to the development of "locking" devices that fix the spinal needle in the epidural needle once the dura has been punctured. Their efficacy has not yet been confirmed.

Catheter Migration

Another problem with the needle-through-needle technique is the possibility of catheter migration through the dural puncture caused by the introduction of the spinal needle.[114] Studies that assessed the risk of catheter migration through a dural puncture site demonstrated little to no risk if the dural puncture was made with a 25-gauge or smaller spinal needle, but an increased risk if the dural puncture was made by a larger (18-gauge) Tuohy needle.[116-118] Many factors may result in catheter placement in, or migration into, the subarachnoid space, including patient movement, undetected dural puncture with the epidural needle with

subsequent catheter placement, and (least likely) diffusion of local anesthetic from the epidural space into the subarachnoid space through the dural puncture. The prudent practitioner is advised to adopt a conservative approach that includes a high index of suspicion and frequent aspiration and testing of the catheter.

However, even the question of when to test the epidural catheter can be problematic. The purpose of the epidural catheter test dose is to rule out inadvertent placement or migration of the catheter into the subarachnoid space or into an epidural vein. A preestablished subarachnoid block may preclude the ability to reliably test for subarachnoid catheter placement and mask intravascular placement. To date, no published studies have demonstrated reliable detection of inadvertent subarachnoid catheter placement in someone with a preexisting spinal block.

Increased Spinal Level After Epidural Administration

The CSE technique is known to cause an increased spread of spinal anesthesia after injection of solutions through the epidural catheter. Although controversial, several theories may help explain this phenomenon. The first, the "volume effect" theory, states that the volume of fluid injected into the epidural space compresses the subarachnoid space and the CSF within it, thereby increasing the spread of the intrathecal local anesthetic. This effect has been documented clinically and by the use of contrast media and radiography. The second theory presupposes a "leak" or flow of local anesthetic from the epidural into the subarachnoid space through the dural puncture. This effect also has been demonstrated clinically and by radiography.[119,120] Other radiographic studies have been unable to confirm these results.[118,121]

Metallic Particles

Eldor and Levine[110] noted the production of metallic particles when passing a spinal needle through a Tuohy epidural needle. Subsequently, Eldor[122,123] has implied that scratches in the spinal needle and metallic particles may be associated with an increase in aseptic meningitis and cancer in patients who have received CSE anesthesia via the needle-through-needle technique. No studies have been published to support these assertions, but several studies have examined the issue of metallic particle formation.[124] These studies used electron microscopy, atomic absorption spectrography, photomicrography, and microscopy; none were able to detect metallic particle formation.[118,125]

Postdural Puncture Headache

Conflicting evidence exists regarding whether a greater risk of PDPH is associated with the CSE technique compared with conventional epidural anesthesia and analgesia. Both techniques involve the placement of an epidural needle, with its attendant risk of dural puncture. In addition, the CSE technique involves a dural puncture, usually with a small-gauge, pencil-point spinal needle. Because this type of spinal needle is associated with an extremely low incidence of PDPH, one would expect an equally low incidence with the CSE technique. A review of the literature on the CSE technique shows a PDPH rate between 0% and 2.3% in laboring patients.[126] Theoretic reasons for a low incidence with the CSE technique include the following:

- The epidural needle serves as an introducer for the smaller-gauge spinal needles and allows for a straight approach at the dura.
- CSF leakage through the dural puncture is abated because of the presence of the epidural catheter and fluids, which increases pressure in the epidural space.
- The spinal needle penetrates the dura at a slight angle, which may help dural fibers seal the hole on withdrawal.

Studies suggest that the use of intrathecal opioids as part of the CSE technique may offer a protective effect from PDPH.[127,128] In addition, the success rate in obtaining CSF may be higher when the patient is in the sitting position, rather than the lateral position. The sitting position allows for correct midline placement of the epidural needle and makes it more likely that CSF will be obtained with the spinal needle (higher hydrostatic pressure). Both of these factors contribute to minimization of the number of dural punctures and may decrease the risk of PDPH.

Infection

The incidence of infectious complications associated with epidural and spinal anesthesia has always been considered to be very low—in the range of 0% to 0.04%.[30,129,130] However, perhaps because of close monitoring of this newer technique, an increase has occurred in the number of case reports of patients who have developed complications that may be associated with the use of the CSE technique. Bouhemad et al.[131] cite several cases (three between 1994 and 1998) of bacterial meningitis associated with the use of CSE. The authors believed that potentially infectious skin matter was first introduced into the epidural space during the insertion of the epidural needle and was then introduced into the CSF by the passage of the spinal needle into the subarachnoid space. Because the CSE technique requires invasion of both the epidural and subarachnoid spaces, strict aseptic technique should be practiced. As with other complications associated with the use of CSE, further study of this area is warranted.

Neurologic Injury

Neurologic injury associated with spinal and epidural anesthesia is also very low, ranging from 0.02% to 0.1%, and is usually transient in nature.[5] Although there does not appear to be any increased risk inherent in the CSE technique as compared with either spinal or epidural anesthesia alone, there have been several case reports of cauda equina syndrome in patients who underwent CSE anesthesia.[132,133] In none of these cases was the cause ever identified. Possible causes include preexisting spinal deformity (present in one case), use of lidocaine (present in one case), and an intrathecal catheter (never proved or disproved).

A final concern with the use of the CSE technique is paresthesia on epidural catheter insertion. A preexisting spinal block may mask a significant paresthesia on catheter insertion and result in neurologic injury. Paresthesias during epidural catheter placement range in frequency from 20% to 44%.[134] However, studies show no significant difference in the frequency of paresthesias reported for either technique.[112,134]

CAUDAL ANESTHESIA

Caudal anesthesia can be thought of as a distal approach to the epidural space. Therefore, anesthetics administered or catheters placed via the caudal route will act as epidural administered anesthetics, but first on the sacral dermatomes. A caudal technique is useful for perirectal surgery, urologic surgery, and orthopedic surgery of the lower extremity. Caudal techniques are especially useful in pediatrics but also can be used for labor and delivery and for chronic pain states. With the success of lumbar epidural catheters for labor and delivery, caudal anesthesia is rarely used in this population currently and is less likely to be used in the adult population in general. After the age of 12, sacral anatomy changes and bone growth makes identification of the epidural space by this approach

difficult and the spread of anesthesia less reliable.[8] Therefore, caudal anesthesia is most often used in combination with a light general anesthetic to augment postoperative analgesia in preadolescent pediatric patients.

Equipment and Techniques

The patient can be placed either prone or in a lateral position. The posterior iliac spines and the sacral hiatus are identified. Positioning the patient prone with the legs slightly apart, the heels rotated outward, and a pillow under the buttocks facilitates the palpation of the cornua of the sacral hiatus. In the lateral, Sims, or knee-chest position, identification of the cornua can be enhanced by adjusting the amount of hip flexion. Excess flexion can stretch the skin, making landmark identification difficult. An assistant is often useful when one is positioning patients who are anesthetized.

In pediatric patients, general anesthesia is usually induced, the airway and intravenous access secured, and the patient turned prone or placed in a lateral decubitus position. After aseptic preparation is performed, the index and second fingers of one hand are placed on the cornua of the sacrum, with the hand cephalad and against the patient's back. A 22- to 25-gauge short needle attached to a 10-mL syringe filled with local anesthetic is inserted midline between the cornua at a steep angle to the skin into the sacral hiatus. Alternatively, a 20-gauge over-the-needle intravenous catheter is sufficiently long enough for the block, and the catheter can be passed into the epidural space while the needle is removed. This allows the anesthetist better control when administering the local anesthetic. The needle is inserted, with the bevel of the needle directed toward the sacrum. As the membranes are penetrated and the ventral canal of the sacrum is entered, a popping sensation can be felt. At this point the needle angle is lowered parallel to the sacrum and the spinal canal. The needle is advanced into the epidural space for a distance of 1 to 3 cm but no farther than the second sacral interspace. The second sacral interspace lies 1 to 2 cm below a line drawn between the posterior iliac spines. The needle position is evaluated for entrance into the subarachnoid space or epidural veins via gentle aspiration and examination for CSF or blood return through the needle. Once the appropriate location of the needle is verified, the anesthetic is incrementally injected as with an epidural. During injection the skin area above the end of the needle is palpated. Bulging over the needle tip indicates subcutaneous or superficial injection rather than injection into the epidural space. If the needle is in the subperiosteal area, resistance to injection is felt, and the needle must be repositioned.

Agents

In children, 0.5 to 1 mL of solution per kilogram of body weight is injected to reliably achieve a level of analgesia to the umbilicus. Bupivacaine or ropivacaine, in concentrations of 0.125% to 0.5%, are usually administered with epinephrine 1:200,000, to a maximum dose of 2.5 mg/kg body weight. These dosing regimens have been shown effective for children undergoing subumbilical surgical procedures providing analgesia or anesthesia for the lower extremities and the abdomen, urogenital surgery, inguinal hernia repair, or orthopedic procedures with analgesia that lasts 3 to 5 hours postoperatively.[8,135,136] Clonidine 1 mcg/kg of body weight added to the local anesthetic has been shown to be comparable with opioids that are added to enhance analgesia. Clonidine has fewer side effects than caudal opioids (e.g., delayed recovery, respiratory depression, and nausea).[137] Some patients may be unable to tolerate the loss of lower-extremity motor control. These patients should be identified before the anesthetic is administered and be offered another technique. For example, infants too young to walk greatly benefit from caudal analgesia, but toddlers may be frightened by their inability to move their legs. Ropivacaine may have benefits over bupivacaine, because analgesia in the postoperative period is equivalent, but ropivacaine offers shorter duration of motor blockade and less risk of CNS and cardiotoxicity.[8,135-138]

In adults, the principles of epidural drug administration should be followed, with use of a 3-mL test dose and incremental injections and aspiration. Only 12 to 15 mL is necessary for sacral anesthesia, and up to 20 to 30 mL offers sufficient spread for lower-extremity procedures to approximately the 10th thoracic dermatome. The spread of drug, duration of anesthesia, and desired level of anesthesia are less predictable than with epidural anesthesia because of the variability in the volume, content, and leakage of the caudal canal. The maximum recommended dose of lidocaine or mepivacaine is 10 mg/kg of body weight and 2.5 mg/kg of body weight for bupivacaine.[8] All agents injected into the epidural or subarachnoid spaces should be preservative free.

Management of Caudal Anesthesia

Caudal anesthesia, like epidural anesthesia, is adaptable to a continuous catheter technique. However, if a Tuohy needle is used, the angle of the tip must be kept in mind when one attempts to pass the catheter into the epidural space. Management is similar to that with an epidural catheter.

Complications of Caudal Anesthesia

Caudal anesthesia has complications that are very similar to those of epidural anesthesia. The caudal canal has a sacral epidural venous plexus with vessels that can be unintentional recipients of a needle or catheter tip, with subsequent intravenous injection of local anesthetic. Dural puncture is also possible, although the dural sac usually ends in adults at the lower border of L2, and in infants the sac can extend to S4. High spinal punctures are less likely but have been reported. In addition, the anatomy of caudal anesthesia is variable enough, especially in adults, to cause a high (10% to 15%) failure rate as the needle is unintentionally inserted into false passages. The proximity of the caudal canal to the rectum theoretically makes infection a potential risk, although clinically significant infection is rarely reported.[8,139] The risk of infections, perhaps, will best be shown to be minimized with the use of chlorhexidine solutions instead of povidone-iodine solutions.[140]

In 1899, Alice Magaw described the job of an anesthetist and best summarized the reality of the practice of regional anesthesia. She stated, "While one should be competent in the theoretical part of this important work, there is nothing so helpful to the anesthetist as the hard school of practical experience."[141]

SUMMARY

Regional anesthesia techniques are a vital part of modern anesthesia practice. Our ability to understand and apply neuraxial anesthesia continues to evolve. These techniques are increasingly being used for all types of anesthetics, including many outpatient procedures. Their utility in providing for perioperative pain management has greatly enhanced our ability to provide comfort to our patients.

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CHAPTER 45

Regional Anesthesia

Upper and Lower Extremity Blocks

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The advantages of regional anesthesia techniques as opposed to general anesthesia are numerous and include reduction in nausea and vomiting, decreased urinary retention, reduction in the surgical stress response, fewer recovery room admissions, earlier patient discharge, reduction in blood loss, better communication with and easier positioning of the patient, avoidance of airway compromise and cervical manipulation, reduced environmental exposure to anesthetic gases, and improved postoperative analgesia.[1-4]

The use of long-acting local anesthetics, the introduction of peripheral nerve stimulators, ultrasonography, and the placement of peripheral nerve catheters have significantly altered the landscape with respect to the practice of regional anesthesia and pain management. The best strategy for achieving maximum successful conduction block may be to use a combination of these advances. Although the type of complications associated with peripheral nerve block as compared with general anesthesia are different, the frequency and severity of the complications are likely similar.[2]

SELECTION OF REGIONAL ANESTHESIA TECHNIQUES

When regional anesthesia is chosen for management of pain, the technique should be thoroughly discussed with the patient beforehand. The patient is informed of all optional procedures available, their potential risks, and their potential complications before an anesthesia technique is selected. Once this conversation takes place, the most appropriate anesthesia technique can be selected, and true informed consent can be obtained. Regional anesthesia is used extensively for surgical procedures involving the extremities or the lower abdomen, for the management of labor pain, for the management of obstetric procedures, and for the control of chronic pain syndromes. Frequently, regional anesthesia techniques are used in combination with other techniques to provide analgesia or anesthesia during surgical or obstetric procedures. Regional anesthesia may be the technique of choice when local anesthesia requires supplementation with heavy sedation. These techniques provide the patient with additional anesthesia options when selecting an anesthetic for surgical or obstetric procedures. It is the preferred technique for obstetrics and many other types of procedures.[5-10]

The administration of regional anesthesia to patients with a difficult airway or a full stomach presents both additional benefits and potential risks. The use of regional anesthesia, when appropriate, permits the patient to retain upper airway and pharyngeal reflexes while providing surgical anesthesia. Unless the sedation is reduced to a minimum, the airway may not be protected after the administration of the regional technique. Furthermore, block of the sympathetic nervous system theoretically results in increased gastric and intestinal motility, causing the stomach to empty sooner. However, this benefit may be negated by the perception of pain and anxiety that accompanies injury. If hypotension develops, the patient may have increased nausea and vomiting. When the block is instituted, the patient may lose consciousness as a result of the effects of alcohol if the patient is intoxicated at the time of treatment. At this point, airway support is required, and other problems may arise as well. Regional anesthesia should not be considered an alternative to securing the airway. If the patient's airway cannot be secured in a safe manner in an emergent situation, use of a regional anesthetic should be avoided. The airway concerns must be addressed before the anesthetic technique is initiated so that the patient's safety is maximized.[11]

Absolute Contraindications

Contraindications to the selection of regional anesthesia techniques are few, and some remain controversial. Absolute contraindications include patient refusal, uncorrected coagulation deficiencies, and infection at the site of the block. The most significant absolute contraindication to regional anesthesia is patient refusal. Each patient must be informed of the acceptable techniques that will provide analgesia or anesthesia, as well as significant risks and potential benefits. The discussion must include the advantages and disadvantages of each proposed technique. The patient's questions should be answered completely. This level of communication helps the practitioner uncover misconceptions while educating the patient about regional anesthesia.[12]

Another absolute contraindication is systemic anticoagulation in the patient. Certain drugs and systemic diseases can cause alterations in the coagulation profile. The long-term or extended use of aspirin products or nonsteroidal antiinflammatory drugs (NSAIDs) can prolong bleeding time without significantly altering other laboratory data. The patient's medical and pharmacologic history may provide information about increased bleeding time. Asking the patient about frequent bruising without injury may reveal the first indication of a problem. For instance, physical evaluation of the skin may show evidence of bruising or subcutaneous bleeding of which the patient may not recall the cause. If injury to a large epidural vessel were to occur during the performance of either a spinal or an epidural technique, significant bleeding could develop in the epidural space. A similar injury to the axillary artery in the confined space of the axilla might result in a hematoma that would produce further complications. Injury to a large vessel in the neck during an interscalene technique could result in compromise of the airway. Guidelines for the use of regional techniques in a patient receiving anticoagulation therapy are given in Chapter 44.

Severe bleeding with or without symptomatic hypovolemia or the potential for severe bleeding is a contraindication to the administration of a regional anesthetic. The contraindication can be considered either absolute or relative, depending on the clinical presentation of the patient. Trauma, along with physiologic or pathophysiologic conditions that cause contracted volume states and abruptio placentae, can result in the development

of significant hypotension and tachycardia after the initiation of regional anesthesia, especially spinal or epidural anesthesia. A blockade of the sympathetic nervous system quickly develops, resulting in significant relaxation of the smooth muscles of the vascular bed. When the patient demonstrates symptoms of hypovolemic shock on evaluation, his or her ability to safely tolerate peripheral vasodilation and the subsequent reduction in systemic vascular resistance is reduced. The patient's ability to compensate for falling blood pressure by increasing systemic vascular resistance places the patient at risk for potential hypoperfusion to vital organs and subsequent hypoxic tissue injury.[13]

When an obstetric patient experiences abruptio placentae with or without fetal distress, the anesthesia practitioner must consider other anesthetic procedures. These alternatives should be considered so that hypotension and the compromise to fetal oxygen supply that results from decreased uterine blood flow can be minimized. Regional techniques require time to administer in addition to the reduction in blood pressure that occurs with establishment of the block. Uterine blood flow is dependent on arterial pressure and has few autoregulatory capabilities. However, when an epidural anesthetic has been established for labor, the time required for surgical anesthesia to be instituted may be less with epidural than with general anesthesia. The choice of anesthesia technique must focus on the possible effects of the sympathectomy, even if its development can be slowed or controlled. With the onset of the sympathetic blockade, the fall in blood pressure may be more than the mother and baby can tolerate. The anesthesia practitioner caring for the patient, in consultation with the patient's obstetrician, must decide whether administration of the regional anesthetic should be continued or whether another anesthesia procedure should be selected.[14] Finally, if an active infectious process is present near the location at which regional anesthesia is to be performed, another anesthetic should be chosen.

Relative Contraindications and Precautions

One relative contraindication to regional anesthesia is patient age. In neonates with impairment in ventilatory regulation, regional anesthesia techniques are recommended when either surgery or pain management is required.[15,16] Small children tolerate the administration of a combination anesthetic for many surgical procedures, including hernia procedures, extremity procedures, and circumcision. A general anesthetic can be administered for the surgical procedure, and a regional technique can be used for postoperative pain management. Anatomic landmarks are easily identified in children, which permits implementation without extensive difficulty. Precautions must be taken when the patient is of short stature. This technique should be avoided in children who are unable to tolerate the loss of feeling and strength in the legs. As children begin to acquire independence through increased ambulation, the loss of feeling and movement in the legs may increase their fear. This phenomenon is especially common in children between the ages of 3 and 9 years.[17,18]

Interscalene and axillary blocks have been used to permit immobilization and analgesia of the upper extremity for extended periods of time. Intravenous regional anesthesia (Bier block) has been used in small children aged 8 to 12 years; in these cases a reduced amount of local anesthetic medication is used for the reduction of an arm fracture.[17]

Patients who have difficulty understanding the procedures to be performed or who are unable to cooperate with the practitioner should undergo another type of anesthesia. Such patients may respond negatively to the presence of anyone behind them who may create confusion or cause discomfort; they could perceive this presence as an imminent threat and could respond inappropriately.

Patients with a history of headaches or backaches are at increased risk for experiencing these problems after spinal and epidural analgesia or anesthesia. Such patients should be evaluated and counseled regarding this potential before the administration of subarachnoid or epidural anesthesia. Postanesthesia symptoms of backache or headache become difficult to evaluate without information about the patient's previous pattern of headaches or backaches. Information about the position of the patient during the surgical or obstetric procedure assists in the evaluation of the patient.

Patients with chronic neurologic disorders must be well informed of the potential effects of the regional anesthetic technique. The regional anesthetic may not cause an increase in the patient's symptoms; however, if symptoms of the disorder increase or deterioration results, the regional anesthetic technique may be identified as the cause of the problem.[19,20]

Patients with a history of a documented local anesthetic allergy should undergo further evaluation in a controlled situation by an allergist. A true allergy to local anesthetic agents is rare. The problem may be caused by a preservative in the anesthetic solution or by a metabolic product of local anesthetic hydrolysis (para-aminobenzoic acid [PABA]). Skin testing is helpful but not always practical. Alleged allergic reactions may be related to an intravenous injection of a local anesthetic solution that contains epinephrine. If a regional technique is used in a patient with an allergy, a local anesthetic that is unrelated to the suspected agent should be selected. For example, if the patient is allergic to an ester anesthetic, an amide anesthetic agent should be chosen. Before the anesthetic is administered, the patient should be medicated with histamine-1 and histamine-2 receptor blockers.[21-23]

Patients with fixed-volume cardiac states are at risk for cardiovascular compromise after the initiation of a regional anesthetic. If the patient is unable to respond to changes in systemic vascular resistance by increasing stroke volume as a means of maintaining cardiac output, selected regional anesthesia techniques, including spinal and epidural anesthesia, should be reconsidered. As the heart rate increases to compensate for the falling pressure, the heart may fail, or ischemia may develop. Absolute and relative contraindications to regional block are noted in Box 45-1.

BOX 45-1

Absolute and Relative Contraindications to Regional Block

Absolute Contraindications

- Patient refusal
- Infection at injection site
- Coagulopathy or other bleeding diathesis
- Severe hypovolemia
- Severe aortic or mitral valve stenosis
- Increased intracranial pressure

Relative Contraindications

- Uncooperative patient/psychiatric disease
- Septicemia/bacteremia
- Preexisting neurologic disease
- Chronic headache or backache
- Stenotic valvular disease
- Severe spinal deformity

COMPLICATIONS OF REGIONAL ANESTHESIA

Complications of regional anesthesia can be immediate or delayed. Cardiovascular problems are the most critical immediate complications. However, effects on the respiratory and gastrointestinal (GI) systems can have equally serious consequences. Delayed complications include problems involving the cardiovascular, musculoskeletal, genitourinary, and neurologic systems.

Immediate Complications

The potential of an intravascular injection is increased when local anesthetics are injected into the tissues around nerves and blood vessels. It is especially important to be prepared for a local anesthetic systemic toxicity (LAST) reaction when performing peripheral blocks because high volumes are frequently injected into vascular areas. A complete discussion of the management of LAST is given in Chapter 10. A functional intravenous line and all of the necessary equipment and drugs must be immediately available prior to administration of any regional block.

Delayed Complications

The anesthesia practitioner must be prepared to manage complications that occur after the block has been established or during the postanesthesia recovery period. The choice of needle type may play a role in peripheral nerve injury when the injury is caused by intraneural injection. Nerve fascicles move away from the needle tip, especially when using a short-beveled needle. The use of a long-beveled needle, which tended to impale the nerve, resulted in a greater number of injuries, especially if the needle tip was oriented transversely to the nerve fibers. Patients with preexisting nerve pathology, such as diabetic neuropathy, are at increased risk for prolongation of the block and local anesthetic neurotoxicity. The absence of a motor response to a peripheral nerve stimulator does not exclude the possibility of intraneural needle placement, and seeking nerve stimulator confirmation of apparent intraneural needle position noted on ultrasound can lead to unnecessary trauma to the nerve. Local inflammation is an infrequent occurrence with the use of a peripheral nerve catheter technique; however, bacterial colonization rates of the catheter are high. Even so, the incidence of local infection, abscess formation, and sepsis is rare. The use of aseptic technique and chlorhexidine, which is considered to be the best skin disinfectant currently available, is recommended.[23,24]

Complications Associated with Continuous Peripheral Nerve Blocks

Continuous peripheral nerve blocks (CPNBs) have been shown to improve postoperative pain control and hemodynamic stability, reduce opioid requirements, and decrease nausea and vomiting. There are few studies evaluating the adverse effects and complications of this technique. Permanent neurologic complications are rare after peripheral blocks, but transient neuropathies occur in approximately 3% of patients.[25] Wiegel et al.[26] analyzed 1398 CPNBs performed in 849 orthopedic patients. The CPNBs included interscalene, femoral, sciatic, and a combination of femoral and sciatic blocks performed preoperatively in addition to general or spinal anesthesia. The standard technique included use of a nerve stimulator, injection of a bolus of local anesthetic, placement of the catheter, application of a transparent dressing, a single dose of antibiotic prophylaxis, and infusion of 0.2% ropivacaine at 5 to 8 mL per hour commencing in the postanesthesia care unit for a period of 24 hours. Following this period, bolus doses of 0.2% ropivacaine (10 to 20 mL) were administered every 6 hours on an orthopedic ward.

Patients were questioned about complications during their 3-month postoperative visit. The primary study end-point was the rate of complications, including nerve injury, bleeding requiring surgical intervention, catheter-associated infection, dyspnea, pneumothorax, and local anesthetic toxicity. A unique feature of this study was the extended period of time catheters remained in situ—up to 12 days in some cases. Local inflammation at the catheter insertion site occurred in 9 patients (0.6%), and local infection occurred in 3 patients (0.2%)—all femoral CPNBs. There were 12 patients with transient neurologic deficits (0.9%), and 1 with a permanent neurologic deficit (0.1%). Vascular puncture occurred at a rate of 5.2%, and a catheter was broken in one patient as a result of withdrawing the catheter back into the needle, a practice that should always be avoided. The authors found that while major complications of CPNBs are rare, minor adverse events are not uncommon.[26] A number of potential risks and complications of continuous peripheral nerve block are discussed throughout this chapter, including inaccurate catheter placement, dislodgement or migration, vascular puncture and hematoma, delayed local anesthetic toxicity, nerve injury, infection, pulmonary complications associated with phrenic nerve block, and catheter knotting, retention, or shearing.

Technical Difficulties

Technical problems include difficulties with equipment and supplies. Broken needles, broken catheters, microscopic glass in the epidural and subarachnoid spaces, and injection of the wrong drugs are some of the problems that can be encountered.

Disposable needles are made in two parts: the hub and the barrel. The two parts are joined together and then fused to create a single unit. The weakest point on the needle is at the joint with the hub. Precautions should be taken so that the needle is not inserted so far that the hub abuts the skin surface. In addition, the needle should not be bent. If extreme force is used while the needle is being inserted, the needle is stressed at the hub; this stress could cause the needle to break at the hub. If the needle is not inserted with the hub abutting the skin surface, some portion of the needle can be secured and removed, thus preventing its loss.[10,27,28]

Broken or sheared catheters are a concern in continuous regional anesthesia techniques. A visual inspection of the catheter should occur before it is inserted. The portion of the catheter that is inserted should have a radiopaque marker on the tip. Markings are placed at 1-cm divisions along the catheter, thereby providing an approximate measure for estimations of the length of the catheter that is inserted into the epidural or intrathecal space. When removed, the catheter should be inspected and its intactness verified and recorded on the patient's record. An epidural catheter should not be pulled back through the needle once the tip has passed beyond the bevel opening. The point where the two sides of the bevel join is the sharpest point of the entire needle. As the catheter is pulled back, it is forced against the joint and may be sheared off.

If the catheter is sheared off, radiography can be used to locate the catheter, verify its position, and document the shearing. Catheters in use today have a radiopaque tip and are made of a material of low tissue reactivity. Surgical procedures used in the search for a catheter can delay a patient's recovery. The patient should be told of the problem, where the catheter is located, the composition of the catheter, and any other information that might help reduce concerns about the catheter's location. Most catheters can remain in place without causing problems. However, when the remaining catheter is located in the subarachnoid

space, it must be retrieved. The potential exists for the catheter to migrate cephalad, causing further problems once it reaches the level of the spinal cord or is directed through a foramen into a nerve root.[20]

Glass from broken ampules can be injected into the subarachnoid or epidural space or in the area of the nerve if care is not exercised during preparation of the medication. Ampules should be broken away from the tray and enclosed within a sponge that is then discarded. A filter needle should be used during the withdrawal of all medications from ampules. The filter needle should then be discarded to prevent injection of the particles that have been filtered. The glass particles may act as a foreign body, causing a local reaction and the development of a sterile abscess.

Discharge Information

A useful tool to provide patients who have received a regional anesthetic is a discharge information sheet (Box 45-2). This sheet provides the patient with information about the nature of the anesthetic and what to expect as the block resolves. Most importantly, it should alert the patient to contact the anesthesia provider in the event certain symptoms, which may indicate a potential complication of the regional anesthetic, occur after discharge.

BOX **45-2**

Regional Anesthesia Discharge Information Sheet

What is regional anesthesia?
Regional anesthesia is the injection of a local anesthetic (such as Novocaine) near the nerves that sense pain from the area of your body that had surgery. Regional anesthesia is the same as a dentist injecting local anesthesia into your mouth—it numbs an area of your body so that procedures won't hurt.

What should I expect after regional anesthesia?
After regional anesthesia, the area of your body that had surgery will be numb for several hours. In fact, the area may be numb for up to 24 hours. The block will wear off slowly, and your first sensations will be a tingling feeling in the area that was numb.

What should I do when the block starts to wear off?
As soon as you develop any feeling in the numb area, begin taking the pain medications your surgeon has prescribed. It is much easier to treat pain before it begins than try to catch up later.

What should I be careful about after regional anesthesia?
Because part of your body is numb, you won't know if you injure it. You should take care to protect that part of your body from being bumped, cut, and otherwise harmed, and you should look at it frequently to make sure it isn't injured. You should also avoid lying on the numb area while you sleep.

What complications should I watch for after regional anesthesia?
The site of your body where the injection was made will be sore for a few days. This pain should go away with any over-the-counter pain-relief medicine (e.g., Tylenol, Advil, Motrin). It is not uncommon for the area that was numb to have some strange sensations (e.g., mild numbness, tingling) for a few days after the block.

If you experience any of the following changes, you should immediately phone your health care provider:

- Sensation doesn't begin to return to the numb area after 24 hours.
- The area that was numb regained sensation but is becoming numb again.
- The skin in the numb area turns blue or feels cool.
- There is persistent pain in the area that was numb, even several days after the surgery.

ELECTRICAL STIMULATORS IN REGIONAL ANESTHESIA

Peripheral nerve stimulators are a valuable tool in the practice of regional anesthesia. Although ultrasound-guided blocks are becoming more common, nerve stimulator techniques may be used for select blocks or as an adjunct to an ultrasound technique. Often listed among the benefits of the use of a peripheral nerve stimulator are a reduction in the volume and dose of local anesthetic required to produce a block, increased success rate, and the ability to block nerves that are difficult to locate.

Electrical translocation devices provide a controlled stimulating pulse of variable amplitude that is administered through a conducting device. Location of neural fibers is improved without the need for eliciting repeated paresthesias. Specialized shielded needles have been designed to localize the distribution of the stimulating charge to the tip of the needle. This characteristic reduces confusion from wide-field stimulation of the area around the nerve, thereby enhancing the isolation of the appropriate nerve fibers.

The needle must be advanced slowly, and the amplitude of the unit must be adjusted as the needle approaches the nerve. The negative lead is attached to the skin with an electrocardiogram electrode, and the positive lead is attached to the needle. The electrical device must be equipped with an accurately adjustable amplitude from 0 to 5 mÅ with a digital readout of the amplitude.

When this technique is used, the stimulator should not be turned on until the needle has entered the skin. This measure reduces the discomfort experienced by the patient during the initial advancement of the needle. The patient must be instructed to identify discomfort verbally and to not move during the advancement of the needle.[29] Limiting the sedation helps the patient tolerate the procedure, maintain sufficient alertness to respond to the stimulus, and be cooperative.

Use of an electrotranslocation device can assist the practitioner during the administration of nerve block anesthesia to patients with sensory perception difficulties or neural degeneration, such as that experienced during end-stage renal disease. The use of an electrotranslocation device should not be restricted to brachial plexus techniques. Such a device can be used for enhancing any technique including ultrasound-guided nerve block, in which identification of specific nerve roots improves the success of the block and reduces the amount of medication required for anesthesia of the nerve root.

During a brachial plexus block, the stimulator is adjusted to deliver 2 mÅ after the needle has been introduced into the subcutaneous tissues. As the needle approaches the sheath, the amplitude is continuously reduced so that the muscle response to the stimulus is maintained. When the needle enters the sheath, the amplitude should be reduced to 0.5 mÅ. The muscle response to the stimulus continues to be the same as that obtained when the needle is outside of the sheath. The lower amplitude decreases the discomfort experienced by the patient while enhancing the ability to accurately identify the neurovascular bundle.

Patients may complain of aching or weakness along the path of the stimulated nerve after the regional anesthesia is terminated. This phenomenon is seen after the posterior tibial or the common peroneal nerves are stimulated. Severe or prolonged discomfort occurs when the stimulus is delivered over a long period or at a high current. The response to a stimulus with a lower amplitude is often adequate and results in less discomfort. Placement of the negative electrode has been important in the enhancement of electrotranslocation of the nerve. If the path of the nerve fiber is

BOX **45-3**

Advantages of Using Ultrasound Guidance for Nerve Blocks

- Direct visualization of the nerves and adjacent anatomic structures
- Observing the local anesthetic spread in real time
- Detecting variations in anatomy
- Faster onset times
- Improvement in block quality
- Use of lower, more precise doses of local anesthetics
- Possible increase in safety
- Less painful administration compared with nerve stimulator techniques
- Higher patient satisfaction

located under the negative electrode, a lesser stimulus produces a significant response.

ULTRASOUND-GUIDED REGIONAL ANESTHESIA

The technology and clinical understanding of anatomic sonography has evolved greatly over the past decade. In anesthesia departments throughout the United States, ultrasound-guided regional anesthesia (UGRA) has become a routine technique and may become the "gold" standard for performing regional anesthetic nerve blocks.[30-32] Direct visualization of the distribution of local anesthetics with high-frequency probes can improve the quality and avoid the complications of upper/lower extremity nerve blocks and neuroaxial techniques. Ultrasound guidance enables more accurate needle position and monitoring of the distribution of the local anesthetic in real time. The advantages over conventional guidance techniques, such as nerve stimulation and loss-of-resistance procedures, are significant. The key requirement for successful regional anesthetic block is to ensure optimal distribution of local anesthetic around nerve structures. This goal is most effectively achieved under sonographic visualization. Advantages of using ultrasound-guided techniques are noted in Box 45-3.[33,34] When compared with other forms of nerve localization, UGRA decreases performance time and onset time, and therefore decreases the time for surgical readiness from regional anesthesia. The quality of peripheral nerve block is also improved. To date, there are insufficient data to declare that UGRA improves overall block success. Whether UGRA improves safety has not been proven with large-scale randomized trials. Empirically, by allowing for the use of smaller volumes of local anesthetic as well as visualization of the real-time interaction of the needle, the nerve, and the local anesthetic, it appears the risk of LAST or neuronal toxicity will be reduced.[35,36] An interesting report noted that novice trainees learn the technique at variable rates but generally require 28 supervised trials before competency is achieved.[37]

As noted previously, the key condition for a successful regional anesthetic block is the confirmation of an appropriate volume of local anesthetic around the targeted nerve structures. Proper placement of local anesthetic is most effective under ultrasound visualization. A medical ultrasound machine operates frequencies between 2 and 13 MHz. The average wavelength of an ultrasound beam is less than 1 mm. This limits the use of ultrasound technology to structures that are 1 mm in diameter or larger. In general, higher-frequency ultrasound probes (10-13 MHz) are best suited for visualizing structures less than 4 cm deep from the skin. For deeper structures, lower-frequency ultrasound probes (2-5 MHz) are more clinically useful. Nerve tissue that appears dark or hypoechoic appears dark because it does *not* reflect ultrasound waves. Nerve tissue appears white or hyperechoic because it does reflect ultrasound waves.

The handheld probe emits and collects the ultrasound waves in a fan-shaped beam, which is represented on the display screen in a two-dimensional plane. The on-screen vertical axis represents the distance an anatomic structure or block needle is from the ultrasound probe, whereas the horizontal axis represents the distance to the right or left of the center of the probe. Therefore, the ultrasound waves are used to construct an image of the "slice" of tissue centered on and beneath the ultrasound probe, much like a single image on a computed tomography (CT) scan.

The standard ultrasound image is rendered in shades ranging from white to black depending on the amount of energy that returns to the probe from structures being examined. Hyperechoic tissues reflect a large amount of the ultrasound waves back to the probe and therefore appear white. Hypoechoic tissues reflect fewer ultrasound waves and therefore appear as shades of gray. Anechoic areas do not reflect ultrasound waves and therefore appear black. The amount of reflection of ultrasound waves back to the probe is dependent on the amount of resistance to passage of the waves through a particular tissue. This characteristic is known as *acoustic impedance*. Differences in acoustic impedance at tissue interfaces results in the ability to identify specific anatomic structures. For example, bone has much greater acoustic impedance than soft tissue; therefore the interface between these two tissues will produce a hyperechoic image.[38]

Needles used for regional anesthesia are echogenic but have very small cross-sectional areas. Therefore, the orientation of the needle with respect to the ultrasound beam affects the amount of sound energy reflected and hence the visibility of the needle on the screen. A needle oriented perpendicular to the ultrasound beam (i.e., "side on" to the beam) reflects a large amount of sound energy and is more easily visualized. In contrast, a needle that is parallel to the ultrasound beam (i.e., "end on" to the beam) reflects relatively little sound energy and is more difficult to visualize.

The orientation of the needle to the ultrasound probe during the administration of a regional anesthetic block is typically described in relationship to the image plane. The in-plane or axial/longitudinal approach allows the entire length of the needle (including the tip) to be visualized within the plane of the ultrasound image (Figure 45-1). In contrast, the out-of-plane, or tangential/short axis approach allows only the cross section of the needle to be visualized as a hyperechoic dot where it pierces the plane of the ultrasound image (Figure 45-2). The in-plane approach is favored when possible because it permits visualization of the entire length of the needle at all times; however, the anatomy associated with certain blocks may necessitate the use of the out-of-plane approach.

UPPER-EXTREMITY BLOCK

Frequent injury of the hand, arm, and shoulder, combined with the accessibility of the nerves of the brachial plexus, has encouraged the development of regional anesthesia techniques for surgical procedures of the upper extremity, as well as the diagnosis and control of pain.[39] The widespread use of upper-extremity regional anesthesia is the result of numerous factors, including the availability of equipment to locate and deliver local anesthetics to the nerves of the plexus, the development of local anesthetics that can be applied alone and in combination to produce an appropriate duration of action for the procedure at hand, and the variety of techniques and approaches that can be used.

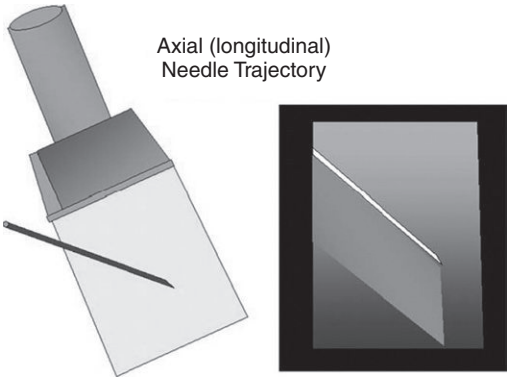

FIGURE **45-1** Hyperechoic image of an in-plane (axial/longitudinal) needle insertion. From Grau T. Ultrasonography in the current practice of regional anesthesia. *Best Practice and Research Clinical Anaesthesiology.* 2005;19:175-200.

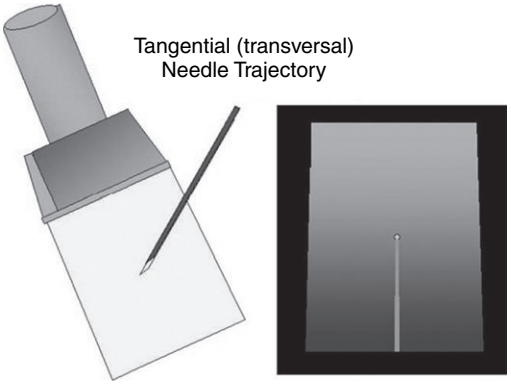

FIGURE **45-2** Hyperechoic image of an out-of-plane (tangential/short axis) needle insertion. From Grau T. Ultrasonography in the current practice of regional anesthesia. *Best Practice and Research Clinical Anaesthesiology.* 2005;19:175-200.

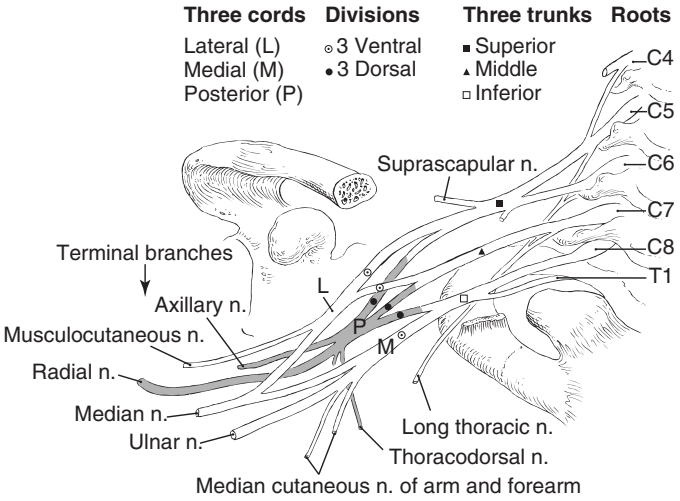

FIGURE **45-3** Derivation of the brachial plexus from the cervical spine. *n.*, Nerve.

The four primary approaches for blocking the brachial plexus are axillary, interscalene, supraclavicular, and infraclavicular. Because of the ease of performance, the relatively high success rate and low incidence of complications, and the ability to produce anesthesia of the forearm and hand, the most frequently used technique is the axillary approach. The requirement for anesthesia of the upper arm and shoulder is most often met through use of the interscalene approach. This is because of the potential complications associated with needle placement in close proximity to the apex of the lung necessary with supraclavicular and infraclavicular block. The infraclavicular block is a safe and simple technique for providing surgical anesthesia of the lower arm, with an efficacy comparable to other approaches. The disadvantage is a higher risk of pneumothorax. Advantages of the infraclavicular approach include a lower likelihood of tourniquet pain and more reliable blockade of the musculocutaneous and axillary nerves when compared with a single-injection axillary block.[40,41]

The decision to use regional anesthesia rather than general anesthesia (which may be viewed by the surgeon as failure-free and more expedient) for elective and emergency surgical procedures of the upper extremity requires a strong commitment to and expertise in the use of these techniques. Moreover, the astute practitioner with experience and expertise in regional anesthesia does not lose sight of the fact that even in the most skilled hands, upper extremity block is associated with a degree of failure. In this regard, one can never rule out the potential requirement for conversion to general anesthesia and therefore must be cognizant of elements of the patient's history and physical examination that would affect the ability to manage the airway and deliver general anesthesia safely.

Despite the fact that existing patient pathology may suggest a regional anesthetic, it is unwise to base the decision to use an upper extremity block (or any regional technique) solely on the premise that general anesthesia should be avoided, because ultimately, it may be unavoidable. The circumstances should dictate the degree to which "plan B" is considered and executed before administration of the block.

Brachial Plexus Anesthesia

Applied Anatomy of the Brachial Plexus

An understanding of brachial plexus anatomy is mandatory if effective clinical application of regional block techniques of the upper extremity is to be achieved. This includes familiarity with muscle, facial, and vascular anatomy in relation to the origin and distribution of the brachial plexus. However, intimate knowledge of many of the anatomic details with regard to the evolution of nerve roots distributed to the brachial plexus and ultimately to peripheral nerves is not clinically essential for successful blockade. The brachial plexus is a large network of nerves that extend from the neck through the axilla and innervate the upper extremity (Figure 45-3). It is composed of ventral rami, trunks, divisions, cords, and their branches. The supraclavicular portion of the plexus, including the five primary ventral rami and the three nerve trunks and their six divisions, lies in the posterior triangle of the neck. The infraclavicular portion of the plexus, including the three cords and their four terminal branches, lies in the axilla. These nerves combine, divide, recombine, and divide again as they pass between the anterior and middle scalene muscles, through the posterior triangle of the neck, and into the axilla, where they end in the four terminal branches that supply the upper extremity. The resulting nerve pathway, when pictured and contemplated in two dimensions and without the associated bone, muscle, and vascular structures, often leads to difficulty in understanding and applying this textbook anatomy in the clinical setting. When learning brachial

plexus blockade, the value of augmenting written material with an apprenticeship at the hands of a master of the art cannot be overestimated.[42-44]

The archetypal brachial plexus is formed by the rami from the fifth (C5) to the eighth (C8) cervical nerves and the first thoracic (T1) nerve. In a small percentage of individuals, the fourth cervical (C4) or the second thoracic (T2) nerve or a combination of the two contributes to the plexus. After the rami pass the lateral border of the scalene muscles, they reorganize into trunks. The rami from C5 and C6 combine to form the superior or upper trunk, and the ramus from C7 continues alone as the middle trunk. The rami from C8 and T1 combine to form the inferior or lower trunk, which lies on the first rib posterior to the subclavian artery. The nerve trunks are enveloped by a fascial "sheath," the origins of which are from the posterior fascia of the anterior scalene muscle and the anterior fascia of the middle scalene muscle. This forms a closed space at this level known as the *interscalene space*, or more generally as the *sheath of the brachial plexus*.

Cadaver studies have demonstrated the existence of extensive velamentous septa that can form compartments around the contents of this sheath. These septa appear to be incomplete and therefore may not function as mechanical barriers to the spread of local anesthetics. Indeed, a single injection of local anesthesia into this sheath commonly produces complete block of the upper extremity. Nevertheless, anatomic variations do exist, and it is possible that in certain individuals, septa occur that isolate nerves, resulting in so-called "patchy blocks" by preventing exposure to the injected local anesthetic. It has also been shown that injection even outside the sheath can produce neural blockade, albeit with a considerably greater latency period. The lesson to be learned with regard to clinical application of this information is that failure to allot a sufficient amount of time to perform an upper extremity block, and in particular to allow it to "set up," generally produces an unsatisfactory result.[42-44]

At the lateral border of the first rib and posterior to the clavicle, each of the three trunks divides into ventral and dorsal divisions. These divisions are of significant clinical importance to application and evaluation of brachial plexus blockade, because the ventral divisions generally supply the ventral (flexor) portion of the upper extremity, and the dorsal divisions generally supply the dorsal (extensor) portions. As these divisions enter the axilla, the three posterior divisions combine to form the posterior cord, the anterior divisions of the superior and middle trunks combine to form the lateral cord, and the anterior division of the inferior trunk continues to become the medial cord. At that point, the cords are named according to their position in relation to the axillary artery. At the lateral border of the pectoralis minor muscle, each of these cords divides into two branches that reorganize to form the peripheral nerves of the upper extremity. The lateral cord divides and generates the musculocutaneous nerve and the lateral root of the median nerve. The medial cord divides and generates the ulnar nerve and the medial root of the median nerve. The posterior cord divides to generate the axillary and the radial nerves.

Understanding the anatomic relationships that result as the nerve cords give rise to the nerve branches and knowing the areas of the upper extremity these branches innervate are of paramount importance in the clinical application, evaluation, and supplementation of brachial plexus block. The branches of the lateral and medial cords (median, ulnar, and musculocutaneous nerves) predominantly supply the ventral portions of the upper extremity, and the branches of the posterior cord (radial and axillary nerve) predominantly supply the dorsal portions. However, in certain areas of the upper extremity, such as the posterior portion of the fingers and hand, there exists considerable cutaneous representation of the "predominantly ventral" median and ulnar nerves.

The radial nerve (C5 to C8 and T1) is the major nerve supply to the dorsal extensor muscles, such as the triceps, of the upper limb below the shoulder. It supplies sensory innervation to the extensor region of the arm, forearm, and hand. The musculocutaneous nerve (C5 to C7) supplies the flexor muscles, such as the biceps, brachialis, and coracobrachialis, of the ventral portion of the arm. It supplies sensory innervation to the lateral aspect of the forearm between the wrist and elbow as the lateral antebrachial cutaneous nerve. The median and ulnar nerves pass through the arm and provide sensory and motor innervation to the forearm and hand. The median nerve (C6 to T1) is better represented than the ulnar nerve in the forearm, where it supplies most of the flexor and pronator muscles. It also supplies sensory innervation to the ventral portion of the thumb, the first and second fingers, the lateral half of the third finger, and the palm of the hand. The ulnar nerve (C8 and T1) is better represented than the median nerve in the hand, where it supplies motor innervation to most of the small flexor muscles. It has no sensory innervation of the forearm but supplies sensation to the medial part of the third finger, the entire fourth finger, and the remaining portion of the palm of the hand.

Approaches to Brachial Plexus Block

There are multiple approaches to local anesthetic block of the brachial plexus and various techniques applied with each approach. The choice of approach should be based on several factors, including patient considerations, the location of the planned surgical intervention, and especially the skill and experience of the anesthesia practitioner. Although surgical site and practitioner preference often drive the decision regarding which approach and technique are used, the patient's body habitus, comfort, and coexisting disease and the nature and location of the injury are as important, if not more so, than these other concerns. Patient-related considerations should be weighed in the context of the risk of potential complications associated with a given approach, technique, and local anesthetic solution. The following discussion provides a practical approach to anesthesia of the brachial plexus, with a focus on axillary and interscalene approaches.[41]

Interscalene Approach. The interscalene approach to the brachial plexus was first described in 1970 by Dr. Alon Winnie. The interscalene approach is the most proximal brachial plexus block and is typically used to provide anesthesia for surgical procedures involving the shoulder and proximal humerus. It is the only technique that can provide adequate anesthesia and analgesia to the shoulder and the rest of the upper extremity. The catheter is placed at the level of the trunks, where the brachial plexus is relatively compact in size.[45] With the patient in the supine position, the anesthetist asks the patient to lower the shoulder on the side of the proposed anesthetic and surgery site to pull the shoulder away from the brachial plexus, intentionally trying to stretch the neck muscles and improve visualization and access. The patient's head can then either be turned so that the patient looks away from the area of the anesthetic or moved laterally away from the site, maintaining forward vision.

The cricoid cartilage ring is then palpated just below the thyroid cartilage. This anatomic landmark correlates to the vertebral body of C6 and the corresponding area of the transverse process called *Chassaignac's tubercle*. A straight line is drawn posteriorly to cross over the sternocleidomastoid (SCM) muscle, and the lateral border of the SCM is palpated. If this border is difficult to assess, the patient can be asked to raise the head against gentle resistance

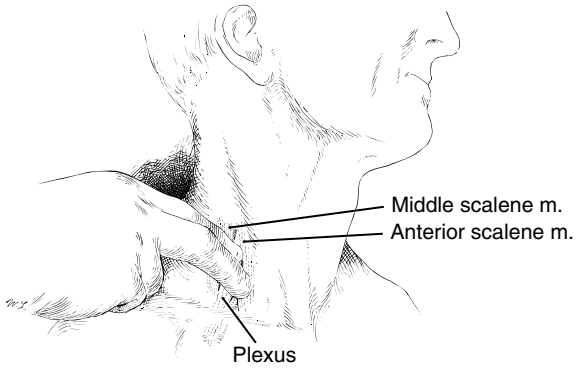

FIGURE **45-4** Technique for identifying the anterior and middle scalene muscles and the major vessels so the interscalene perivascular technique can be accomplished. *m.*, Muscle.

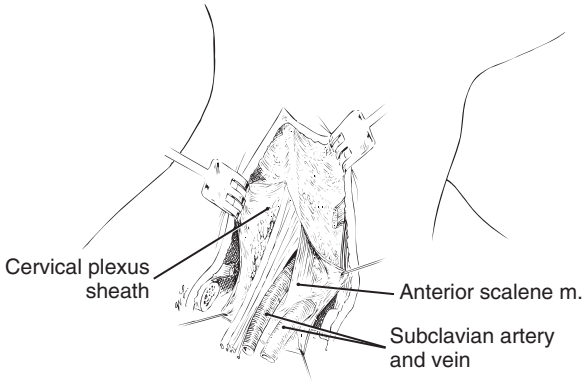

FIGURE **45-5** Three trunks of the cervical plexus are revealed lying alongside the subclavian vessels. *m.*, Muscle.

and then relax. Posterior to this border, the anesthetist palpates for the groove between the anterior and middle scalene muscles with two fingers (Figure 45-4). This is the level of the trunks of the brachial plexus (Figure 45-5).

After cleansing the patient's skin, an intradermal skin wheal of local anesthetic is made at this point on the groove. A 22-gauge, insulated B-bevel needle, usually 1½ inches long, is inserted gently through the skin wheal perpendicularly to the skin and then angled slightly caudad. The needle is attached to an intravenous extension tube with an anesthetic-filled syringe. The patient is told what to expect, and the needle is slowly advanced until a motor twitch response is elicited. The nerve stimulator current is lowered from 1 to 0.5 mÅ to minimize excessive current to the patient and to ensure proper needle position. After gentle aspiration is negative for blood or CSF, a test dose of 1 mL of local anesthetic solution is injected. A fade will be observed in the quality of the motor twitch experienced by the patient. This indicates that the needle is probably within the brachial plexus sheath. If no subjective symptoms of toxicity reaction are present, incremental injections of 3 to 5 mL of local anesthetic, each followed by aspiration to detect blood, are administered until the intended volume is given. In adult patients, the volume is usually 30 to 35 mL.[41,46]

Ultrasound-Guided Interscalene Block. The patient is placed in the supine position with the head rotated toward the nonoperative side and a high-frequency ultrasound probe is placed at the level of the first rib. The anchoring landmarks to be visualized are the subclavian artery and the first rib. The three roots of the brachial plexus are visualized lateral to the

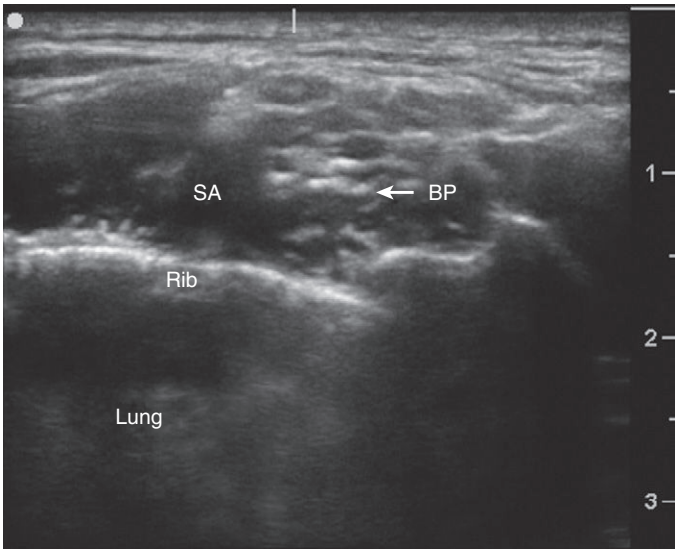

FIGURE **45-6** Transverse view of the brachial plexus lateral to the subclavian artery at the level of the first rib. *SA*, Subclavian artery; *BP*, roots of the brachial plexus, which are reflected as hypoechoic oval structures.

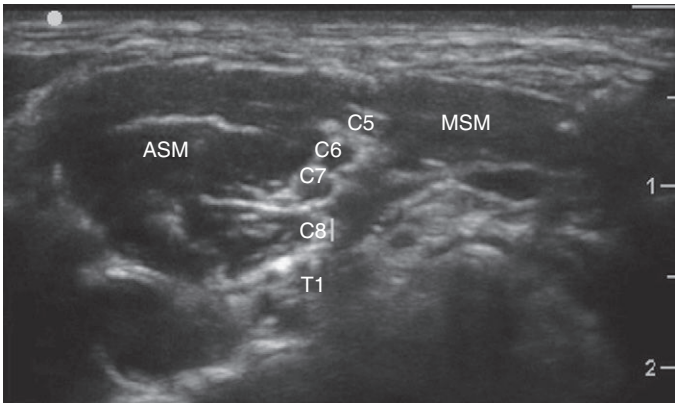

FIGURE **45-7** Transverse view of the brachial plexus at the lateral border of the sternocleidomastoid muscle, at the level of the posterior interscalene space between the anterior and the median scalene muscles. *C5-T-1*, Roots of the brachial plexus, which are reflected as hypoechoic oval structures; *ASM*, anterior scalene muscle; *MSM*, median scalene muscle.

subclavian artery (Figure 45-6). The ultrasound probe is then slid from the first rib up to the level of, or just below, the cricoid cartilage where the brachial plexus is visualized as a group of hypoechoic circular structures lying between the anterior and middle scalenus muscles (Figure 45-7). A 22-gauge, 2-inch needle is inserted posterior to the plexus, in-plane to the ultrasound beam, (Figure 45-8) with the tip of the needle coming to rest in close proximity to the roots of the brachial plexus. Up to 20 mL of local anesthetic solution is injected under direct observation. The local anesthetic solution should create an expanding hyperechoic area that surrounds and engulfs the nerve plexus (Figure 45-9).

Subclavian Approach. The patient is positioned and prepared as for the interscalene approach (Figure 45-10). In addition, some practitioners may place the patient's bed in a 30- to 45-degree head-up position or place a pillow under the patient's shoulder to accentuate the anatomy. The area above and including the clavicle on the surgical side is cleansed and draped.

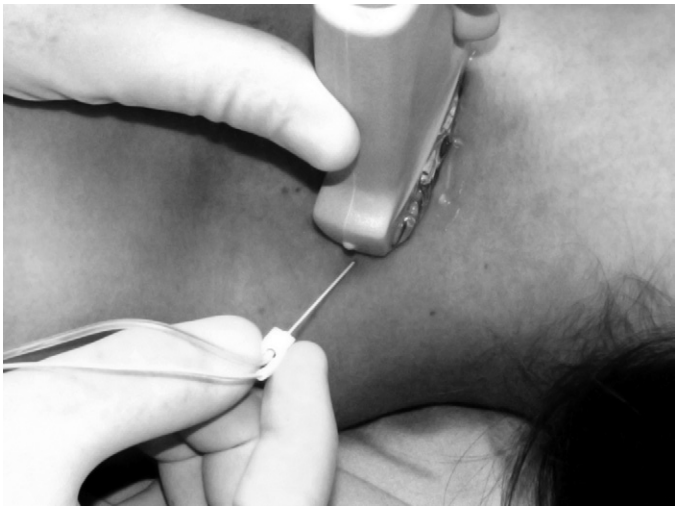

FIGURE **45-8** Needle inserted in-plane at the lateral border of the sternocleidomastoid muscle, at the level of the posterior interscalene space.

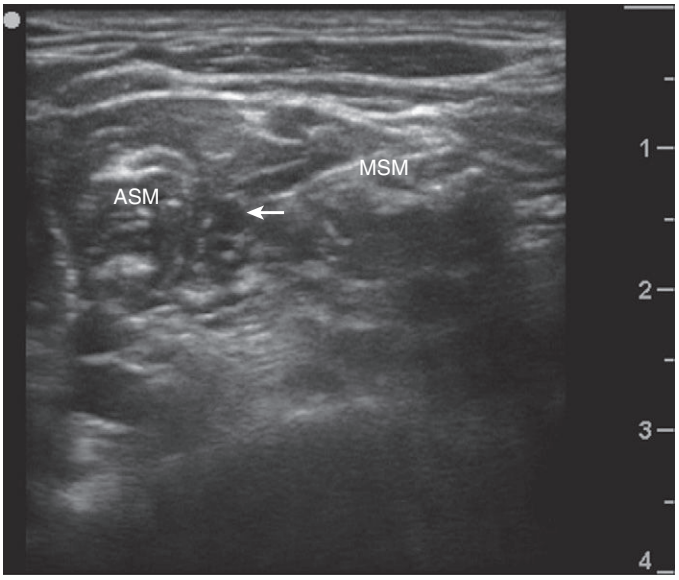

FIGURE **45-9** Transverse view of the brachial plexus at the lateral border of the sternocleidomastoid muscle and at the level of the posterior interscalene space between the anterior and the median scalene muscles after administration of 15 mL of local anesthetic. *ASM*, Anterior scalene muscle; *MSM*, middle scalene muscle; *arrow* indicates the nerve roots of the brachial plexus surrounded by local anesthetic.

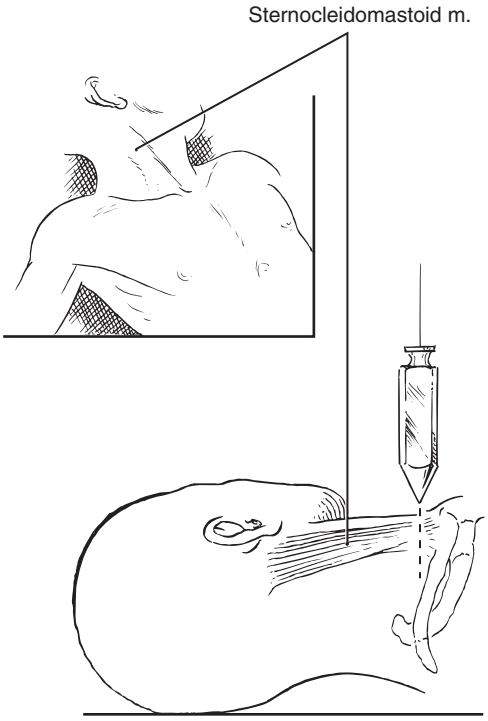

FIGURE **45-10** The patient is placed in the supine position with the head supported and turned toward the opposite shoulder. *m.*, Muscle.

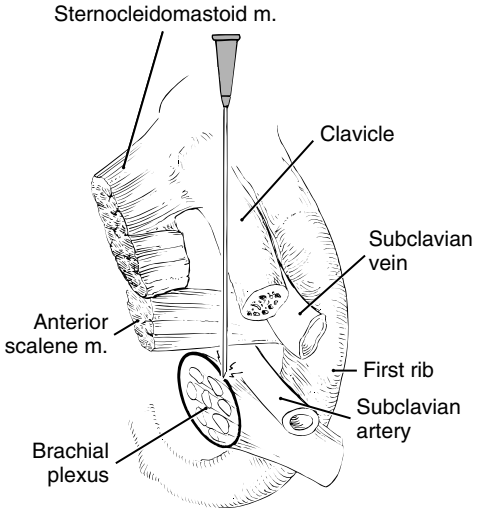

FIGURE **45-11** The needle enters the sheath of the brachial plexus at the farthest possible distance from the subclavian artery. *m.*, Muscle.

The pulsations of the subclavian artery in the plexus are behind and below the clavicle, just above the superior surface of the first rib and between the scalene muscles; the artery is palpated behind the midpoint of the clavicle. The anesthetist uses the nondominant hand to palpate for pulsations behind and 1 to 2 cm above the clavicle at this point and uses the dominant hand to place a skin wheal of local anesthetic immediately lateral to this site. Through the skin wheal, the 22-gauge, insulated B-bevel needle, attached to a nerve stimulator, is advanced perpendicularly to the skin, inward, and caudad until a motor twitch is noted in the lower portion of the upper extremity (Figure 45-11). The nerve stimulator current is lowered from 1 to 0.5 mÅ to minimize excessive current to the patient and to ensure proper needle position. After gentle aspiration is negative for blood, a test dose of 1 mL of local anesthetic solution is injected. A fade will be observed in the quality of the motor twitch experienced by the patient. This indicates that the needle is probably within the brachial plexus sheath. If no subjective symptoms suggesting toxicity reactions are present, incremental injections of 3 to 5 mL of local anesthetic followed by aspiration to detect blood are administered until the intended volume is given. In adult patients, the volume is usually 30 to 35 mL.

The anesthetist must watch for the onset of Horner syndrome (i.e., triad of miosis, partial ptosis, and loss of hemifacial sweating) as a positive sign of a successful block. The most important complication of the supraclavicular approach is pneumothorax. The pleura of the lung is immediately inferior to the first rib, and

careful needle placement as described previously is imperative. If landmarks are difficult to define, if the patient is very thin, or if the pleura of the lung is unusually high, the incidence of pneumothorax may increase. The increased incidence of pneumothorax with the supraclavicular approach and the high incidence of Horner syndrome with the interscalene approach led to Charles Pham Dang's development in 1997 of a new approach to the brachial plexus called the *intersternocleidomastoid* (ISCM) *block*.[47]

Intersternocleidomastoid Approach. In the newest supraclavicular approach to the brachial plexus, the ISCM, the puncture site is situated between the heads of the SCM muscle. The novelty of the technique arises from many features, including simple surface landmarks, minimized risk of pleural puncture, and no risk of epidural, subarachnoid, or intravertebral artery injection or catheterization of the perineural space.

Depending on the direction of the needle with the ISCM approach, the brachial plexus can be reached at the level of the trunks (i.e., superior, middle, and inferior). The needle passes successively between the heads of the SCM, behind the clavicular head, through the middle cervical fascia, next to the phrenic nerve, and through the anterior scalene muscle before arriving at the brachial plexus. The following nerves can be reached and stimulated, depending on the direction of the needle, at a depth varying from 3 to 8 cm: suprascapular nerve, superior trunk, middle trunk, and the divisions and cord.[47]

The patient lies supine with the head turned away, arm at the side, and hand positioned on the abdomen. The anesthetist stands next to the patient's head, opposite the side to be blocked. The sternal and clavicular heads of the SCM, as well as the midclavicle, are marked. The puncture site is situated two fingerbreadths above the sternal notch, between the heads of the SCM, medial to the clavicular head. After disinfection and skin-wheal infiltration, the stimulating needle of appropriate length is introduced behind the posterior border of the clavicular head of the SCM. The needle, practically leaning on the sternal head, is advanced laterally, posteriorly, and caudally in the direction indicated by a point situated 1 cm lateral to the midclavicle. The needle makes an angle of 45 degrees to the table and 15 degrees to the clavicle (Figure 45-12). This initial orientation of the needle leads to the suprascapular nerve, the stimulation of which evokes glenohumeral coaptation and contraction of the supraspinatus and infraspinatus muscles. Stimulation of the superior trunk evokes contraction of the biceps brachii and deltoid muscles, elbow flexion, and abduction of the arm. Stimulation of the middle trunk evokes contraction of the triceps brachii muscle and elbow extension. Stimulation of the divisions and cord evokes flexion pronation of the hand and digit flexion in conjunction with pectoral contraction. Movements of the abdomen can be seen from stimulation of the phrenic nerve. They imply withdrawal and redirection of the needle. These motor responses are obtained at a depth of 2 to 8 cm, depending on the collar size. The nerve stimulator current is lowered from 1.0 to 0.5 mÅ to minimize excessive current to the patient and ensure proper needle position. After gentle aspiration is negative for blood, a test dose of 1 mL of local anesthetic solution is injected. A fade will be observed in the quality of the motor twitch experienced by the patient. This indicates that the needle is probably within the brachial plexus sheath. If there are no subjective symptoms suggesting intraneural needle placement, incremental injections of 3 to 5 mL of local anesthetic, followed by aspiration to detect blood, are administered until the intended volume is given. In adult patients, the volume is usually 30 to 35 mL.[47]

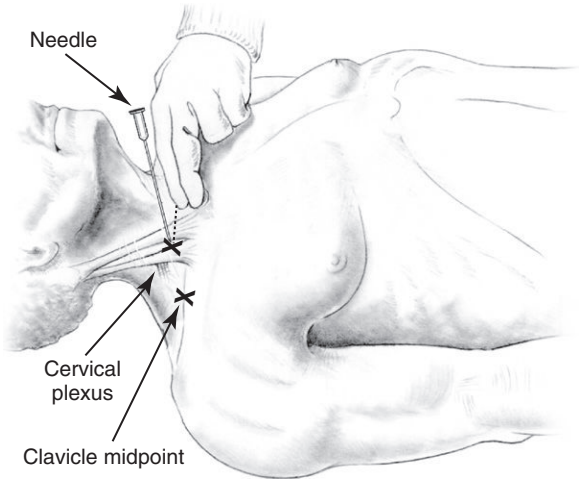

FIGURE **45-12** Technique for intersternocleidomastoid block of the brachial plexus.

Axillary Approach. The axillary approach to anesthesia of the brachial plexus is best suited to surgical procedures at or below the elbow (hand and forearm). However, an injury to the hand or forearm such as a fracture—which also limits the range of motion of the extremity because of patient discomfort—reduces the versatility of this approach. Under these conditions, patient comfort must be weighed against the need for profound anesthesia of the hand or forearm, often in the presence of a full stomach and the desire to avoid general anesthesia. In this instance, access to the axilla can generally be gained by the judicious use of intravenous opioids before slow, careful positioning and support of the extremity in preparation for placement of the block.[48]

The patient is placed in the supine position, with the arm to be blocked abducted 90 degrees from the body. The forearm is flexed to 90 degrees and rested parallel to the long axis of the body. The anesthetist uses the index and third fingers to identify the axillary artery, starting at the lateral margin of the pectoralis major muscle and tracing the artery into the mid- to lower axilla (Figure 45-13). Needle insertion need not occur high in the axilla, as some authors suggest, for successful block. Insertion in the mid- to lower axilla is just as effective; however, it reduces the chances that a local anesthetic will reach the point at which the musculocutaneous nerve leaves the sheath. A well-defined, localized pulsation of the axillary artery is more important to successful blockade than the point at which needle insertion occurs within the axilla. After appropriate preparation of the skin, a local anesthetic intradermal skin wheal is raised just proximal and superior to the palpating index finger. During needle insertion, moderate digital pressure should be applied to the artery to minimize the distance between the skin and subcutaneous tissue and the neurovascular bundle. An appropriate needle connected to a sterile extension tubing and syringe containing 50 mL of local anesthetic is inserted through the skin wheal. At this point the technique diverges, depending on the end-point used to determine when the needle tip lies within the sheath. These end-points include loss of resistance to the advancing needle, penetration of the axillary artery, and elicitation of a paresthesia.[41]

Loss-of-Resistance Technique. The loss-of-resistance technique uses a distinct change in tissue resistance often described as a "pop" as the needle penetrates the fascia and enters the sheath.

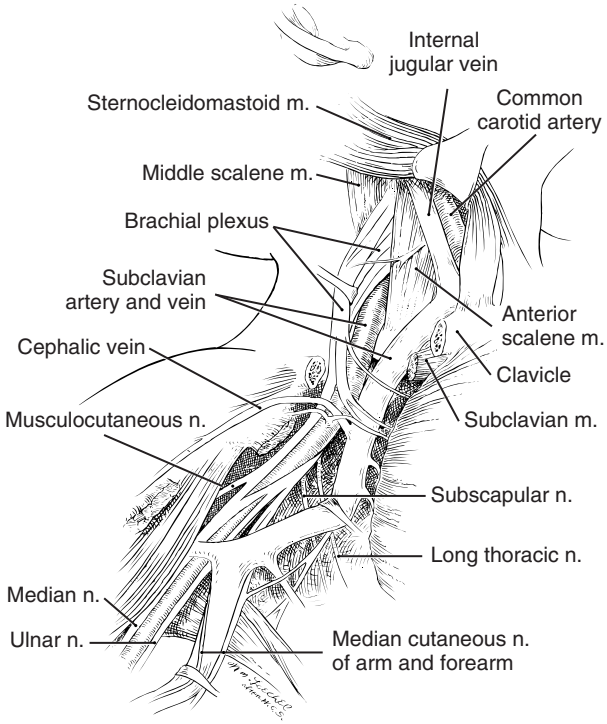

FIGURE **45-13** The brachial plexus at the axilla. *m.*, Muscle; *n.*, nerve.

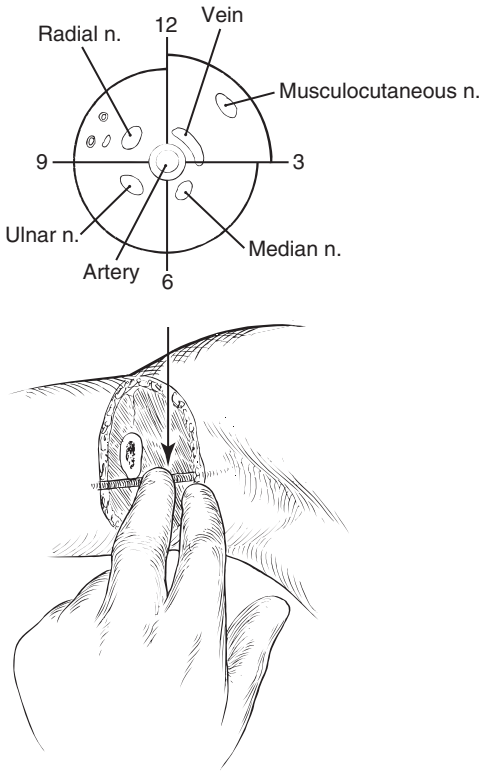

FIGURE **45-14** Identification of the intercostobrachial and brachial cutaneous nerves after completion of the axillary block. *n.*, Nerve.

After the axillary artery is identified, a 22-gauge, 1½-inch, short-bevel ("B-bevel") needle is inserted medially at approximately a 20-degree angle to the skin and parallel to the longitudinal course of the artery (Figure 45-14). Use of a short-bevel needle enhances the loss-of-resistance sensation on penetration of the sheath; however, the drag associated with the attachment of an extension tubing decreases this sensation. Some practitioners disconnect the extension tubing and observe the free needle for a pulsatile movement associated with the needle tip's close proximity to the axillary artery. This is considered a further indication of correct needle placement within the sheath, but it does not guarantee proper placement. The needle is then advanced medially an additional ½ to 1 inch parallel to the axillary artery at an acute angle to the skin.

Before local anesthesia is injected, the patient is instructed to immediately inform the anesthetist if symptoms indicative of rapid intravascular uptake or direct intravascular injection occur. These include dizziness, tinnitus, metallic taste in the mouth ("mouth full of nickels"), circumoral numbness or tingling, visual disturbances, and muscle twitching. If epinephrine has been added to the local anesthetic to reduce vascular absorption of the solution, the patient may also be instructed to report the sensation of having a "rapid" or "hard" heartbeat.

The needle is held fixed in position, and an assistant gently aspirates the syringe while the operator observes for blood in the extension tubing, which would indicate that the needle has entered the axillary artery or vein. In the absence of frank blood in the aspirate, a 3- to 5-mL test dose of the local anesthetic solution is injected and the patient observed and queried for the existence of any of the vascular warning symptoms for a minimum of 1 minute. Barring an untoward event, the remainder of the local anesthetic solution is injected in 5-mL increments, with each injection preceded by gentle aspiration and observation for blood in the extension tubing. During the injection, firm pressure should be applied with several fingers to the area immediately behind the needle insertion site to prevent retrograde flow of the anesthetic solution. Injection of each 5 mL of local anesthetic should be considered a "test dose," because unrecognized penetration of the artery or rapid uptake of the local anesthetic remains a possibility throughout the procedure.

When 40 mL of the local anesthetic solution has been injected, the needle is withdrawn to the level of the skin in preparation for field block, if desired, of the musculocutaneous, medial brachial cutaneous, and intercostobrachial nerves (see Figure 45-14). These nerves may require individual blockade because they exit the sheath high in the axilla (musculocutaneous and medial brachial cutaneous) or lie outside the sheath altogether (intercostobrachial). If care is taken to apply continuous digital pressure immediately below the site of needle insertion during injection of a 40-mL bolus of local anesthetic solution, and the arm is adducted after injection, anesthesia of the musculocutaneous nerve and its terminal distribution, the lateral antebrachial nerve (sensory innervation to the lateral forearm from the elbow to the wrist), can be achieved.

Before the needle is withdrawn from the skin, the musculocutaneous nerve can be independently blocked by injecting 3 to 5 mL of the remaining local anesthetic into the body of the coracobrachialis muscle. The coracobrachialis muscle is located immediately superior to the axillary artery and inferior to the biceps brachialis muscle. After block of the musculocutaneous nerve has been performed, the needle is again withdrawn to the level of the skin and redirected inferior and perpendicular to the artery into the subcutaneous tissue.

The remaining 3 to 5 mL of local anesthetic is injected into the subcutaneous tissue as the needle is advanced to the hub. This subcutaneous "bracelet" of local anesthetic produces conduction block of the medial brachial cutaneous and intercostobrachial nerves necessary to prevent discomfort if a tourniquet is to be used.

After completion of the block, the arm is immediately adducted and held close to the body to promote the cephalad spread of the local anesthetic solution, which can be obstructed by the abducted humeral head.

Transarterial Technique. The transarterial technique uses intentional penetration of the axillary artery and aspiration of blood as the end-point for determining that the needle is within the sheath. After the axillary artery is identified, a local anesthetic skin wheal is raised directly above the artery at the planned point of needle insertion (see Figure 45-14). A 21-gauge, 1½-inch needle is inserted perpendicularly to the skin and advanced slowly until blood is aspirated into the extension tubing by an assistant, who provides gentle aspiration of the syringe. The needle is then advanced along the same plane until blood can no longer be aspirated because the bevel has exited the posterior wall of the artery. Care must be taken to avoid advancing the needle through the posterior wall of the sheath after the artery is exited, which would result in deposition of the local anesthetic outside the sheath.

Failure rate of the transarterial technique has been shown to be significantly reduced when a 26-gauge, ½-inch needle is used as opposed to a 22-gauge, 1½-inch needle.[49] Presumably the shorter needle reduces the chance of exiting the posterior wall of the sheath and deposition of local anesthetic outside the sheath. Before local anesthetic is injected, the patient is instructed to immediately inform the anesthetist if symptoms indicative of rapid intravascular uptake or direct intravascular injection occur. The needle is held fixed in position, and an assistant gently aspirates the syringe while the operator observes for blood in the extension tubing, which would indicate that the needle has entered the axillary artery or vein. In the absence of frank blood in the aspirate, a 3- to-5 mL test dose of the local anesthetic solution is injected, and for a minimum of 1 minute, the patient is observed for and queried regarding the existence of any of the symptoms previously noted.

Barring an untoward event, the remainder of the local anesthetic solution is injected in 5-mL increments, with each injection preceded by gentle aspiration and observation for blood in the extension tubing. Again, to prevent retrograde flow of the anesthetic solution, firm pressure with several fingers should be applied to the area immediately behind the needle insertion site during the injection. Injection of each 5 mL of local anesthetic should be considered a "test dose," because unrecognized penetration of the artery or rapid uptake of the local anesthetic remains a possibility throughout the procedure. When 40 mL of the local anesthetic solution has been injected, the needle is withdrawn to the level of the skin in preparation for field block, if desired, of the musculocutaneous, medial brachial cutaneous, and the intercostobrachial nerves, as noted previously.[38,41]

Ultrasound-Guided Axillary Block. With ultrasound-guided axillary block, the patient is positioned supine and a high-frequency ultrasound probe is placed in the axilla at the crease formed by the pectoralis major and biceps muscles with the ultrasound beam positioned perpendicular to the axillary artery. The anchoring landmarks to be visualized are the axillary artery and the terminal nerve branches of the plexus located in a variable fashion around the axillary artery. The median nerve can be readily visualized, because it is located in close proximity to the axillary artery and tracks down to the cubital area of the elbow. The ulnar nerve is located medial to the artery and remains closer to the skin surface than the median nerve as it tracks down to the proximal forearm. The radial nerve is located just below the artery (Figure 45-15).

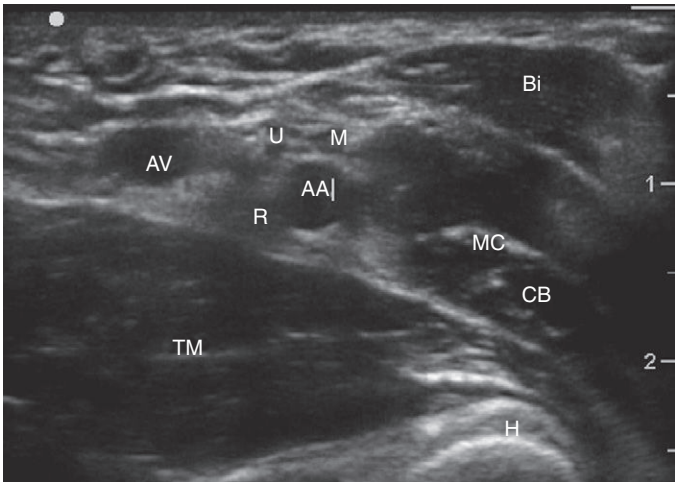

FIGURE **45-15** Transverse view of the axillary segment of the brachial plexus. *AA*, Axillary artery; *AV*, axillary vein; *M*, median nerve; *R*, radial nerve; *U*, ulnar nerve; *MC*, musculocutaneous nerve; *H*, humerus; *CB*, coracobrachials muscle; *Bi*, biceps muscle; *TM*, triceps muscle.

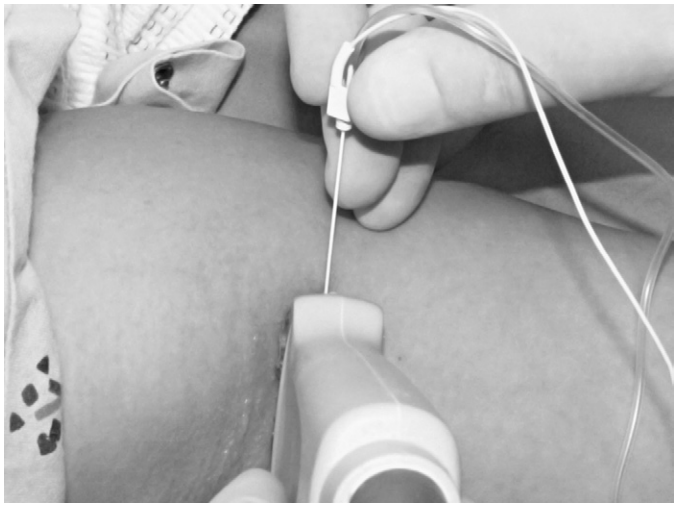

FIGURE **45-16** Needle inserted in-plane in the axilla.

A 22-gauge, 2-inch needle is inserted anterior to the plexus in-plane to the ultrasound beam (Figure 45-16) and advanced until the needle tip comes to rest in close proximity to the terminal branches of the brachial plexus; 20 to 30 mL of local anesthetic is injected under direct observation. The local anesthetic solution should create an expanding hyperechoic area that surrounds and engulfs the nerve plexus (Figure 45-17).

The musculocutaneous nerve is located between the corabrachial and pectoralis major muscles and is usually separated from the radial, median, and ulnar nerves at the level of the axilla (see Figure 45-15). The musculocutaneous nerve generally cannot be blocked by the injection of local anesthetic into the axillary sheath. The musculocutaneous nerve may be blocked independently using a 2-inch, 22-gauge needle in an in-plane or out-of-plane position relative to the ultrasound beam approach. The musculocutaneous nerve will appear as a large, singular hyperechoic structure with small, internal hypoechoic fascicles. A volume of 5 to 10 mL of local anesthetic solution is injected under direct observation.

Continuous Catheter Technique. Postoperative pain control after upper extremity surgery requires adequate analgesia not only

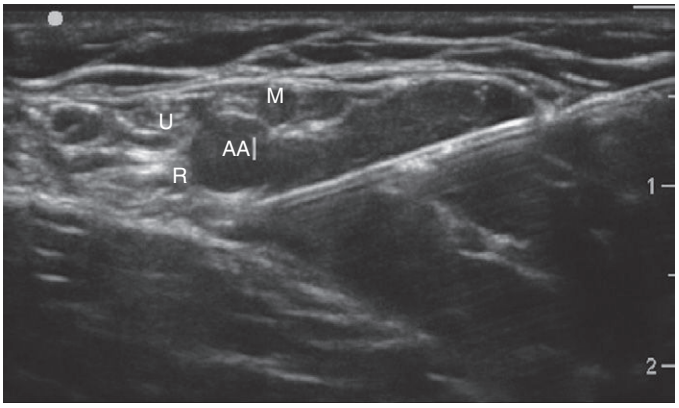

FIGURE **45-17** Transverse view of the axillary portion of the brachial plexus with a needle positioned just below the axillary artery and the formation of a hyperechoic area as a result of local anesthetic injection. *AA*, Axillary artery; *M*, median nerve; *R*, radial nerve; *U*, ulnar nerve.

at rest but also for incident pain. Especially after joint surgery, mobilization is required, as is the need to assess neurologic function. The use of brachial plexus catheters for the surgical anesthetic can have significant benefits by reducing postoperative analgesic requirements, including superior control of incident pain, and can be extended to aid in postoperative rehabilitation of the patient.[49]

Continuous administration of local anesthetics via a brachial plexus catheter inserted at the cervical level can markedly improve analgesia and decrease opioid requirements. The advent of cheaper and reliable pump technology has given rise to a significant growth in the use of continuous peripheral nerve blocks in general, especially continuous brachial plexus blocks.[49]

Under strict sterile technique, a 22-gauge, insulated block needle should be advanced at the level of C6 or the cricoid cartilage into the anterior and middle scalene groove and directed 45 degrees in a caudal, dorsal, and medial angle to reduce the risk of a punctured vertebral artery or inadvertent subarachnoid or epidural placement. The practitioner may feel a slight "pop" as the needle enters the sheath. Before placement of the catheter, the patient should be instructed to report any paresthesia experienced. Use of an insulated needle and a nerve stimulator or ultrasound technology may allow more accurate placement, reduce the risk of intraneuronal injection and trauma, and reduce time for placement of the catheter. When the desired motor stimulation is identified—movement in the upper or lower arm—the current should be gradually reduced to 0.5 mÅ with continued stimulation to ensure close proximity to the neural target. Normal saline, 5 to 10 mL, should then be injected incrementally with intermittent aspiration to guard against accidental intravascular injection. The addition of normal saline will expand the sheet and allow for the passage of the continuous catheter. The catheter should be inserted 3 to 5 cm and secured at the skin. Local anesthetic solution in a volume of 30 to 35 mL should now be injected incrementally, with intermittent aspiration to guard against accidental intravascular injection and to ensure that the continuous catheter works. Continuous infusions of 0.125 to 0.25 mL at a rate of 4 to 6 mL/hr have been shown to be very effective.[49-51]

Selective Blocks at the Elbow

Several other blocks of the upper extremity can be of benefit and may become techniques of choice, especially in outpatients. Selective blocks at the elbow and wrist permit the surgeon to complete the procedure while minimizing the amount of anesthesia

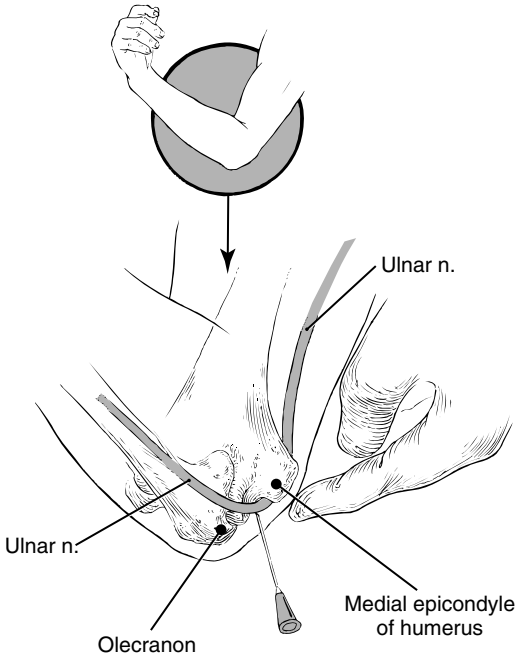

FIGURE **45-18** Technique of ulnar block at the elbow. The patient's elbow is flexed 90 degrees, and the medial condyle of the humerus is identified. *n.*, Nerve.

administered. The blocks at the elbow and wrist are primarily sensory blocks. The patient retains the ability to move the hand during the procedure. Reduction of the area anesthetized, the amount of sedation administered, and the potential for complications minimizes the patient's stay in the outpatient center. The mastery and use of selective nerve blocks of the upper extremity avoids the use of a general anesthetic when the regional anesthetic technique fails to completely block all the nerves that innervate the surgical site.[52-54]

Each nerve that supplies sensory branches to the arm can be blocked at the elbow and the wrist. Use of a nerve locator at the level of the elbow (for the median and radial nerves) and at the level of the wrist (for the ulnar and median nerves) can improve the success rate of the block.

When a tourniquet is used during the surgical procedure, the intercostobrachial nerve and the brachial cutaneous nerve should be blocked in the axilla. These blocks provide sufficient anesthesia to permit the patient to tolerate a tourniquet. The coracobrachial muscle also can be blocked at the level of the shoulder to provide anesthesia so the patient may better tolerate the tourniquet.

Ulnar Nerve Block at the Elbow

As the ulnar nerve traverses the ulnar sulcus of the humerus, it is tightly fixed in the groove. Performing a regional anesthetic technique in this location can increase the risk of nerve entrapment. The volume of the solution should be limited to reduce the amount of pressure exerted on the nerve and the ischemia that could develop from injection of a large volume (greater than 3 mL).[44]

The technique should be performed 1 to 2 cm proximal to the sulcus. The patient's elbow is flexed 90 degrees, and the medial condyle of the humerus is identified. A finger is placed in the ulnar sulcus, extending approximately 1 cm proximal to the condyle (Figure 45-18). The insertion point for the needle is between the medial condyle of the humerus and the olecranon process of the ulna. The needle is inserted at a 45-degree angle to the skin

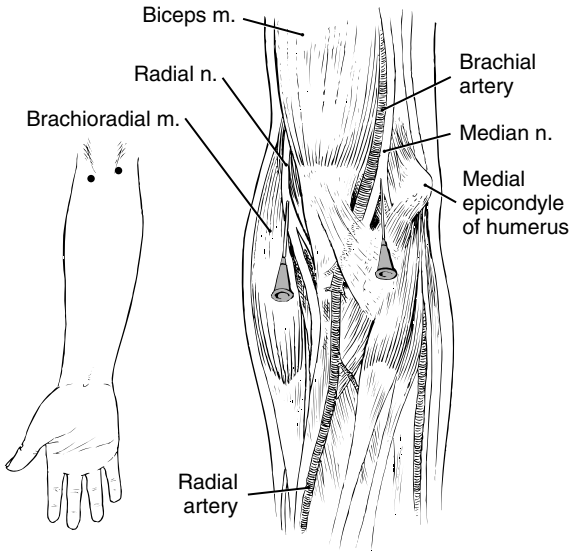

FIGURE **45-19** Performance of median nerve block, positioning the patient's arm on a stable surface with the elbow slightly flexed. After the brachial artery is identified, a short B-bevel needle is inserted slightly medial to the brachial artery. *m.*, Muscle; *n.*, nerve.

and perpendicularly to a line drawn between the medial condyle and the olecranon process. If a paresthesia is elicited on introduction of the needle, the needle is withdrawn approximately 1 mm, and 2 to 3 mL of the solution is injected. If a paresthesia is not elicited, the volume of the solution can be increased. The total volume of the local anesthetic solution is 3 to 5 mL. The onset of action is determined by the local anesthetic used for the procedure. Epinephrine can be used at this level; however, this agent delays the onset.[52-54]

Median Nerve Block at the Elbow

Anesthesia of the forearm and hand can be achieved by a combination of median and ulnar nerve block as either a supplement to another technique or as a primary anesthetic technique. The combination of median and ulnar nerve block provides adequate anesthesia for procedures on the cutaneous portions of the lower forearm, the hand, and the second, third, and fourth fingers. The median nerve block can be used to supplement a partially successful brachial plexus block. The median nerve block should be avoided in patients with carpal tunnel syndrome, if neuritis is present, or if the artery is perforated. If anesthesia is administered to two of the three nerves in the foramen, limited function of the hand remains.

The median nerve block is performed by positioning the patient's arm on a stable surface with the elbow slightly flexed. A line is drawn from the medial to the lateral condyles of the humerus on the anterior surface of the elbow. The brachial artery is then identified as it crosses this line (Figure 45-19). A short B-bevel needle is inserted slightly medial to the brachial artery to a depth of 0.5 to 0.75 cm. Median nerve blocks at the elbow can be facilitated with the use of a nerve locator. When the nerve locator is used, a stimulus of low amplitude elicits a response along the path of the median nerve. If a nerve locator is not used, a paresthesia can be elicited by fan-wise movement of the needle. Identification of the median nerve is necessary for a successful block. Local anesthetic solution (3 to 5 mL) is injected after the nerve is located. As the needle is withdrawn through the fascia, an additional 1 to 2 mL of solution is injected to block cutaneous branches of the nerve.[55,56]

Radial Nerve Block at the Elbow

Block of the radial nerve can be used as an adjunct to axillary perivascular techniques. This block also can be used for surgery of the forearm and hand that is within the distribution of the radial nerve or in conjunction with other nerve blocks.

With the elbow extended and stabilized on a firm surface, the brachioradialis muscle and biceps tendon are identified. The radial nerve is located in the groove formed by the fascial border of the brachioradialis muscle (see Figure 45-19) on the lateral edge and the biceps tendon medially. A line is drawn between the medial and lateral condyles. A short B-bevel needle is inserted along the medial border of the brachioradialis muscle toward the lateral condyle at the point at which the line between the condyles crosses the facial groove. The needle is directed toward the anterior aspect of the lateral condyle so that gentle contact occurs. After contact with the condyle, the needle is withdrawn 2 mm. Local anesthetic solution (3 to 5 mL) is injected. This procedure is repeated two or three times while the needle is moved slightly more proximally for each injection. As the needle is withdrawn into the subcutaneous tissue, 3 to 5 mL of local anesthetic is injected.

An alternate approach to the radial nerve requires identification of the lateral border of the brachioradialis muscle. Measuring 3 to 5 cm proximal from the lateral condyle along the border of the brachioradialis muscle enables palpation of the radial nerve as it parallels the humerus. The nerve is adherent to the bone at this level and can be easily injured during trauma or during the performance of the regional anesthesia. By slight movement of the nerve, a paresthesia can be elicited. A short B-bevel needle is inserted in a plane perpendicular to the humerus and advanced to the proximity of the identified radial nerve. Because of its fixation against the humerus, the needle must be advanced slowly and the position evaluated to avoid injury to the nerve.[55,56]

Selective Blocks at the Wrist

Selective blocks of the ulnar, median, and radial nerves at the wrist can be used for supplying limited anesthesia for the outpatient or as a supplement to brachial plexus anesthesia. Procedures that require a motor block in addition to the sensory blockade should be accomplished by use of another anesthesia technique. Epinephrine is not included in solutions used in nerve blocks below the elbow because of the relatively small blood vessels of the wrist, hand, and fingers and the risk of compromising circulation to these areas.[55,56]

Ulnar Block at the Wrist

With the wrist slightly flexed and stabilized on a firm surface, the ulnar flexor muscle of the wrist is identified (Figure 45-20). A line is then drawn across the forearm at the level of the styloid process of the ulna. A short B-bevel needle is inserted perpendicularly to the skin on the radial side of the ulnar flexor muscle of the wrist, where it is crossed by the line. At this location, the needle is slightly lateral to the ulnar artery, and a small deviation medially can place the needle over the artery. The ulnar artery can be palpated when the wrist is in moderately exaggerated extension. However, severe extension causes the artery to collapse. After the needle is inserted, 2 to 4 mL of local anesthetic solution is injected. An additional 2 mL is injected as the needle is withdrawn from the deep fascia. The dorsal branch of the ulnar nerve is blocked by injection of 3 to 5 mL of local anesthesia in a half-ring around the ulnar aspect of the wrist. The needle is placed subcutaneously at the radial margin of the ulnar flexor muscle of the wrist and advanced to the midportion of the dorsal aspect of the wrist.[55,56]

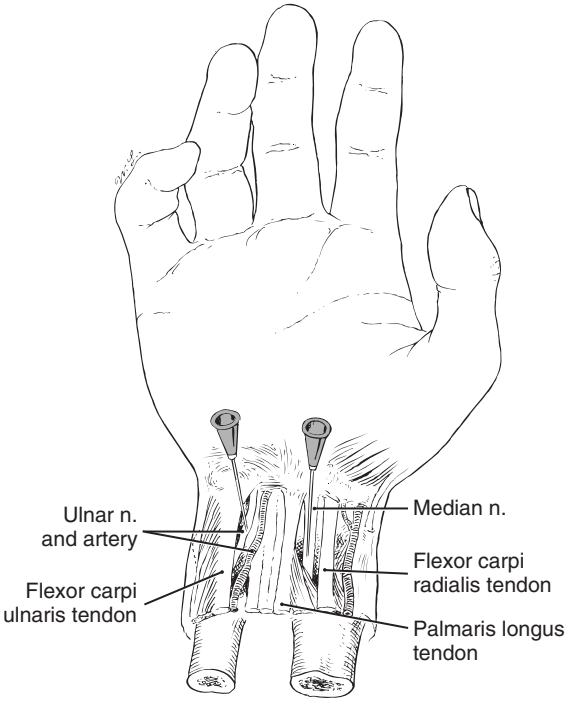

FIGURE **45-20** With the patient's wrist slightly flexed and stabilized on a firm surface, the ulnar flexor muscle of the wrist is identified. A short B-bevel needle is inserted perpendicular to the skin on the radial side of the ulnar flexor muscle of the wrist. *n.*, Nerve.

Median Block at the Wrist

The wrist is stabilized on a firm surface and slightly flexed against resistance. When the wrist is flexed, the long palmar muscle and the radial flexor muscle of the wrist are easily identified (see Figure 45-20). A line is drawn across the wrist that parallels the proximal crease. A short B-bevel needle is inserted perpendicularly to the skin between the two tendons to a distance of 0.5 to 1 cm. The carpal tunnel is a tightly confined space. The nerve is located in the superficial portion of the carpal tunnel. A paresthesia can be elicited during the performance of the procedure. If the sensation persists, the needle must be withdrawn and repositioned. Local anesthetic solution (2 to 5 mL) is injected within the carpal tunnel, and another 2 to 3 mL is injected after the needle is withdrawn from the fascia of the carpal tunnel.[55,56]

Radial Block at the Wrist

The sensory fibers of the radial nerve to the hand are superficial branches at the wrist. Anesthesia of the radial fibers is achieved through the injection of a subcutaneous ring of local anesthetic solution, beginning at the radial flexor muscle of the wrist and extending to the dorsal surface of the ulnar styloid (Figure 45-21). The formation of a continuous ring of local anesthetic around the wrist should be avoided when this procedure is accomplished in conjunction with an ulnar block because circulation to the hand could be compromised.

Another approach to anesthesia of the radial nerve is the identification of the brachioradialis muscle proximal to the wrist. Approximately 6 to 8 cm proximal to the wrist, 5 to 7 mL of local anesthetic solution is injected under the brachioradialis muscle. This technique is the least well tolerated of all of the supplemental blocks and has limited success.[55,56]

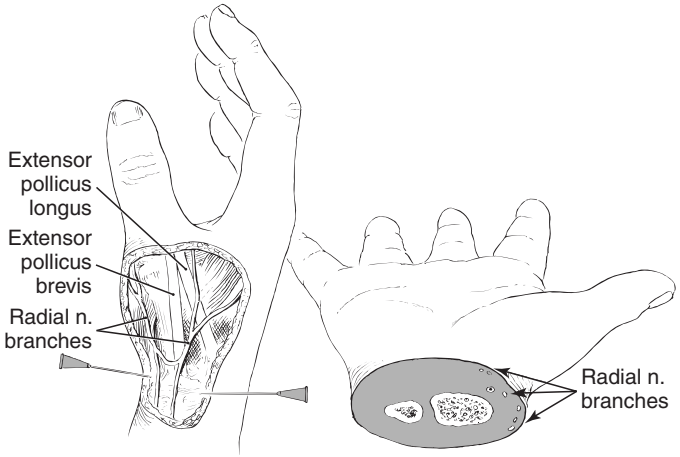

FIGURE **45-21** Anesthesia of the radial fibers is achieved by injecting a subcutaneous ring of local anesthetic solution at the radial flexor muscle of the wrist, extending to the dorsal surface of the ulnar styloid. *n.*, Nerve.

INTRAVENOUS REGIONAL ANESTHESIA (BIER BLOCK)

Intravenous regional block is a technically simple, safe, and rapid means of producing surgical anesthesia of the extremity. The technique is best suited for upper extremity (hand and wrist) soft-tissue surgical procedures of 1 hour or less; however, it has also been used for lower extremity surgical procedures of the foot and ankle. The factor limiting the duration of anesthesia to approximately 1 hour is most commonly discomfort produced by the tourniquet required to initiate and maintain the block. Use of a dual tourniquet system and preoperative and or intraoperative administration of small doses of opioids may extend this time limit to the maximum tourniquet time of 2 hours. The greatest risk associated with intravenous regional anesthesia (IVRA) is the potential for rapid transfer of a large volume of local anesthetic from the extremity to the central circulation in the event of an improperly fitted or inflated tourniquet or tourniquet failure. Therefore, it is important to have emergency equipment, medications, and monitors immediately available when this block is administered. Because of the rapid onset of the block and the limited duration, it is almost always performed in the operating area, where the emergency items needed are readily available. The necessity for intravenous access and manipulation of the affected extremity, the prerequisite for a tourniquet, and the density and duration of the block influence the clinical application of this technique.[55-57]

Intravenous Regional Anesthesia: Upper Extremity Block

A small-bore (23-25 gauge) intravenous catheter is placed in a distal vein of the affected extremity and secured in place, and a heparin lock is attached and flushed with normal saline. The preferred location for access to the venous system of the upper extremity is the dorsum of the hand; however, forearm and antecubital fossa veins have been used. Evidence suggests that use of forearm or antecubital fossa veins increases the possibility of a partial or complete failure of the block when the hand or wrist is the surgical target. It is reasonable to assume that consideration should be given to the area on which surgery is to be performed with regard to access to the venous system because attainment of surgical anesthesia is predicated on the adequate spread of the injected local anesthetic. The patient is placed supine, and several

layers of a suitable padding material are wrapped around the arm in preparation for application of the tourniquet. Although a single tourniquet can be used, a dual tourniquet is recommended because it provides a means to extend the length of the block after the initial onset of tourniquet pain.

After application of the tourniquet, the extremity is elevated and exsanguinated. Exsanguination is accomplished by wrapping an Esmarch bandage at close overlapping intervals tightly around the arm, starting at the fingertips and continuing until the bandage overlies the tourniquet itself. In cases in which application of an Esmarch bandage would cause undue discomfort, exsanguination by simple elevation of the extremity for a minimum of 5 minutes may be attempted. This method may or may not result in adequate block. In addition, an air-inflated splint may be used as an alternative to the Esmarch bandage. After exsanguination, the proximal tourniquet is inflated to 250 mmHg or 100 mmHg above systolic blood pressure, and the Esmarch bandage is removed. A total of 50 mL of 0.5% lidocaine is then injected via the intravenous catheter. The local anesthetic should be free of preservatives (e.g., methylparaben, metabisulfite) and contain no vasoconstrictor. The patient should be carefully monitored during the injection for signs of local anesthetic toxicity. At the conclusion of the procedure the cuff may be deflated for as long as 20 minutes after injection of the local anesthetic. This allows enough time for substantial amounts of the drug to diffuse into the tissues; therefore the drug released systemically will not reach toxic levels.

An alternative block technique uses an additional "tourniquet" (Penrose drain) applied at midforearm in the manner used to start an intravenous line after primary distal tourniquet inflation. Half of the 50-mL volume of local anesthetic is injected with the forearm tourniquet in place; the tourniquet is removed, and the remaining local anesthetic is injected. This technique results in a faster onset and a denser block. Numerous additives to the local anesthetic have been tested, including opiates, clonidine, muscle relaxants, and ketorolac. Ketorolac appears to be the only agent that provides a significant clinical benefit.[58] The addition of 15 to 30 mg of ketorolac to the local anesthetic solution can provide a degree of postoperative analgesia without increasing the risk of postoperative bleeding.[55-57]

Intravenous Regional Anesthesia: Lower Extremity Block

Indications for IVRA of the lower extremity include orthopedic surgery of short duration on the foot, removal of fixation plates and screws from the bones below the knee, and foreign body removal from the foot.

Two significant differences exist between IVRA of the upper and lower extremities. First, the local anesthetic volume (and dose) for IVRA of the lower extremity is approximately double that used for the arm. This obviously increases the risk of local anesthetic intoxication resulting from leakage under the inflated cuff and from release of a large bolus dose of local anesthetic when the cuff is deflated. Second, in order to occlude the arterial inflow at the thigh level (femoral artery), the tourniquet pressure must be higher than in the arm (usually 350 to 400 mmHg), which increases the occurrence and intensity of tourniquet pain.

Two separate 9-cm–wide tourniquet cuffs (adult patient) are applied, and care must be taken that the pneumatic parts of the tourniquets surround the thigh by more than 1.5 turns. Otherwise, the technique is similar to that described for IVRA of the arm.

During brief surgical procedures of the foot or the ankle, the distal tourniquet cuff may be applied on the calf, clearly below the head of the fibula (away from the peroneal nerve), and the proximal cuff left on the thigh. The local anesthetic solution is injected with the distal tourniquet cuff inflated; therefore, the volume and the dose can be the same as for the arm of an adult, that is, 35 to 45 mL of 0.5% lidocaine. The proximal tourniquet is usually not inflated but can be rapidly inflated in the event the distal tourniquet fails.[56,59]

INTERCOSTAL NERVE BLOCKS

The use of the intercostal nerve block has increased in the past several years. The anatomic landmarks are easily identified, thereby facilitating the performance of the block. The procedure is not extremely painful, has a high rate of success, has a low incidence of complications, and provides the patient with significant analgesia. The most common complications are pneumothorax and toxicity from the local anesthetic. The patient who has pain with respiratory effort is able to cough and breathe deeply with reduced discomfort. In the outpatient or ambulatory care setting, surgical procedures can be accomplished with the aid of this regional anesthesia technique.[60]

The use of multiple-level intercostal nerve block can lead to the highest local anesthetic plasma levels of any regional techniques. The high vascularity of the area and large intercostal veins contribute to high plasma levels of local anesthetic. The high plasma concentration can produce toxicity with lower-than-toxic injected doses.

Intercostal nerve block is used for supplementing balanced anesthesia techniques to increase tolerance of the surgical procedure. Sufficient analgesia can be provided to permit the performance of surgical procedures involving the abdominal wall without the need for supplemental blocks. For more involved procedures, additional anesthesia may be required.

Intercostal nerve block can provide analgesia for postoperative pain control when epidural analgesia is not desired or possible. The procedure can provide analgesia during or after chest-tube insertion to limit the patient's discomfort. The landmarks are easily identified in most patients. The procedure can be accomplished with the patient prone, in the lateral position, or sitting comfortably with the upper body supported over a table or a stand. Having obese patients sit up enables easier identification of landmarks. One advantage of using multiple-level intercostal nerve blocks is the reduction in the amount of pain medication required to facilitate normal respiration in the postoperative period. These factors result in a reduction in the potential development of respiratory depression related to the use of intravenous or intramuscular opioids, especially in obese patients.

The intercostal nerve emerges from the intervertebral foramen and follows the rib in the costal groove. This groove is located on the anteroinferior aspect of the rib. The intercostal artery and vein accompany the nerve in the groove. Medial to the posterior angle of the rib, the neurovascular bundle lies between the pleura and the internal intercostal fascia. As the nerve passes the angle of the rib, it begins to run between the two layers of the internal intercostal muscle. At the midaxillary line, the nerve branches send sensory fibers anteriorly and posteriorly to supply skin and subcutaneous tissue. Fibers also provide motor and sensory innervation to the bundles of the superior rectus muscle in the upper abdomen.

Positioning the patient may require modification to facilitate breathing during the procedure. The area of pain may have to be splinted, or other measures may need to be taken to reduce pain-induced movement during the procedure. Ideally the patient should be positioned in the prone position with the arms hanging down. This position pulls both scapulas away from the midline

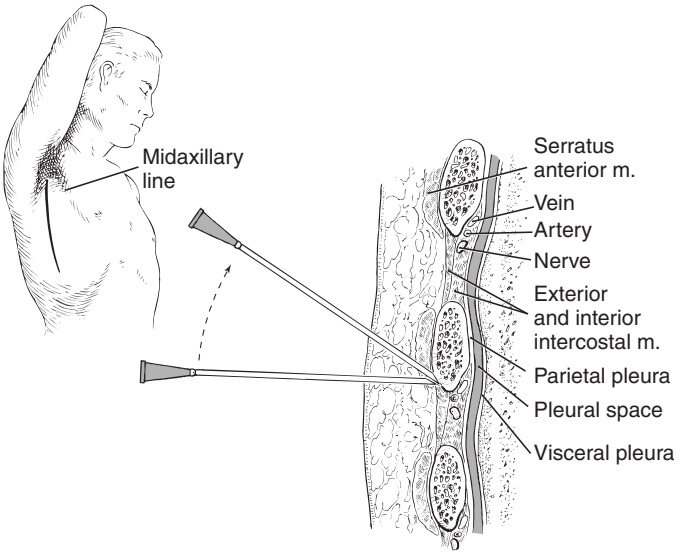

FIGURE **45-22** A 22-gauge, B-bevel needle is inserted perpendicular to the rib and advanced until contact is made with the rib. The needle is slowly walked caudad off the rib. *m.*, Muscle.

and permits the practitioner to perform the block as the nerve root begins to travel in the intercostal groove.

The block can be performed with the patient lying on the unaffected side with the arm extended over the head. This technique is helpful in obese patients and in patients experiencing severe pain, especially when such a patient is prone. When the patient is in the lateral position, preservation of circulation in the downward arm must be preserved.

In postoperative patients, the supine position can be used with the anterior approach to the intercostal nerve. This position is less satisfactory and is associated with a higher incidence of complications.

The rib is palpated posterior to the midaxillary line in the prone patient so that the appropriate landmarks can be identified. In this position, the rib becomes superficial to the muscle bodies. The lateral border of the sacrospinal muscle must be identified before the block is attempted. The sacrospinal muscle lies approximately 7 to 10 cm from the midline.

With a small-gauge (27- to 30-gauge) needle, a skin wheal is raised over the point chosen for the injection. A 22-gauge, B-bevel needle is then inserted perpendicularly to the rib through the skin wheal and advanced until contact with the rib is made. The needle is slowly walked caudad off the rib. As the edge of the rib is cleared, the needle is advanced another 2 to 3 mm (Figure 45-22). The needle should be gently aspirated for verification of needle placement. Use of a "free needle," as described in brachial plexus anesthesia, can facilitate the maneuverability of the needle and increase control.

Once the needle is located in the appropriate location, 3 to 5 mL of the local anesthetic solution is injected. The procedure can be repeated for anesthesia at each dermatome level. If resistance is encountered during the injection, the injection should be terminated and the needle repositioned. If the patient begins to cough or move, the needle position should be reevaluated before injection. Advancing the needle several millimeters can place the needle within the nerve itself, resulting in severe pain or direct injury to the nerve.

Procaine, bupivacaine, tetracaine, and lidocaine have all been used for blocking the intercostal nerves, with varying effects. Because the goal is to provide the patient with extended pain relief, a longer-acting agent is most commonly used. An injection of 3 mL of bupivacaine (0.5%) into the tissues surrounding the intercostal nerve provides the patient with 3 to 9 hours of anesthesia and analgesia. Patient factors such as temperature, presence of infection, and the response to local anesthetics affect the duration of action. The addition of low-molecular-weight dextran to the solution in a ratio of 1 mL of dextran to 3 mL of bupivacaine further extends the duration of action. Dextran slows the absorption of the local anesthetic, thereby reducing the plasma level of the anesthetic and permitting more of the concentrated local anesthetic solution to remain in close proximity to the neural tissue.

Epinephrine 1:200,000 or 1:400,000 should be added to the local anesthetic solution. Bupivacaine's duration of action may be unchanged; however, the rise in the plasma concentration of the local anesthetic is slowed. The addition of epinephrine to tetracaine or lidocaine prevents the rapid absorption of the anesthetic and increases the duration of action. With the use of epinephrine, increased vasoconstriction occurs, an effect that reduces absorption of the local anesthetic. The increased contact time between the neural tissue and the local anesthetic increases the amount of local anesthetic present to be absorbed into the neural fibers.

In addition to the single-shot technique described previously, a continuous intercostal block can be used for providing additional pain relief. The technique was originally described in the mid-1960s. However, it did not gain popularity until 1983, when it was reintroduced as a "new" technique. The continuous technique permits the reinjection of the intercostal fibers without the need for additional invasive procedures. Opioids have been injected in the intercostal nerve sheath with limited enhancement of the analgesia.

The continuous intercostal technique is performed by use of an epidural needle and a catheter in place of a single-shot needle technique. The intercostal groove is located using the technique described for the single-shot technique. When an epidural needle is used for the procedure, resistance is met as the needle passes through the sheath. The nerve can also be identified with a nerve locator or nerve stimulator. After the intercostal neural sheath is identified, the needle is adjusted so that the bevel of the needle directs the catheter toward the midline posteriorly. The epidural catheter is inserted slowly along the intercostal groove 2 to 3 cm. If severe pain or discomfort occurs during advancement of the catheter, the procedure is terminated, and the catheter is removed. Advancement of the catheter may produce electric-like shocks as the catheter brushes the nerve fibers. Severe pain should alert the practitioner of the possibility of an intraneural injection.

As the medication is injected, a band of analgesia develops along the path of the catheter and spreads anteriorly and posteriorly. Other than the direct action of the local anesthetic on the neural fibers, the exact mechanisms of action are unknown. However, paravertebral or epidural distribution of the local anesthetic may facilitate and enhance the block. The medication is injected in 3-mL increments until the desired level and intensity of block are achieved.

Tachyphylaxis develops with repeated injections of local anesthetic. Permitting resolution of the block before reinjection or using another local anesthetic reduces this effect. If an ester is used for the initial blockade, an amide local anesthetic can be used when symptoms of tachyphylaxis develop.

Small doses of fentanyl and morphine have been injected through the catheter. However, the uptake of medication into the vascular compartment is rapid, essentially negating the advantages of this route of administration. The use of opioids in the

intercostal space may increase the incidence of complications, including respiratory embarrassment.

The likelihood of complications, such as pleural injection and pneumothorax, can be reduced by use of a short B-bevel needle. To avoid an intraneural injection, the needle is directed cephalad as it passes over the ridge of the rib. A symptomatic pneumothorax can occur; however, use of a single 22-gauge, short-beveled needle reduces the risk. A leak created by this needle can be minimal. When a larger or A-bevel needle is used, the risk of complications is increased.

In most patients a small leak of air does not cause a symptomatic pneumothorax. Most patients are able to compensate for any reduced ventilatory capacity, and the pneumothorax resolves without intervention. In a small percentage of patients, intervention is needed for relief of the discomfort and dyspnea. Radiologic studies should be performed after completion of the procedures so the status or occurrence of a pneumothorax can be established. The studies can be used during follow-up evaluations and therapy if required.

The use of intercostal nerve block has enhanced the practice of anesthesia and pain control. This technique provides the patient with increased flexibility in the control of pain and reduces the need for opioids. In the ambulatory surgery center, this technique offers increased options to the patient who desires a regional anesthetic technique.[60]

LOWER-EXTREMITY BLOCK

Lower-extremity nerve blocks are well described and can provide high-quality anesthesia and analgesia for lower-extremity surgical procedures. Lower-extremity nerve blocks, although underused, have significant advantages compared with central neuraxial techniques, especially in the ambulatory setting.

Advantages of lower-extremity nerve block include reduced recovery room admissions, decreased nausea and vomiting and urinary retention, and improved postoperative analgesia. These benefits may translate into shortened hospital stays, decreased probability of hospital admission, and an overall reduction in hospital costs and patient charges.

Anatomy of the Lumbar Plexus

The lumbar plexus is formed from the first, second, third, and fourth lumbar nerve roots. Contributions to the plexus originate in the twelfth thoracic nerve. The plexus is formed in front of the quadratus lumborum muscle and behind the psoas major muscle (Figure 45-23). As the major branches from the plexus begin their descent into the leg, the muscle bodies and the connecting fascia tightly bind them. The lateral femoral cutaneous nerve is formed from the second and third lumbar nerves and is the first to leave the compartment. It emerges from the lateral border of the psoas major at its midpoint. The nerve then traverses the iliac muscle obliquely toward the anterior iliac spine. The lateral femoral cutaneous nerve passes under the lateral border of the inguinal ligament and provides the sensory innervation to the lateral aspect of the thigh (Figure 45-24).

The obturator nerve arises from the second, third, and fourth lumbar nerves as an extension of the lumbar plexus. It emerges from the medial border of the psoas major at the level of the sacroiliac joint and is covered by the external iliac artery and vein. The nerve passes into the pelvis minor and runs anteroinferiorly to the obturator canal, which it traverses near the obturator vessels. Because of the proximity of the nerve to the external iliac artery, it can be injured during surgical procedures. This nerve is frequently injured when patients undergo extensive pelvic surgery. The obturator nerve is primarily a motor nerve that has some mixed sensory fibers to the hip, the medial aspect of the femur, and the skin and soft tissue of the lower portion of the thigh.

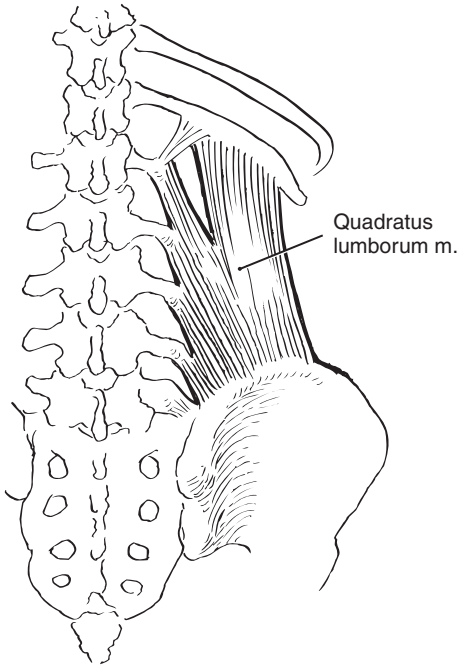

FIGURE **45-23** Location of the lumbar plexus. *m.*, Muscle.

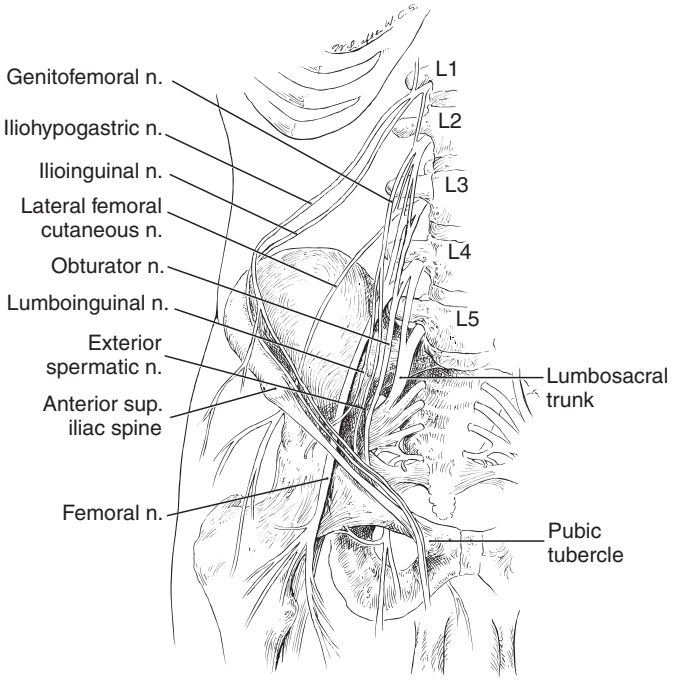

FIGURE **45-24** Origin and position of the nerves of the lower extremity. *n.*, Nerve.

The third nerve in the lumbar plexus is the femoral nerve, which is formed from the contributions of the second, third, and fourth lumbar nerve roots. This nerve forms and appears at the junction of the middle and lower third of the psoas major muscle. It remains within the groove of the psoas major and the iliac muscles and runs deep under the inguinal ligament, where it comes to lie anterior to the iliopsoas muscle and lateral to the femoral artery.

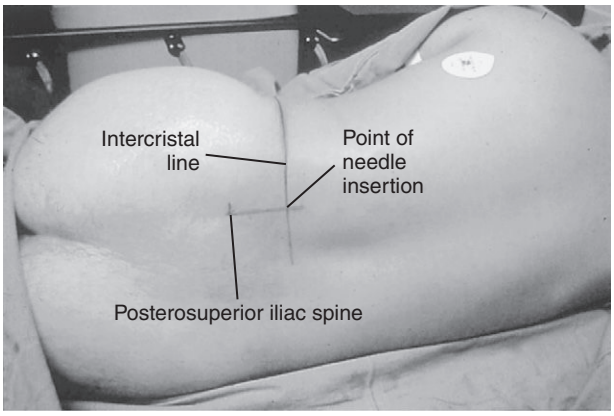

FIGURE **45-25** Lumbar plexus block.

The femoral nerve forms two branches: the anterior and the posterior bundles. This formation usually occurs just after the nerve passes under the inguinal ligament but may occur before it passes under the ligament. The anterior branch provides innervation to the anterior surface of the thigh and the sartorius muscle. The posterior branch provides innervation to the quadriceps muscles, the knee joint, and its medial ligament and is the origin of the saphenous nerve. The femoral nerve is bound by several structures above and below the inguinal ligament. Above the inguinal ligament, the iliaca fascia encapsulates the femoral nerve laterally, the psoas fascia medially, and the transverse fascia anteriorly. The posterior border of this capsule or sheath is made up of the bony structure of the pelvis.

As the femoral nerve joins the femoral artery to enter the leg, the iliopsoas fascia forms the posterolateral wall. The inguinal ligament and the fascia lata form the anterior wall, and the iliopectineal fascia forms the medial wall of the capsule. Winnie et al.[61] suggested that the neural sheath originating with the femoral artery in conjunction with the fascial attachments form a structure similar to the neural sheath in the brachial plexus. With this anatomic design, anesthesia can be provided for the lower extremity through techniques used in upper extremity anesthesia.

Psoas Compartment Block

Immediately after emerging from the intervertebral foramina, the nerve roots form the lumbar plexus. Blockade of the lumbar plexus as a unit can be accomplished by injecting local anesthetic into the fascial sheath surrounding the plexus. This can be done at the level of the psoas compartment.[56,62]

This approach attempts to block the plexus as it lies in the fascial plane bordered medially by the vertebral column, dorsally by the quadratus lumborum muscle, and ventrally by the psoas major muscle.

The patient is placed in either the lateral or sitting position. If placed in the lateral position, the patient should be in a relaxed but curled position similar to that used for spinal or epidural anesthesia, with the operative side uppermost (Figure 45-25).

From the spinous process of L4, a 3-cm line is drawn caudally in the interspinal line. From the end of this line, a 5-cm line is drawn perpendicularly and laterally toward the side to be blocked, usually ending at the medial edge of the iliac crest. This spot identifies the point of needle insertion. A 120-cm insulated block needle is used. A skin wheal is raised, and the needle is inserted perpendicularly to all planes and advanced until contact with bone is made, which identifies the transverse process of L5 and usually occurs at a depth of 5 to 10 cm.

The needle is then withdrawn, redirected slightly cephalad, and advanced until it slides over the transverse process of L5. Using the loss-of-resistance technique, the psoas compartment is usually encountered at the depth of 8 to 12 cm. The tip of the needle now lies in the psoas compartment. Needle placement can be confirmed with the aid of a nerve stimulator, by checking for stimulation of the quadriceps muscles, by eliciting paresthesias into the thigh, or by advancing the needle slightly into the psoas muscle and reconfirming a loss of resistance while withdrawing the needle slightly into the psoas compartment.

After the needle is properly placed, and after careful aspiration, 30 to 40 mL of local anesthetic is injected in 5-mL divided doses. It is often helpful to have the patient remain in the lateral position for a few minutes after injection to limit spread of the drug.

Inguinal Perivascular Technique and Femoral Nerve Block

The inguinal perivascular technique is also known as the *three-in-one block* of the lower extremity. The lumber plexus is "sandwiched" among the psoas major, quadratus lumborum, and iliacus muscles and is enclosed by the fascia of these three muscles.[63-66]

After the patient is positioned supine, the groin is prepared and draped by use of aseptic technique. One possible complication is contamination of the deeper tissues. An immobile needle can be used for improved control of the needle.

The site of injection is 1 cm lateral to the femoral artery and 1 cm inferior to the inguinal ligament. The identified area is prepped with a povidone-iodine (Betadine) solution and then infiltrated with 2 to 3 mL of 1% lidocaine solution subcutaneously. A 22-gauge, 4-cm insulated B-bevel needle is advanced perpendicularly to the skin just lateral to the artery until the femoral nerve is located with the aid of a peripheral nerve stimulator. With a stimulation frequency of 2 Hz, the intensity level is set at 1 mÅ until quadriceps extension is elicited, then decreased to less than 0.5 mÅ. Local anesthetic solution (20 to 30 mL) is injected in 3- to 5-mL increments, with intermittent syringe aspiration. Digital pressure is applied firmly but gently distal to the needle. This action assists in limiting the distal spread of the anesthetic solution by forcing it proximal into the channel formed by the neural sheath and other structures. Digital pressure is continued after the injection for approximately 5 to 10 minutes. Winnie et al.[61] indicated that the total volume of anesthetic solution required to maximize the block must exceed 20 mL. Volumes of less than 20 mL provide a spotty and unpredictable block. Increasing the volume of the solution to 30 mL increases the ability of the solution to contact all three nerves. Bupivacaine (0.5%), ropivacaine (0.5%), and lidocaine (1.5%) are commonly used for this procedure. Anesthesia to the sciatic distribution does not occur with this technique. If the surgical procedure requires anesthesia along the sciatic distribution, a separate procedure must be performed (Figure 45-26).[64-66]

Ultrasound-Guided Femoral Nerve Block

The femoral nerve emerges just below the inguinal ligament, lateral to the femoral artery, and deep to the fascia iliaca. The patient is positioned supine with the groin exposed. The ultrasound probe is placed axially anywhere between the inguinal crease and the inguinal ligament. The anchoring landmarks for visualization are the femoral artery and vein and the femoral nerve (Figure 45-27). The femoral nerve will appear triangular, hyperechoic, and lateral to the femoral artery. A 22-gauge, 2-inch needle is inserted lateral to the femoral nerve, in-plane to the ultrasound beam, and 20 mL of local anesthetic is injected.

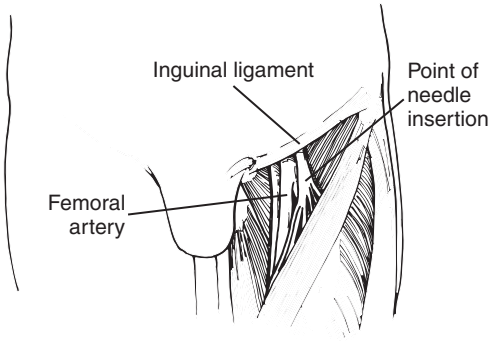

FIGURE **45-26** Femoral nerve block.

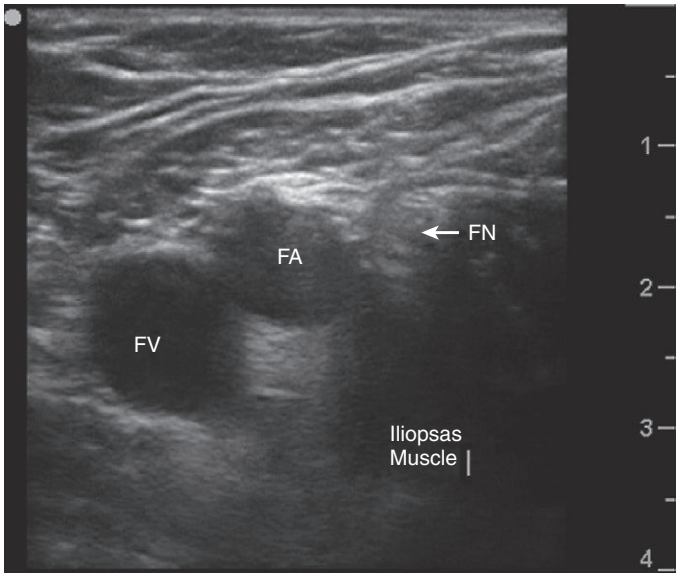

FIGURE **45-27** Transverse view of the femoral nerve lateral to the femoral artery and femoral vein. *FA*, Femoral artery; *FV*, femoral vein, *FN*, femoral nerve.

Continuous Femoral Nerve Block

Extension of the anesthesia and analgesia provided by a femoral nerve block through the use of a continuous catheter technique after surgical procedures of the femur and knee has grown in popularity and application. The success rate is high as long as the surgical procedure does not extend beyond the innervations of the femoral nerve. The landmarks are readily identifiable and include the femoral artery and the femoral crease immediately inferior to the inguinal ligament.

The patient is placed in the supine position and the skin is thoroughly prepped with an antiseptic solution. The practitioner stands on the side to be blocked. Sterile gloves are donned, and the needle insertion site is located at the lateral border of the femoral artery (approximately 1 cm lateral to the arterial pulse) in the femoral crease. A 17-gauge, 3½-inch insulated needle connected to a nerve stimulator set at 1 mÅ, 2 Hz, 100 to 300 μsec is inserted and advanced in the sagittal plane at a 45- to 60-degree cephalad angle. The technique is similar to single-injection femoral nerve block except for the more acute cephalad angle of needle insertion to facilitate threading of the catheter. Following a quadriceps muscle twitch (patellar twitch) at 1 mÅ, the current is reduced to 0.5 mÅ, and the twitch response is reestablished. If a quadriceps twitch is not elicited after initial needle placement, the needle should be withdrawn and redirected slightly more lateral to the femoral artery until the desired twitch response is achieved. An initial bolus of local anesthetic (15 to 20 mL) is injected slowly after negative aspiration for blood, and the catheter is then threaded 5 to 10 cm beyond the tip of the needle. The nerve stimulator can be connected to the catheter to confirm that the tip lies in close proximity to the femoral nerve. The catheter is then secured by one of several mechanisms. Kits available for continuous nerve block often contain a securing device, but the catheter may be secured through use of a suture and/or a clear dressing applied over the catheter. The continuous infusion of local anesthetic is initiated immediately after the bolus injection at a rate of 8 to 10 mL per hour. Typical local anesthetics and concentrations used for this purpose are 0.2% ropivacaine and 0.25% bupivacaine.

Strict aseptic technique should be adhered to during placement and maintenance of the catheter, and it has been recommended that the catheter be removed after 48 hours. In addition, as with all peripheral nerve blocks, complaints of pain during needle insertion or injection suggest intraneural penetration. In this event, the needle should be withdrawn and redirected. Insertion of the needle medially is likely to produce femoral artery and or vein penetration. If this occurs, constant pressure should be applied to the site for a period of not less than 2 to 3 minutes prior to another attempt at locating the nerve. The patient should be counseled with regard to the extended loss of sensation and motor control of the extremity and what action to take in the event of a potential complication upon discharge (see Box 45-2).

Fascia Iliaca Compartment Block

The fascia iliaca compartment block is an anterior lumbar plexus approach with a puncture point distant from the neurovascular sheath. A nerve stimulator is not necessary for this procedure. Described for the first time in children in 1989, fascia iliaca compartment block is widely used for postoperative analgesia after lower limb surgery in children and adults and provides effective postoperative analgesia after hip, femoral shaft, or knee surgery. Compared with three-in-one block, it provides a faster and more consistent simultaneous blockade of the lateral femoral cutaneous and femoral nerves. The fascia iliaca compartment block is performed as described by Dalens et al.[67] and others.[68,69] With the patient in a supine position, a projection of the inguinal ligament is drawn on the skin from the pubic tubercle to the anterior superior iliac spine and trisected. The puncture site is marked 1 cm caudal to the point at which the lateral meets the middle third of the inguinal ligament line. After disinfecting the skin using topical 10% povidone-iodine, a short-bevel needle (24 gauge, 50 mm) is inserted at a 90-degree angle to the skin. An initial loss of resistance is felt as the needle tip crosses the fascia lata. The needle is advanced at the same angle until a second loss of resistance is felt as the fascia iliaca is pierced (a paresthesia is not intentionally elicited), and 30 mL of local anesthetic is injected.

Sciatic Nerve Block

Sciatic nerve blocks, in combination with lumbar plexus, femoral, or saphenous nerve blocks, provide complete anesthesia and postoperative analgesia for lower-extremity surgery. Contrary to common belief, sciatic nerve block is relatively easy to accomplish and master.[70] In a recent review of outpatients undergoing complex knee surgery, it was noted that among the patients who received a combination sciatic nerve block with a femoral nerve block, a lower incidence of nursing interventions for pain occurred in the step-down unit.[63] In addition, patients had fewer hospital admissions and were more satisfied with their surgical procedures.[63,71]

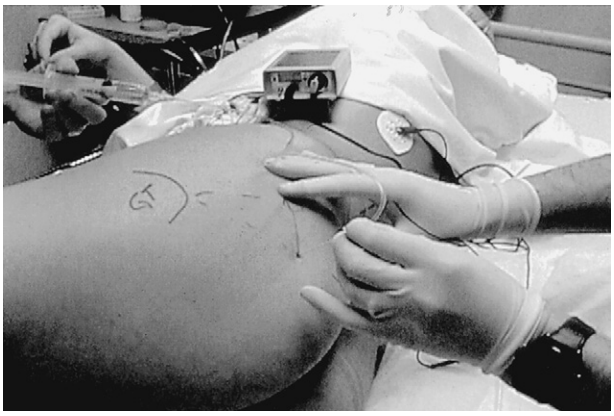

FIGURE **45-28** Sciatic nerve block.

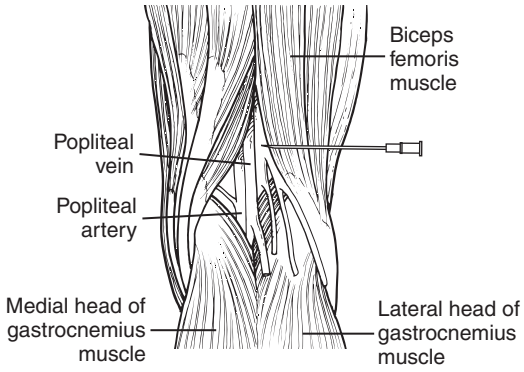

FIGURE **45-29** Popliteal nerve block.

Anatomy of the Sciatic Nerve

The sciatic nerve is the continuation of the upper division of the sacral plexus and is the largest nerve trunk in the body. It supplies the muscles of the back of the thigh, the skin of the leg, and the muscles of the lower leg and foot. It passes out of the pelvis through the great sacrosciatic foramen, below the piriform muscle. It descends between the major trochanter and the tuberosity of the ischium to the lower third of the thigh, where it divides into the internal and external popliteal nerves.[42,43]

Technique of Sciatic Nerve Block

Although posterior and lateral popliteal approaches to the sciatic nerve are performed most commonly for ankle and foot surgery, and higher approaches to the sciatic nerve are performed more commonly for surgery below, above, and at the knee, there is no clinical evidence to support one particular sciatic approach over another. The indications for a given approach are based on the specific surgical requirement (Figure 45-28).[63,71,72]

After standard monitors are placed, the patient is positioned in the Sims position with the operative leg positioned superiorly and flexed at the knee. A line is drawn from the posterior superior iliac spine to the greater trochanter of the femur. A second line is drawn from the sacral hiatus to the greater trochanter, and a third line is drawn perpendicular to and bisecting the first line. The intersection of the second and third lines is the point of needle entry. The identified area is prepared with a Betadine solution and then infiltrated with 2 to 3 mL of 1% lidocaine solution subcutaneously. A 22-gauge, 10-cm insulated B-bevel needle, inserted perpendicularly to the skin, is advanced until the posterior tibial nerve distribution is elicited with the aid of a peripheral nerve stimulator. A stimulation frequency of 2 Hz and an intensity level of 1 mÅ is used until a plantar flexion motor response is elicited. The intensity level is decreased to less than 0.5 mÅ as long as motor response is still present. Local anesthetic solution (10 mL) is injected in 5-mL increments, with intermittent syringe aspiration. The needle is redirected laterally and advanced until peroneal nerve distribution is elicited with the aid of a peripheral nerve stimulator. A stimulation frequency of 2 Hz and an intensity level of 1 mÅ is used until a dorsal flexion motor response is elicited. The intensity level is decreased to less than 0.5 mÅ as long as motor response is still present. Local anesthetic solution (10 mL) is injected in 5-mL increments, with intermittent syringe aspiration. Bupivacaine (0.5%), ropivacaine (0.5%), and lidocaine (1.5%) are commonly used for this procedure.[73,74]

Popliteal Fossa Approach to the Sciatic Nerve Block

The popliteal fossa approach is based on the use of the three anatomic landmarks that define the posterior popliteal fossa: the popliteal crease, the medial border of the femoris biceps muscle laterally, and the tendon of the semitendinous muscle medially.

A line is drawn joining the medial border of the femoris biceps muscle laterally and the lateral border of the semitendinous muscle medially at the level of the popliteal crease. From the middle of this line, a perpendicular line is extended 15 cm cephalad. The site of insertion of the needle is 1 cm laterally. A 10-cm insulated needle connected to a nerve stimulator is introduced through a skin wheal of local anesthesia at a 45- to 60-degree anterosuperior angle. The sciatic nerve usually is located at a depth of 1 to 2 cm in an adult. After careful aspiration, 35 to 40 mL of a local anesthetic is injected (Figure 45-29).

Ultrasound-Guided Popliteal Fossa Approach to Sciatic Nerve Block

The popliteal artery and vein can be located with the ultrasound probe placed in the popliteal region of the knee parallel to the flexor crease. The tibial nerve can usually be visualized at this level, just lateral and/or superficial to the popliteal vessels. Lateral to the nerve lies the biceps femoris muscle. Medial to the nerve lie the *semimembranosus* and *semitendinosus* muscles. Once the tibial nerve is identified at the flexor crease, the ultrasound probe is slid slowly proximal. The tibial nerve is joined by the common peroneal nerve approximately 5 to10 cm above the flexor crease to form the sciatic nerve (Figure 45-30). A 22-gauge, 2-inch needle is inserted lateral to the nerve, in-plane to the ultrasound beam, and advanced until the needle tip is adjacent to the nerve; 20 mL of local anesthetic is then injected under direct observation to envelope the tibial and common peroneal nerves (Figure 45-31).

Ankle Blocks

The ability to administer anesthesia to patients who require surgery of the foot offers valuable additional regional block options. Either a complete or partial block of the foot can provide adequate anesthesia for many of the surgical procedures performed by podiatrists and orthopedic surgeons. The nerves are easy to locate, and the procedures can be rapidly accomplished. This tool can prove invaluable in the care of certain patients, such as those with gangrene of the foot or those with diabetes who have foot ulcers, in whom a local anesthetic procedure would be inadequate.[75]

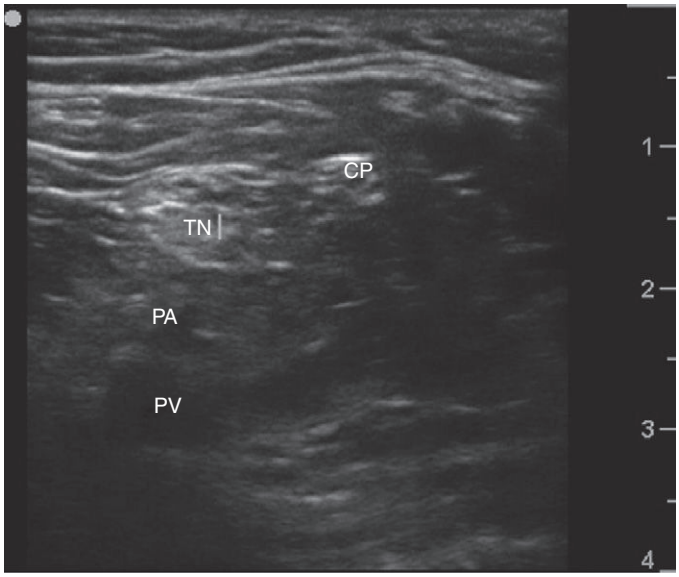

FIGURE **45-30** Transverse view of the popliteal fossa before injection of local anesthesia. *CP*, Common peroneal nerve; *TN*, tibial nerve; *PA*, popliteal artery; *PV*, popliteal vein.

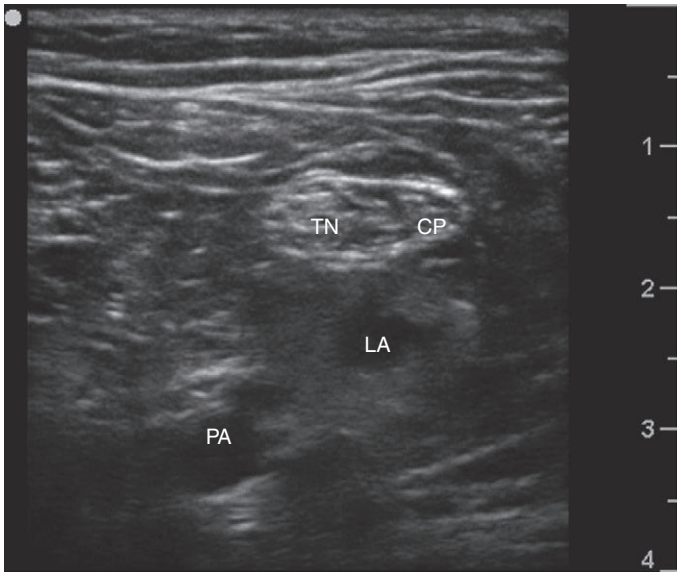

FIGURE **45-31** Transverse view of the popliteal fossa after injection of local anesthetic. *CP*, Common peroneal nerve; *TN*, tibial nerve; *PA*, popliteal artery; *LA*, local anesthetic.

Anatomy of the Ankle

The ankle block is performed by the blocking of five nerves at the level of the ankle: the tibial nerve, the sural nerve, the superficial peroneal nerve, the deep peroneal nerve, and the saphenous nerve.

Tibial Nerve. The tibial nerve arises from the nerve roots of the fourth and fifth lumbar roots, along with the first, second, and third sacral roots. It is the larger of the two branches of the sciatic nerve. The path of this nerve lies on the medial side of the Achilles tendon. It passes into the ankle with the posterior tibial artery (Figure 45-32). At the level of the ankle this nerve lies behind the posterior tibial artery and between the tendons of the long flexor muscles of the toes and the long flexor muscles of the great toe. The nerve is covered by the flexor retinaculum. Several branches

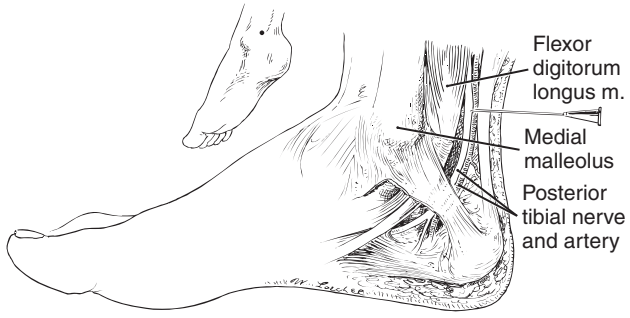

FIGURE **45-32** Path of the posterior tibial nerve, with the posterior tibial artery past the Achilles tendon. *m.*, Muscle.

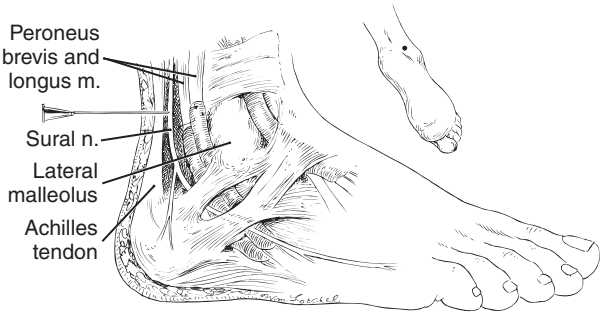

FIGURE **45-33** Path of the sural nerve behind the lateral malleolus into the ankle. *m.*, Muscle; *n.*, Nerve.

leave the neural bundle at the level of the medial malleolus. Two of the branches, the medial and the lateral plantar nerves, traverse the ankle, following under the cover of the abductor hallucis. They provide sensory innervation to the foot.[56,62]

Sural Nerve. The sural nerve is formed from the union of a branch of the tibial nerve and the common peroneal nerve. This nerve travels superficially with the short saphenous nerve behind the lateral malleolus into the ankle, where it provides the sensory innervation to the posterior portion of the sole of the foot, as well as to the posterior portion of the heel and the portion of the Achilles tendon immediately above the ankle (Figure 45-33).[56,62]

Superficial Peroneal Nerve. The superficial peroneal nerve arises from the roots of the fourth and fifth lumbar nerve roots, as well as the first and second sacral nerve roots. The nerve becomes superficial in the middle two thirds of the lower leg and remains subcutaneous as multiple branches proceed into the dorsum of the foot. Just above the ankle (Figure 45-34) the nerve begins to branch; for this reason a single injection site does not provide sufficient anesthesia.[56,62]

Deep Peroneal Nerve. The deep peroneal nerve arises from the same nerve roots as the superficial peroneal nerve. However, it remains within the protection of the anterior tibial muscle and the long extensor muscle of the great toe (see Figure 45-34) as it traverses the leg and into the ankle. As it crosses the ankle, it is covered by the extensor retinaculum. The deep peroneal nerve provides innervation to the short extensors of the toes and provides sensory innervation to the skin on the lateral side of the hallux and on the medial side of the second digit. The nerve and the artery cross each other, so the nerve lies lateral to the anterior tibial artery and medial to the long extensor muscle of the great toe that is in the ankle. This nerve is frequently missed when regional anesthesia is administered to the ankle.[56,62]

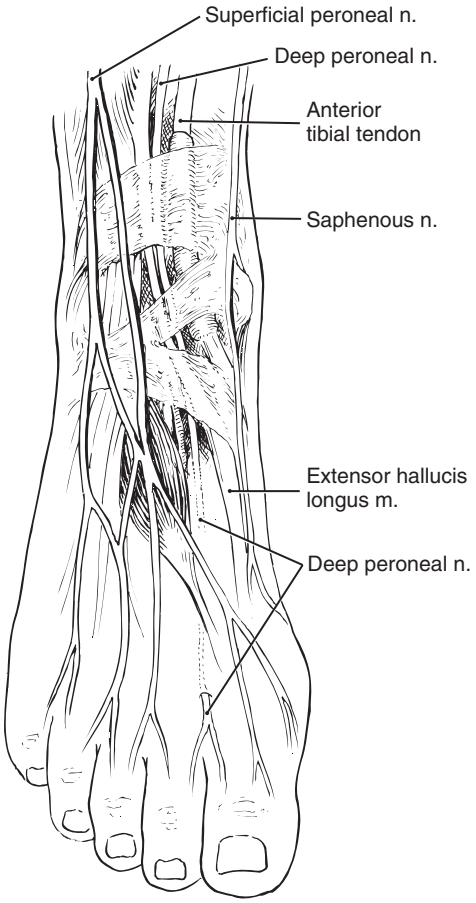

FIGURE **45-34** The superficial peroneal nerve proceeds to the dorsum of the foot subcutaneously through multiple branches. *n.*, Nerve.

Saphenous Nerve. The saphenous nerve is the terminal branch of the femoral nerve and travels subcutaneously from the lateral side of the knee joint. It follows the greater saphenous vein to the medial malleolus and provides sensory innervation to the medial side of the malleolus and the skin of the medial aspect of the lower leg (see Figure 45-34). If the block of this nerve is inadequate, the patient is unable to tolerate a tourniquet above the ankle.[56.62]

Ankle Block Technique

The approach to both the sural and the posterior tibial nerves can be enhanced by placing the patient in the prone position. However, this is not always the most comfortable position. Therefore, the patient should be placed in the most comfortable position that permits sufficient mobility of the foot. Rotation of the foot from side to side can be facilitated by turning the patient onto either side or elevating the foot on towels or pillows. The posterior tibial artery is palpated at the level of the superior portion of the medial malleolus. After the artery is located, the needle is inserted lateral to the artery in a line drawn from the superior portion of the medial malleolus to the lateral malleolus across the Achilles tendon. If the artery is not palpated, the needle is inserted lateral to the Achilles tendon at the level of the superior portion of the medial malleolus. The needle is advanced toward the medial malleolus and lateral to the position of the posterior tibial artery. As the needle is advanced toward the outer aspect of the medial malleolus, a paresthesia may be elicited. If this occurs, 5 mL of the anesthetic solution is injected with the needle held in position, and an additional 3 mL is injected as the needle is withdrawn. If a paresthesia is not elicited, the medial malleolus is gently contacted with the needle tip and withdrawn 2 mm from the bone. The anesthetic solution is slowly injected at this position, and the location is gently massaged after the injection.

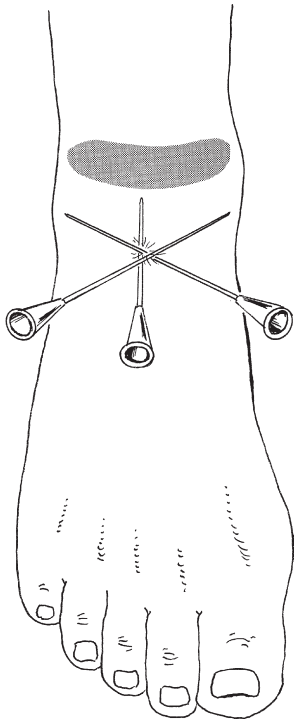

FIGURE **45-35** Direction and redirection of the needle in the ankle block technique.

With the patient in the same position, the line from the medial malleolus across the Achilles tendon is identified on the lateral malleolus. The needle is inserted under the skin along the lateral border of the Achilles tendon in the plane with the line that is between the medial and lateral malleoli. The needle is advanced subcutaneously toward the superior edge of the lateral condyle, and 5 mL of solution is injected in the subcutaneous tissues as the needle is withdrawn. The solution must reach the superior edge of the lateral malleolus to anesthetize all the fibers of the sural nerve.

The patient is then placed in the supine position, and the anterior ankle is prepared for the block. For blocking of the deep peroneal nerve, a line is drawn from the superior edge of the medial malleolus to the superior border of the lateral malleolus across the anterior portion of the ankle. The tendons of the anterior tibial muscle and the long muscles of the great toe are identified by having the patient flex the foot against resistance. Where the line crosses the midpoint between the two tendons, the needle is inserted toward the tibia (Figure 45-35). As the needle advances through the fascia, a paresthesia may be elicited. If the paresthesia is not obtained, the needle is slowly advanced until the needle gently contacts the tibia. As the needle is withdrawn from contact with the tibia, 5 mL of anesthetic solution is injected. The needle is then withdrawn through the fascia, and an additional 3 mL of solution is injected.

With the needle remaining in the subcutaneous tissue, the needle direction is changed. The needle is advanced toward the inferior border of the lateral malleolus. The superficial peroneal nerve is located in subcutaneous tissue at this level. While the needle is

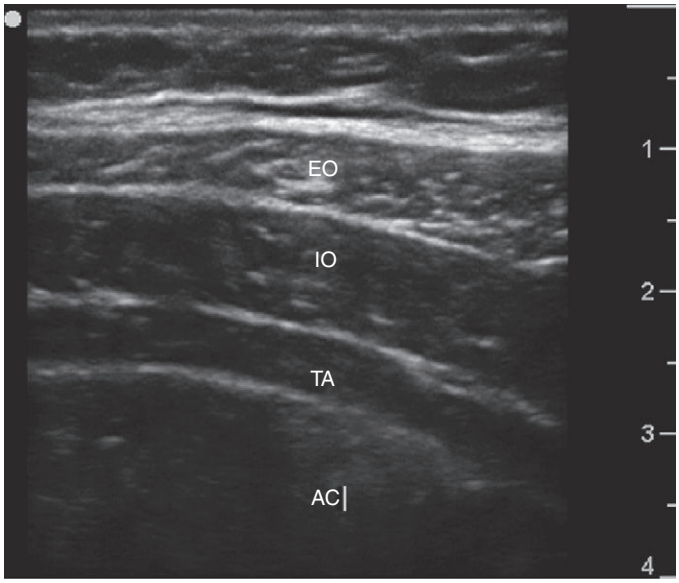

FIGURE **45-36** Anatomy of the transversus abdominis plane block. *EO*, External oblique muscle; *IO*, internal oblique muscle; *TA*, transversus abdominis muscle; *AC*, abdominal contents.

being withdrawn, 5 mL of anesthetic solution is injected. A subcutaneous ring develops that should reach the lateral malleolus.

The needle is withdrawn to the midpoint, and the needle direction is again changed. The needle is redirected to the inferior border of the medial malleolus. The saphenous nerve is in the subcutaneous tissue, superficial to the saphenous vein. If the needle is not superficial, the saphenous vein is entered; 5 mL of solution is injected toward the medial malleolus. As the needle is withdrawn, 3 mL is injected. The deep peroneal and the posterior tibial nerves are the only nerves of the ankle that are not in the subcutaneous tissue.

ULTRASOUND-GUIDED TRANSVERSUS ABDOMINIS PLANE BLOCK

The abdominal wall between the iliac crest and the subcostal margin consists of the external oblique, internal oblique, and transversus abdominis muscles. The transversus abdominis is the deepest muscle layer, and below it lies the peritoneum. The transversus abdominis plane (TAP) block is used to place local anesthetic in the lateral abdominal wall between the internal oblique and the transversus abdominis muscles. The objective is to block the segmental nerves within this plane (T9-12 and L1) with a single injection of local anesthetic. The patient is placed in the supine position with the ultrasound probe positioned transversely between the margin of the twelfth rib and the anterior superior iliac spine. A 21-gauge, 4-inch needle is inserted using an in-plane to the ultrasound beam approach. The needle is inserted through the muscle layers until the tip lies between the internal oblique and transversus abdominis muscles (Figure 45-36). Loss of needle resistance may be appreciated when the needle penetrates the external oblique muscle and again when penetration of the internal oblique occurs; 20 mL of local anesthetic may be injected bilaterally.

SUMMARY

Regional anesthesia techniques for upper- and lower-extremity blocks can be invaluable for specialized surgical procedures and immediate and long-term pain relief. There are a wide variety of techniques to achieve regional anesthesia: subarachnoid, epidural, caudal, brachial plexus, lumbar plexus, selective block of the upper- and lower-extremity nerves, intravenous infusion, intercostal nerve block, and specialized trauma techniques. Placement of these blocks can be facilitated by technology such as the peripheral nerve stimulator and ultrasonographic nerve location. Regional block may be used alone or in combination with general anesthesia and offers patients and surgeons excellent options for safe, effective anesthesia and analgesia.

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Obstetric Anesthesia

◆ *Brian J. Kasson*

CHAPTER 46

Parturients who request or require obstetric anesthesia services represent a unique challenge to anesthesia providers. Techniques for providing pain relief during labor and delivery are continuously being refined in an effort to provide the best care possible. A thorough understanding of the anatomic and physiologic changes that occur during pregnancy and the anesthetic considerations associated with such changes are necessary for a safe and effective anesthetic course.

ANATOMIC AND PHYSIOLOGIC CHANGES DURING NORMAL PREGNANCY

The physiologic changes seen in pregnancy result from increased metabolic demands and hormonal and anatomic changes. These changes begin early in pregnancy and continue into the postpartum period. These marked changes have significant implications for the anesthesia provider.

Cardiovascular Changes

Cardiovascular changes begin as early as the fourth week of pregnancy and then continue into the postpartum period.[1] The heart rate is increased by 20% to 30% at term. This increase begins in the first trimester and peaks by 32 weeks of gestation.[2] Normal heart rate (HR) variability does not appear to be changed until late in pregnancy, when tachyarrhythmias are more common.[3] Cardiac output increases by approximately 40% over nonpregnant values.[4] This increase in cardiac output begins in the fifth week of pregnancy and results from an increase in stroke volume (SV) (20%-50%) and, to a lesser extent, heart rate.[5] Cardiac output increases consistently throughout pregnancy.[6] Some studies previously indicated cardiac output decreased in the third trimester, but these results were likely due to aortocaval compression from studying subjects in the supine position.[7] At term, approximately 10% of the cardiac output perfuses the gravid uterus.[8,9] When a woman is in labor, cardiac output increases during uterine contractions as a result of autotransfusion from the contracting uterus to the central circulation.[10]

Immediately after delivery, cardiac output increases as much as 80% above predator values as a result of an increase in central volume from the now contracted uterus and relief of aortocaval compression. As a result, patients with preexisting cardiac anomalies are at an increased risk for decompensation in the immediate postpartum period. Cardiac output gradually returns to baseline within 14 days as HR and SV normalize.[11]

During pregnancy the diaphragm rises, shifting the heart up and to the left, making the cardiac silhouette appear enlarged on x-ray examination. The ventricular walls thicken and end-diastolic volume increases. A physical examination of the pregnant patient may appear to elicit abnormal findings. A benign grade 1 or 2 systolic murmur or a third heart sound may be heard on auscultation.[12] These findings would not be unusual; however, if the systolic murmur is greater than grade 3 or accompanied by chest pain or syncope, further evaluation is necessary. Diastolic murmurs and cardiac enlargement are considered pathologic. Normal pregnancy also may result in signs of cardiac abnormality such as exercise intolerance, shortness of breath, and edema.

Total blood volume increases 25% to 40% throughout pregnancy, in part to prepare for the normal blood loss associated with delivery. Plasma volume increases 40% to 50% whereas red blood cell (RBC) volume increases by only 20%.[13] As a result, a relative or dilutional anemia is commonly seen as the plasma volume increases to a greater extent relative to the actual RBC volume. The increased plasma volume is likely the result of greater circulating levels of progesterone and estrogen resulting in enhanced renin-angiotensin-aldosterone activity.[14] RBC volume increases as a result of elevated erythropoietin levels seen after the eighth week of gestation.[15] The average blood loss for a vaginal delivery is 500 mL, and for an uncomplicated cesarean section, the blood loss is 800 to 1000 mL. Normal blood losses at delivery are generally well tolerated in the healthy parturient as a result of these compensatory mechanisms. In labor each contraction moves 300 to 500 mL of blood from the contracting uterus to the central circulation.[16] Pregnant women have greater baroreflex-mediated changes in HR at term than at 6 to 8 weeks postpartum.[17] In the presence of adequate neuraxial analgesia and little sympathetic stimulation, there is often a corresponding decrease in maternal heart rate during uterine contractions due to the transiently increased preload.

Systemic vascular resistance (SVR) decreases as much as 21% by the end of a term pregnancy, owing in large part to decreased resistance in the uteroplacental, pulmonary, renal, and cutaneous vascular beds.[18,19] At term gestation 10% of the cardiac output perfuses the low resistance intervillous space of the uterus. Baseline central sympathetic outflow is twice as high in normal, term pregnant women as in nonpregnant women.[20] The venous capacitance system loses tone, allowing pooling of the larger blood volume. This decrease in SVR results in little overall systolic blood pressure change during normal pregnancy, despite the increased blood volume.[21] A decrease in diastolic blood pressure of up to 15 mmHg may occur, resulting in a decrease in mean pressure.

Aortocaval Compression

In the early 1950s a syndrome of supine hypotension was identified in term or near-term pregnant women.[22,23] This syndrome is caused by compression of the vena cava by the gravid uterus, which restricts venous return to the heart when the parturient lies in the supine position. Compression can be more severe when the abdomen is tense or when the uterus is larger than normal, as in polyhydramnios or multiple gestation pregnancies. This decreased venous return results in a significant reduction in SV and, ultimately, cardiac output. The resultant hypotension can be severe enough to cause loss of consciousness in some women.

Maximal decreases in blood pressure may require up to 10 minutes to develop; however, some women experience the decrease almost immediately. The normal physiologic responses to aortocaval compression are tachycardia and vasoconstriction of the lower extremities. Despite this attempted compensation, uterine blood flow and therefore fetal oxygenation are reduced.[24] Figure 46-1 depicts changes in aortocaval compression with changes in position.

In addition to compressing the vena cava, the gravid uterus may compress the abdominal aorta. For this reason, supine hypotensive syndrome is more correctly referred to as *aortocaval compression*. When the abdominal aorta is compressed, upper-body blood pressure remains relatively normal, whereas blood pressure distal to the site of aortic compression (uterus and lower extremities) may be significantly reduced.

Compression of the aorta and vena cava can usually be relieved by shifting the uterus to the left (left uterine displacement) or by lying on the side.[25] Left uterine displacement can be accomplished by rotation of the operating room table 15 degrees to the left or by placing a 15-cm-high wedge under the parturient's right hip and back, as shown in Figure 46-1. Most anesthetists have been shown to underestimate the angle of tilt they provide, so care should be taken to ensure adequate left uterine displacement.[26] In women with an exceptionally large uterus, greater displacement may be necessary to be effective. In a small percentage of women, right uterine displacement may be more effective than left displacement, although in the majority of cases, right uterine displacement results in stroke volumes that are no better than those measured with the patient in the supine position.

Neuraxial anesthetics result in an autonomic sympathectomy, thereby reducing compensatory lower-extremity vasoconstriction resulting in a greater potential for hypotension. There has been much debate regarding the optimal position for performing neuraxial anesthesia for labor analgesia and cesarean delivery. Many clinicians feel that the lateral position is optimal to facilitate both maternal and fetal hemodynamics. Researchers compared four positions: supine with a 15-degree left tilt, sitting with neck and hips flexed, and flexed left lateral and flexed right lateral positions. They found that maternal cardiac index (CI) was significantly higher in the right lateral position compared with the sitting and supine positions. It was also higher in the left lateral compared with sitting position. Maternal stroke volume index, heart rate, and systolic blood pressure were higher in the lateral positions compared with the sitting and supine-tilt positions. There were no significant differences in fetal heart rate, pulsatility index, or resistivity index among positions. Although positioning for neuraxial anesthesia may influence maternal hemodynamic variables, there were no difference in healthy fetal blood flow indices among positions, suggesting that these changes are not clinically significant.[27]

Hematologic Changes

In general, the parturient is said to be "hypercoagulable." Levels of factors VII through X and fibrinogen are increased. In the nonpregnant state, fibrinogen levels average from 200 to 400 mg/dL. Late in pregnancy, fibrinogen levels are normally at least 400 mg/dL and may be as high as 650 mg/dL. These increased levels place the parturient at risk for thromboembolic events, which remain one of the leading causes of maternal mortality. The platelet count remains stable or is decreased slightly in the third trimester. The prevalence of maternal thrombocytopenia (platelet count less than 150×10^9/L) in normal pregnancy has been shown to be 11.6% [28] and is not associated with increased morbidity or mortality. The pathogenesis is not well understood but may involve factors such as hemodilution and/or accelerated platelet clearance.[29,30]

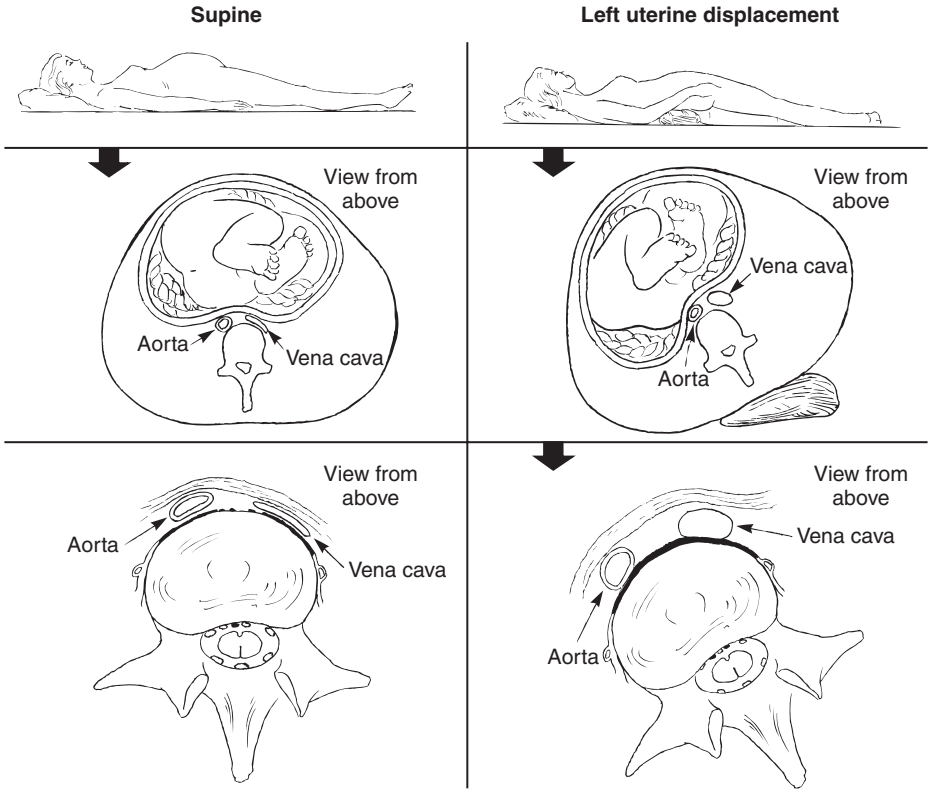

FIGURE **46-1** Effects of left uterine displacement on the diameter of the abdominal aorta and vena cava.

The white blood cell (WBC) count rises in pregnancy. In the third trimester, the mean is 10,500/mm^3, and in labor the count may increase to 20,000 to 30,000/mm^3.[31]

Respiratory Changes

The respiratory changes that accompany normal pregnancy are of particular importance to the anesthesia provider. Capillary engorgement in the upper airway results in a narrowed glottic opening and edema in the nasal and oral pharynx, larynx, and trachea. These changes carry over into labor, as has been shown by the Mallampati score changing as labor progresses.[32] Airway tissues are friable and susceptible to damage and bleeding during placement of airway adjuncts. For this reason, nasal intubation in the parturient should generally be avoided. A 6.5- to 7.0-mm cuffed oral endotracheal tube is recommended when intubation is necessary. Obese patients with enlarged breasts may benefit from the use of a short-handled laryngoscope.

Term pregnancy is accompanied by an increase in oxygen (O_2) consumption of up to 33% at rest and 100% or more during the second stage of labor. Minute ventilation at term is increased by 50%. This is primarily due to a 40% increase in tidal volume, whereas the respiratory rate is stable or increased by only 10%.[33] By 12 weeks' gestation the normal arterial partial pressure of carbon dioxide (CO_2) decreases to approximately 30 to 32 mmHg, and remains in this range throughout pregnancy.[34] Metabolic alkalosis is rarely seen because there is a compensatory decrease in the serum bicarbonate from 26 to 22 mEq/L. The normal arterial partial pressure of O_2 is greater than 100 mmHg.

The functional residual capacity (FRC), expiratory reserve volume, and residual volume are decreased primarily as a result of upward pressure on the diaphragm, with results functionally similar to restrictive lung disease. The FRC plays an important role in preserving O_2 saturation during periods of hypoventilation or apnea. The decrease in FRC (20%) combined with the increase in O_2 consumption in pregnancy commonly results in rapid arterial desaturation in the apneic pregnant patient.[35] Morbid obesity, labor, and sepsis exaggerate this effect.[36] For this reason, pre-oxygenation with 100% O_2 prior to induction of general anesthesia is important. Closing capacity (CC) does not change, which results in a decreased FRC/CC ratio often leading to small-airway closure before the tidal volume has been exhaled. This mechanism may explain the reduction in O_2 saturations seen in parturients during natural sleep. When compared with nonpregnant controls, whose average oxygen saturation during sleep was 98.5%, healthy near-term pregnant women averaged only 95.2%, with temporary desaturations below 90% not being uncommon.[37] The increased cardiac output and a shift to the right in the oxyhemoglobin dissociation curve help to maximize oxygen delivery.

Minute ventilation can increase up to 300% during contractions and cause maternal arterial partial pressure of CO_2 to drop below 15 mmHg. This alkalemia can cause hypoventilation between contractions, resulting in hypoxemia. Some evidence indicates that hyperventilation may cause a decrease in uterine blood flow. However, in animal studies this finding has usually been associated with stressful events such as intubation and invasive procedures. In pregnant, laboring human volunteers, hyperventilation to an arterial partial pressure of CO_2 of 20 mmHg does not appear to harm the fetus. Specifically, the fetus does not develop hypoxia or acidosis as determined by analysis of a scalp blood sample. However, in the presence of a complicated labor with preexisting fetal compromise, the effects could be detrimental.[38]

Nervous System Changes

Beginning in the first trimester pregnant women have an increased sensitivity to local and general anesthetics.[39-42] The exact mechanism remains unclear, but animal studies have demonstrated a variable reduction in the minimum alveolar concentration (MAC) of inhalation agents in rabbits chronically exposed to progesterone.[39] In pregnant rats, the effects of endorphins on pain thresholds are also demonstrated, which may also be an important factor. Additionally, research and clinical experience have demonstrated an increase in the sensitivity of nerves to local anesthetics during pregnancy.[39-43] Mechanical changes within the epidural space also may play a role in the increased block height seen in pregnancy. Epidural veins become engorged as a result of increased intraabdominal pressure and cause a decrease in the volume of both the epidural and subarachnoid spaces.

Gastrointestinal Changes

The parturient is at increased risk for regurgitation and aspiration of gastric contents because of anatomic and physiologic changes associated with pregnancy. A significant number of pregnant women, and women immediately postpartum, have gastric volumes in excess of 25 mL and gastric pH below 2.5.[44] Ultrasound has demonstrated solid food in the stomach of almost two thirds of women in whom neuraxial analgesia had been instituted and in the stomach of more than 40% of laboring women who had not eaten in 12 to 24 hours.[45] Increased levels of gastrin during pregnancy result in greater gastric volume and lower pH. Upward displacement of the stomach by the gravid uterus may result in mechanical obstruction to outflow through the pylorus, delayed gastric emptying, and increased intragastric pressure. Elevated levels of progesterone, a smooth-muscle relaxant, also decrease gastric motility and cause a reduction in lower-esophageal sphincter tone. This explains the heartburn frequently experienced by pregnant women. Gastrointestinal changes do not completely normalize until several weeks postpartum.

The onset of labor is accompanied by a further reduction in the rate of gastric emptying in part due to pain and the use of parenteral opioids. Recently published practice guidelines allow for the modest amounts of clear fluids in uncomplicated laboring patients. Uncomplicated patients undergoing elective cesarean delivery may have modest amounts of clear liquids up to 2 hours prior to induction of anesthesia. The same guidelines state that patients with additional risk factors for aspiration (e.g., morbid obesity, diabetes, difficult airway), or patients at increased risk for operative delivery (e.g., nonreassuring fetal heart rate pattern) may have further restrictions of oral intake.[46] Administration of nonparticulate antacids, H_2 receptor antagonists (to decrease gastric pH), and metoclopramide (to promote gastric emptying, reduce nausea and vomiting, and increase lower esophageal sphincter tone) may be beneficial prior to anesthesia and should be considered. The use of these drugs is advocated when a general anesthetic becomes necessary. When a general anesthetic is used, a rapid sequence induction with cricoid pressure using a cuffed endotracheal tube is necessary from the twelfth week of gestation to the immediate postpartum period.

Hepatic Changes

During pregnancy, levels of aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, and alkaline phosphatase increase to the upper limits of nonpregnant normal levels. Serum albumin concentration decreases somewhat, and this decrease may result in increased free fractions of highly protein-bound drugs. Serum cholinesterase activity decreases by 30% or

BOX 46-1

Key Points Regarding Physiologic Changes in Pregnancy

- Cardiac output increases mostly because of an increase in stroke volume and, to a lesser extent, an increase in heart rate.
- Blood volume is markedly increased and prepares the parturient for the blood loss associated with delivery.
- Plasma volume is increased to a greater extent than red blood cell volume, resulting in a dilutional anemia.
- Minute ventilation increases 45%, and this is due mostly to an increase in tidal volume.
- Oxygen consumption is markedly increased; carbon dioxide production is similarly increased.
- Pregnant women have an increased sensitivity to local anesthetics and a decreased minimum alveolar concentration (MAC) for all general anesthetics.
- Platelet count remains stable or decreases slightly; coagulation factors and fibrinogen are increased, resulting in a hypercoagulable state in pregnancy.
- Aortocaval compression results in profound hypotension and can be relieved by left uterine displacement.
- All pregnant women are at increased risk of aspiration because of the anatomic and physiologic changes to the gastrointestinal system and should be considered to have a full stomach after week 12 of gestation.
- Pregnancy and labor are associated with significant airway changes that can result in a difficult intubation. This highlights the importance of careful airway examination prior to general anesthesia.

more during the first or second trimester. Although activity recovers slightly by term, it remains reduced compared with prepregnant values. Despite these decreases in cholinesterase activity, clinically relevant prolongation of the duration of action of drugs that depend on cholinesterase for elimination, such as succinylcholine and remifentanil, is uncommon in women with genotypically normal cholinesterase enzymes.

Renal Changes

During pregnancy, increased cardiac output leads to increased renal plasma flow and increased glomerular filtration rate (GFR). Creatinine clearance rises to 140 to 160 mL/min. As a result, the level of blood urea nitrogen decreases to approximately 8 mg/dL and creatinine decreases to approximately 0.5 mg/dL. Urinary excretion of glucose is common in the absence of disease and is attributable to increased GFR and reduced renal absorption. The urinary excretion of protein in normal pregnancy is slightly elevated toward the upper limits of normal.[47] The gravid uterus may occasionally produce mechanical obstruction of a ureter. Some key points to remember regarding physiologic changes in pregnancy are given in Box 46-1. A summary of the physiologic changes in pregnancy at term appears in Table 46-1.

Uterine Blood Flow

The uterus undergoes tremendous changes during pregnancy. The uterus enlarges, and its blood flow increases to meet both uterine and fetal metabolic demands. Uterine blood flow is supplied by two uterine arteries that are thought to be maximally dilated throughout pregnancy. Placental blood flow on the uterine side is supplied via the maternal arcuate, radial, and spiral arteries. The spiral arteries expel blood into the intervillous space. The maternal venous sinuses receive blood from the intervillous space and return it to the general circulation. Uterine blood flow at term

TABLE 46-1 Summary of the Physiologic Changes in Pregnancy at Term

Parameter	Change	Amount
Heart rate	↑	20%-30%
Stroke volume	↑	20%-50%
Cardiac output	↑	40%
Systemic vascular resistance	↓	20%
Total blood volume	↑	25%-40%
Plasma volume	↑	40%-50%
Red blood cell volume	↑	20%
Coagulation factors	↑↑	
Platelets	No change or ↓	
Minute ventilation	↑	50%
Tidal volume	↑	40%
Respiratory rate	↑	
Functional residual capacity	↓	20%

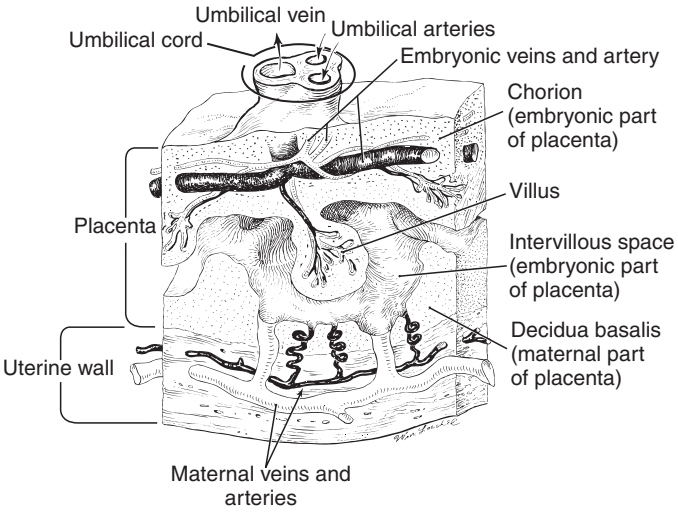

FIGURE 46-2 Cross section of the uteroplacental interface and the maternal and fetal blood supply.

increases to a maximum of 800 mL/min, accounting for approximately 10% of maternal cardiac output. Of this, approximately 150 mL/min supplies nutritive flow to the myometrium, and 100 mL/min flows to the decidua (the lining of the uterus); the remainder flows to the intervillous space.

The fetus sends O_2-poor blood to the placenta via two umbilical arteries. These vessels perfuse capillary networks within placental villi that protrude into the pool of maternal blood. Placental villi are small, fingerlike projections, the purpose of which is to maximize the placental surface area in contact with maternal blood. Each villus contains a capillary network that exchanges respiratory gases, nutrients, and wastes with maternal blood (Figure 46-2). Both O_2 and CO_2 diffuse through placental tissue readily and are considered to be "perfusion limited," meaning their transfer to the fetus is limited only by the perfusion of the placenta, not by the rate of diffusion of the gases. Therefore, decreases in maternal uterine artery blood flow or increases in placental vascular resistance decrease fetal oxygenation.

Autoregulation of intervillous blood flow does not seem to occur. The spiral arteries, however, do constrict in response to α-agonists (e.g., phenylephrine). However, recent human studies indicate phenylephrine does not appear to be harmful to the fetus

when used at clinically relevant doses.[48] Patients with preeclampsia (formerly called *pregnancy-induced hypertension*, or PIH) can develop placental insufficiency at systolic pressures greater than 100 mmHg. Unlike patients who receive neuraxial anesthesia, patients receiving inhalation anesthesia seem to maintain adequate placental blood flow, despite somewhat reduced blood pressure; this may be a function of altered uterine blood flow, altered fetal O_2 requirements, or both.

Placental Transfer and Fetal Effects of Drugs

Placental transfer of free (non–protein-bound) drug is dependent on the magnitude of the concentration gradient, the molecular weight, lipid solubility, and state of ionization. Drugs with molecular weights greater than 1000 daltons (Da) cross the placenta poorly, whereas drugs with weights less than 500 Da cross easily. Most drugs that are administered to the parturient are relatively small compounds and are thus able to cross to the placenta readily. However, size is only one of the determinants of permeability.

Transfer of drugs from the maternal circulation to the fetal unit is determined primarily by diffusion. Factors that favor diffusion include low molecular weight, high lipid solubility, low degree of ionization, and low protein binding. Cell membranes consist primarily of phospholipids such that a drug's degree of lipid solubility favors its passage through a cell membrane. Highly lipid-soluble drugs such as fentanyl cross readily. On the other hand, ionized drugs are polar and water soluble, which inhibits diffusion through lipophilic cell membranes. Local anesthetics are examples of variably ionized basic compounds, whereby the degree of ionization is dependent on the ambient pH; the more alkaline the pH, the greater the degree of nonionization. It is the nonionized portion that crosses phospholipid membranes readily. Nondepolarizing muscle relaxants are an example of large, ionized drugs that are not affected by ambient pH because of the quaternary groups in their structure and are inhibited from crossing the placenta.

When a drug enters the fetal circulation, a variety of factors minimize the effects on the fetus. First among them is dilution. Before reaching the fetus, a drug is diluted in intervillous blood, absorbed by the placenta, further diluted in placental blood, and then circulated to the fetus. Once in the fetus, the drug is distributed within the fetal intravascular volume and redistributed to fetal tissues. Umbilical venous blood from the placenta must first pass through the liver on the way to the fetal heart. The resultant hepatic enzyme activity likely reduces serum drug levels before entering the general fetal circulation. Other factors limit the effects of maternally administered drugs on a fetus. Approximately one fifth of the fetal cardiac output returns directly to the placenta because of shunt flow through the foramen ovale and ductus arteriosus. This shunted blood does not circulate, and any drug it contains does not have a systemic fetal effect.

The acid-base status of the fetus may affect the accumulation of a drug. A fetus who has become acidotic will alter the degree of ionization of a drug, potentially resulting in "ion trapping" leading to accumulation. For a complete discussion of fetal ion trapping see Chapter 10.

LABOR AND DELIVERY

Pain in Labor and Delivery

First-stage labor pain is primarily the result of cervical distension, stretching of the lower uterine segment, and possibly, myometrial ischemia. The resultant nonspecific nociceptor visceral stimulation is carried to the central nervous system by afferent unmyelinated C fibers that enter the cord at the T10, T11, T12, and L1 segments (Table 46-2 and Figure 46-3). Thus the pain of first-stage labor is frequently described as nonlocalized aching or cramping. Second-stage labor begins when cervical dilation is complete and the presenting part descends into the pelvis. At this time, a second pain pathway becomes important. Compression and stretching of the pelvic musculature and perineum produce pain that is mediated by somatic afferent fibers carried via the pudendal nerves that enter the spinal cord at the S2, S3, and S4 levels. A neuraxial anesthetic that extends from T10 to the sacral nerve roots can be effective in relieving the pain of both first- and second-stage labor.

The experience of pain is a highly personal phenomenon, and pain tolerance varies widely from one individual to the next. Many factors outside a parturient's control are also related to the perception of pain; these range from the presence or absence of social support to physical factors such as fetal presentation. Labor and vaginal delivery can be described as a process in which three essential components must work in concert. First, the fetus must be properly positioned and of an appropriate size to ensure passage through the bony pelvis, dilating cervix, and vagina. Second, the uterus must contract regularly and effectively. Third, the pelvic outlet itself must be configured in such a way that the fetus can pass. A flaw in any of these three elements can result in a difficult, painful, and prolonged labor. A few women are able to tolerate labor and delivery without significant discomfort; others experience pain in excess of their ability to cope. When women choose labor analgesia, it can make the birth process more enjoyable and provide the opportunity to better control their bodies and environment, thereby allowing them to maintain personal dignity.

TABLE 46-2 Pain Pathways During Labor

Area	Innervation	Comments
Uterus and cervix	T10 to L1-L2	Pain impulses carried in visceral afferent type C fibers
Perineum	S2, S3, and S4	Pain impulses carried by somatic nerve fibers; pudendal nerves

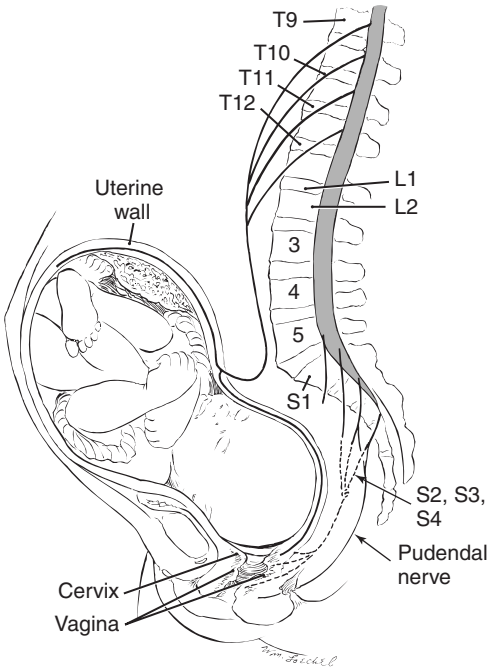

FIGURE 46-3 Lower thoracic, lumbar, and sacral regions of the spine showing spinal cord, nerve roots, and sensory innervation to the uterus, cervix, and vagina.

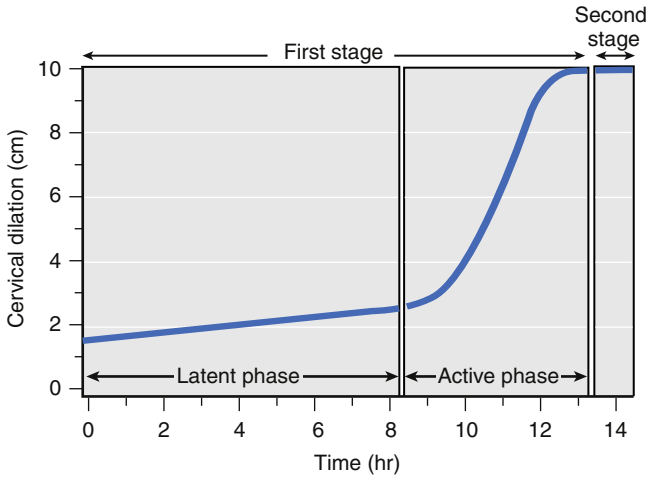

FIGURE **46-4** Curve representing average dilation for nulliparous patients in labor. (Redrawn with modifications from Miller RD, et al. *Miller's Anesthesia*. 7th ed. Philadelphia: Churchill Livingstone; 2010.)

Stages of Labor and Delivery

Labor is defined as progressive dilation of the cervix in response to uterine contractions. Although sporadic and irregular third-trimester contractions are common, labor is not said to begin until those contractions are regular and result in a change to the cervix. Labor is generally divided into three stages. First-stage cervical changes consist of effacement and dilation. The first stage is further divided into at least the latent and active phases. The latent phase is of variable duration and is defined as the period between the onset of labor and the point at which the cervix begins to rapidly change.[49] Active phase usually begins at 2 to 3 cm dilation and is the period during which the cervix undergoes its maximum rate of dilation.

The second stage begins at full cervical dilation (10 cm) and ends with delivery of the fetus. The third stage encompasses the delivery of the placenta. The length of time it takes to progress through these stages is dependent on parity, effective uterine contractions, the size and type of pelvis, and fetal presentation. The Friedman curve is used to track the normal progress of labor (Figure 46-4). Cervical dilation normally progresses 1 to 1.2 cm/hr during the active phase of labor. When labor progress no longer follows the normal pattern, it is considered a "dysfunctional labor," and may require the use of oxytocin to augment contractions.

Intrapartum Fetal Evaluation

Intrapartum fetal heart rate (FHR) monitoring is now used routinely in the United States. Although continuous or intermittent FHR monitoring is not a specific predictor of fetal well-being, it is the most readily available method for the assessment of fetal condition. Intermittent monitoring can be performed using a manual stethoscope known as a fetoscope. Continuous FHR monitoring is accomplished using either external Doppler ultrasonography or an internal fetal electrocardiography electrode. The internal method requires ruptured amniotic membranes and a partially dilated cervix through which the electrode can be inserted. The continuous FHR is recorded in a two-channel format with the FHR displayed directly above a graphic representation of the uterine contractions. In this way it is possible to relate FHR changes to uterine activity. The most commonly used scaling is a paper speed of 3 cm/min on the horizontal axis and 30 beats/min per centimeter of paper for the FHR (vertical axis).[50] In this manner each sequential vertical line is 10 seconds apart and every sixth vertical line (bold) represents a period of 1 minute.

Uterine contractions are monitored either externally via a tocodynamometer or internally with an intrauterine pressure catheter attached to a transducer placed between the fetus and uterine wall. Data obtained from external contraction monitoring is limited to temporal elements such as contraction duration and interval and cannot be used to estimate contraction strength. External monitoring is also subject to a great deal of artifact from maternal movement and errors in transducer placement. Internal contraction monitoring is more reliable and allows for precise determination of intrauterine pressure and, hence, contraction strength. Its use is also predicated on ruptured amniotic membranes and a partially dilated cervix. Internal pressure monitoring is commonly seen with high-risk parturients or those in whom labor augmentation with oxytocin is being used. Most commercially available intrauterine pressure catheter systems also allow for the infusion of fluids into the amniotic space (amnioinfusion), which is thought to reduce the risk of fetal aspiration of meconium-stained amniotic fluid.[51]

Fetal pulse oximetry has been introduced recently but is largely investigational at this time. A wide range in normal values has been reported, and use of oximetry has not been shown to decrease overall cesarean section rates, making its ultimate benefit questionable.[52]

Information about the baseline status of a fetus should be obtained during the preanesthetic assessment. The FHR also can reveal information about the fetal response to anesthetic interventions. This information is useful before neuraxial anesthetic placement, for assisted or operative delivery, and for nonobstetric surgery during pregnancy. Current American Association of Nurse Anesthetists (AANA) practice guidelines state that the Certified Registered Nurse Anesthetist (CRNA) shall be aware of the fetal status prior to each anesthetic intervention and that the fetal status be monitored and documented in the patient's record.[53]

Changes in Fetal Heart Rate

The individual components of the FHR pattern do not occur alone and changes generally evolve over time. Therefore, a full description of a FHR tracing requires a qualitative and quantitative description of baseline rate, variability, presence of accelerations or decelerations, and trends over time.[54] In the presence of a normally functioning uteroplacental unit, fetal oxygenation is limited primarily by uterine blood flow. As stated before, uterine arteries are maximally dilated in pregnancy, which results in the inability of the uterus to autoregulate blood flow. Decreases in maternal blood pressure and uterine artery blood flow ultimately compromise placental blood flow, resulting in fetal hypoxia and acidosis, which can be manifested as fetal heart rate changes. The normal FHR ranges from 110 to 160 beats per minute (bpm). An immature fetus has a higher heart rate. Tachycardia is defined as a HR greater than 160 bpm in a term fetus. It can result from fetal asphyxia, fetal arrhythmias, maternal fever, chorioamnionitis, and maternally administered drugs such as terbutaline and atropine. Ephedrine can increase both FHR and variability if given to the parturient in large enough doses.[55] Fetal bradycardia is present when the FHR is less than 110 bpm. Bradycardia can be caused by maternally administered drugs, hypoxia (fetal or maternal), or fetal head or cord compression.

Variability

FHR variability is thought to be the single best indicator of fetal well-being because it likely indicates adequate fetal oxygen reserve. Variability is the result of interaction between the fetal sympathetic and parasympathetic autonomic nervous systems. Baseline

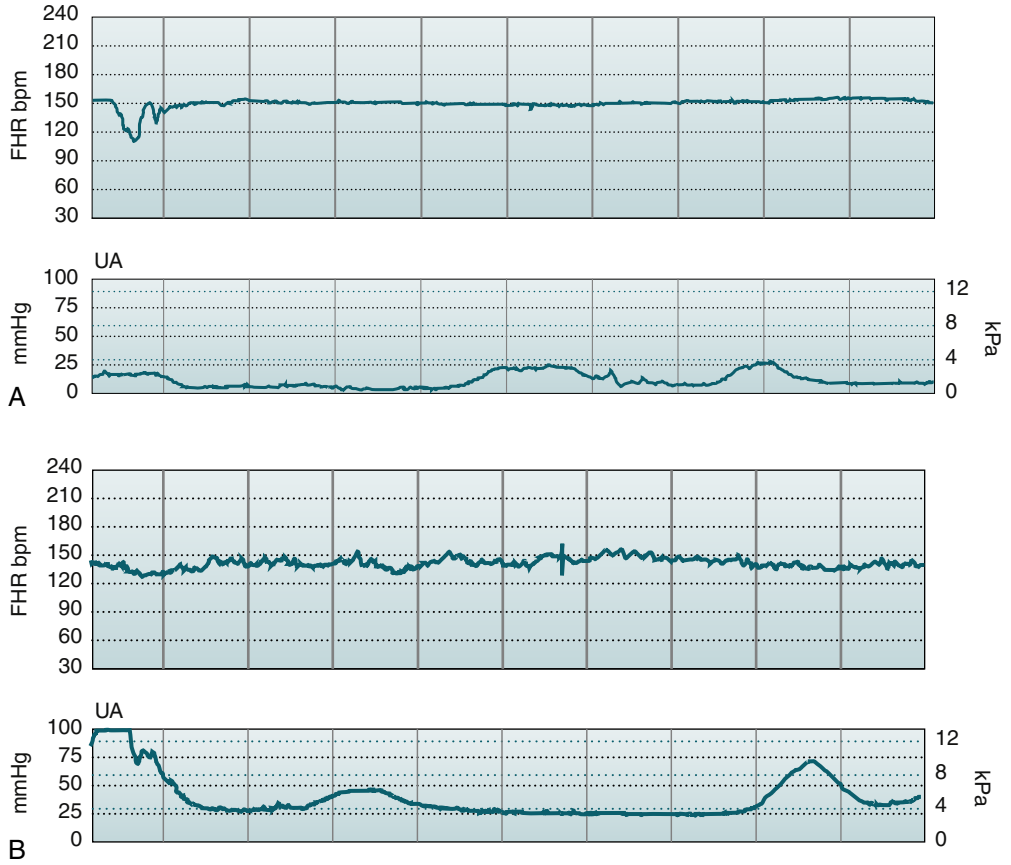

FIGURE **46-5** Examples of fetal heart rate variability. **A,** Absence of variability. **B,** Moderate variability (6 to 25 bpm from peak to nadir). (Redrawn with modifications from Chestnut DH, et al. *Chestnut's Obstetric Anesthesia: Principles and Practice*. 4th ed. St. Louis: Mosby; 2009:98).

variability is defined as fluctuations in the FHR of two cycles per minute or greater that are irregular in amplitude and frequency.[54] It is quantified by measuring the amplitude from peak to trough in beats per minute. Variability is described as absent, minimal (less than 5 bpm), moderate (6-25 bpm), and marked (greater than 25 bpm). In general, baseline FHR variability increases with advancing gestational age. Variability represents an intact central nervous system (CNS) and normal cardiac function. Hypoxia causes CNS depression, which results in decreased variability. Other causes of decreased variability include fetal sleep, acidosis, anencephaly, drugs (CNS depressants or autonomic agents), and defects of the fetal cardiac conduction system. Administration of opioids to the mother, for example, can decreases FHR variability for up to 30 minutes.[56] Maternal magnesium sulfate administration also may attenuate FHR variability.[57] Variability refers to the baseline FHR and, as such, does not include accelerations or decelerations. Beat-to-beat variability can be accurately assessed only by direct FHR monitoring with a fetal scalp electrode. Examples of absent and moderate FHR variability are shown in Figure 46-5.

Accelerations and Decelerations

An acceleration is an abrupt increase in the FHR above baseline. Accelerations occur in response to fetal movement and indicate adequate oxygenation. A FHR pattern is said to be reactive when there are two or more accelerations in a 20-minute period. Decelerations are not normal and are classified as early, variable, or late.

Early Decelerations. Early decelerations occur in concert with uterine contractions. The deceleration begins when the contraction begins, and it returns to baseline when the contraction ends. An early deceleration occurs with each uterine contraction and has the same appearance from one contraction to the next. Compression of the fetal head resulting in vagal stimulation is thought to be the cause of early decelerations. Early decelerations have the following characteristics:

- Occur with each uterine contraction
- Start and end with the contraction
- Gradually decrease in rate and then end in a return to baseline
- Are uniform in appearance
- Are associated with a mild decrease in FHR (20 bpm or less)
- Are accompanied by a loss in beat-to-beat variability during the deceleration

Variable Decelerations. Variable decelerations are sudden decreases in FHR that occur irrespective of uterine contractions. Variable decelerations are abrupt in both onset and recovery and vary in occurrence, onset, depth, duration, and appearance. Beat-to-beat variability is normally still present during the decelerations. Variable decelerations are thought to be caused by a baroreflex-mediated response to umbilical cord compression. If the fetus is compromised, the recovery phase of the deceleration may be delayed. Variable decelerations have the following characteristics:

- Vary in appearance, duration, depth, and shape
- Demonstrate abrupt onset and recovery
- Maintain beat-to-beat variability with the deceleration

Late Decelerations. Late decelerations begin late in the contraction and represent uteroplacental insufficiency. The lowest point of the deceleration occurs after the peak of the contraction. Like early decelerations, they are smooth in both onset and

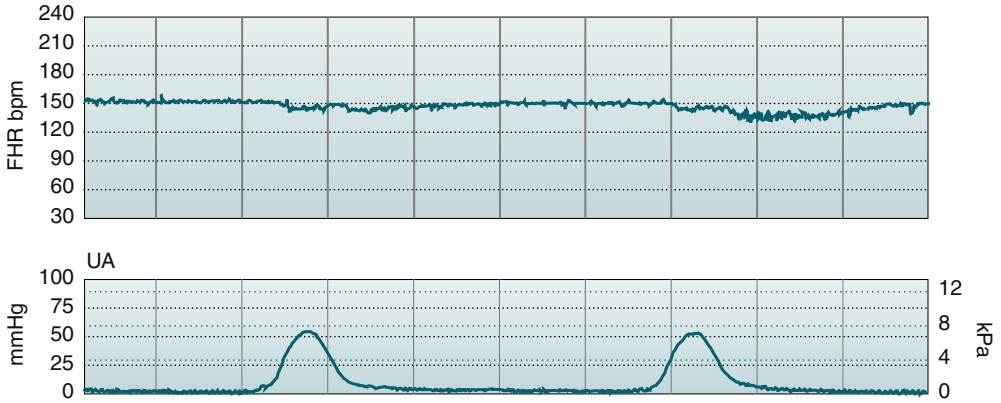

FIGURE **46-6** Fetal heart rate tracing with minimal (0 to 5 bpm peak to trough) variability and repetitive late decelerations. (From Chestnut DH, et al. *Chestnut's Obstetric Anesthesia: Principles and Practice*. 4th ed. St. Louis: Mosby; 2009:96).

recovery. Late decelerations are normally repetitive. Beat-to-beat variability may or may not be present during the deceleration, depending on the degree of fetal hypoxia and myocardial depression. Late decelerations are nonreassuring and should be investigated for potential causes. Figure 46-6 shows a FHT with late decelerations and minimal variability.

Late decelerations have the following characteristics:

- Occur with each uterine contraction
- Low point of the deceleration after the peak of the contraction
- Gradually decrease in rate and end in a return to baseline
- Are uniform in appearance
- Vary in depth according to the strength of the uterine contraction
- May or may not be accompanied by beat-to-beat variability

Anesthetic Considerations in the Presence of a Nonreassuring FHT

If the FHR tracing recorded during the preanesthesia assessment suggests hypoxia, caution should be used in making the decision to proceed with neuraxial analgesia. Careful consideration must be given to the severity of the fetal hypoxia and to the possibility that it may be worsened by anesthetic intervention. On the other hand, the obstetrician may request a neuraxial anesthetic for a patient with a nonreassuring FHT in anticipation of a possible urgent and unplanned operative vaginal delivery or cesarean section.

Intrauterine resuscitation describes interventions that can be used by the obstetric staff and anesthesia provider to improve the condition of a compromised fetus in utero. These interventions include changing maternal position, rapid infusion of IV fluids, discontinuing oxytocin, maternal oxygen administration, intravenous pressor support in the presence of hypotension, and the use of tocolytic agents.

ANALGESIA FOR LABOR AND VAGINAL DELIVERY

Intravenous Analgesia in the Parturient

Although less effective than neuraxial analgesia, systemic medications can be used for labor pain relief when neuraxial analgesia is unavailable, refused, or contraindicated. From an anesthesia perspective, the use of systemic medications presents several disadvantages. The pain relief they afford is often inadequate, and both fetal and maternal respiratory depression, nausea, vomiting, and decreased lower esophageal sphincter tone may result. Controlled, randomized trials investigating neuraxial versus intravenous analgesia in labor are difficult to design and execute due to high protocol failure rates. Namely, large numbers of parturients cross over from the IV to the neuraxial groups. However, when performed, overall patient satisfaction and pain relief scores are higher in women who receive neuraxial anesthetics compared with those who receive intravenous analgesia.[58,59]

Because opioids are lipid soluble and relatively small (less than 500 Da), they rapidly cross the placenta to gain access to the fetal circulation. Opioids may be administered by IV bolus or patient-controlled analgesia (PCA). The advantage of PCA is it allows the parturient greater control over drug dosing and has resulted in greater patient satisfaction. However, in one study PCA was compared with nurse-administered boluses, and there was no difference in pain scores or maternal and fetal side effects.[60] The use of systemic medications in early labor has declined as the practice of obstetric anesthesia has evolved to include those patients in early labor as candidates for neuraxial analgesia. Current American College of Obstetrics and Gynecology (ACOG) guidelines state that maternal request is a sufficient reason for labor analgesia.[61]

Meperidine

Meperidine crosses the placenta easily and has been recovered from the fetus within 2 minutes of IV administration. Like all opioids, it is capable of causing neonatal respiratory depression, although less so than morphine or methadone. Because of differences in pH and protein binding, the level of meperidine in the fetus is likely to be higher than the maternal blood level. Normeperidine is an active metabolite of meperidine with an elimination half-life of 30 hours. Normeperidine remains in the neonate for several days after delivery and may lead to depression of neonatal behavioral assessment scores.[62]

Historically, larger doses of meperidine were used during labor than are used now, often in combination with other depressant drugs. With contemporary doses (generally less than 100 mg in total), neonatal depression is a less frequent problem. The interval from administration of the drug to delivery of the infant is important. A drug-to-delivery interval of 2 to 3 hours results in the greatest neonatal depression. Both meperidine and normeperidine can be antagonized by naloxone.

Fentanyl

The pharmacologic profile of fentanyl, that is, its high potency and short duration of action, make it a reasonable choice for labor. It is highly lipid soluble and can be detected in fetal circulation after 1 minute of IV administration. Depressant effects, including a reduction in beat-to-beat variability, have been seen.[63] Dosages

for labor range from 25 to 100 mcg IV in hourly increments.[64] or PCA bolus 25-50 mcg with a lockout interval of 3 to 6 minutes and a 4-hour limit of 1-1.5 mg.[63,65]

Morphine

Morphine has been used in early labor to provide analgesia and sedation but is no longer widely accepted due to high rates of maternal sedation, neonatal depression, and an undesirable prolonged duration.[66] Morphine crosses the placenta easily and, in animal studies, crosses the fetal blood-brain barrier more readily than in adults.[67]

Butorphanol and Nalbuphine

Butorphanol and nalbuphine are opioid agonist-antagonists that are associated with a "ceiling effect" whereby incrementally higher doses do not result in increasing respiratory depression. They may also result in less nausea and vomiting than pure opioids. Agonist-antagonists have typically been used in first-stage latent-phase labor to provide sedation and a period of rest. A typical butorphanol dose for labor is 1 to 2 mg IV or IM (intramuscularly). Butorphanol is five times as potent as morphine and has a half-life of 3 hours. Unlike morphine, butorphanol increases pulmonary artery pressure and myocardial work.[64] Butorphanol has no active metabolites. The nalbuphine dose in labor is 5 to 10 mg IV, IM, or SC (subcutaneous) and is equivalent to morphine 10 mg. Nalbuphine results in a greater reduction in FHR variability compared with meperidine.[68] Because these compounds possess significant antagonist properties, their use in opioid-dependent patients should be avoided.

Remifentanil

Remifentanil is an ultra–short-acting opioid receptor agonist. It is rapidly hydrolyzed by plasma esterases to an inactive metabolite. The context-sensitive half-life remains short (3.2 min) regardless of prolonged administration times.[69] This unique pharmacokinetic profile makes it suitable for PCA use in labor. It crosses the placenta readily but is similarly rapidly redistributed and metabolized by the fetus.[70] Douma et al.[71] compared remifentanil, fentanyl, and meperidine PCA in labor and found that remifentanil PCA was associated with the greatest reduction in pain scores; however, the relief was described as mild to moderate. The same group has found that remifentanil PCA is less effective when compared with standard epidural labor analgesia.[72] A PCA bolus of 0.25 mcg/kg with a lockout interval of 2 minutes, a 4-hour limit of 3 mg, and a background infusion of 0.025-0.05 mcg/kg/min is common.[63,73,74] Remifentanil use in labor is a relatively new technique that appears to have an acceptable safety profile. However, its use requires careful monitoring due to the potential for adverse maternal events.[75]

Ketamine

Ketamine is a derivative of phencyclidine that produces a dissociative anesthetic effect. It is an excellent analgesic at subhypnotic doses. Its use as a labor analgesic is limited, however, by its short duration of action and high incidence of amnesia. Low-dose ketamine preserves airway reflexes while causing somatic analgesia, sedation, increased blood pressure, and a dreamlike state. It can be used to supplement a suboptimal neuraxial anesthetic when replacement or adjustment of the neuraxial anesthetic is not possible. Consideration should be given to administering a concomitant dose of a benzodiazepine such as midazolam to reduce the incidence of emergence reactions. Ketamine doses of 01.25 to 0.5 mg/kg produce rapid analgesia with a dose-dependent duration of action of approximately 5 to 15 minutes.

A single induction dose of 1 mg/kg of ketamine increases blood pressure during induction. This may be desirable in an emergent cesarean section where the mother is hypovolemic. The hypertensive effects, however, may be problematic in the parturient with hypertension or preeclampsia. It is the agent of choice for induction in the patient with acute asthma requiring urgent cesarean section. The emergence delirium and hallucinations from ketamine limit the effectiveness of ketamine for routine use in obstetrics. Uterine arterial blood flow does not decrease after ketamine administration. Because it has a high lipid solubility, ketamine crosses the placenta easily. Neonatal depression has not been demonstrated after maternal ketamine doses of up to 1 mg/kg. Doses larger than 1 mg/kg may result in neonatal respiratory depression, muscular hypertonicity, and lower Apgar scores.[76]

Nonpharmacologic Methods

A parturient may very well not choose a neuraxial anesthetic for labor analgesia if that is her informed choice. A multitude of nonpharmacologic techniques are currently in use but, as Wong has stated, the effectiveness of these techniques generally lacks rigorous scientific study and conclusions regarding their efficacy cannot be made.[77] Nonpharmacologic alternatives include hydrotherapy, hypnotherapy, massage, movement, and positioning. Although maternal satisfaction is without a doubt influenced by the degree of pain endured, it is influenced to a greater extent by whether the actual birth event met the mother's personal expectations.[78] The role of an obstetric anesthesia provider is to support laboring women such that they can make informed choices that meet their individual expectations, while at the same time ensuring the safety of both the mother and infant.[79]

Neuraxial Analgesia for Labor and Vaginal Delivery

Neuraxial analgesia is currently the best method of pain relief for labor and delivery. When properly placed and dosed, a neuraxial anesthetic is the only modality available that can provide complete relief from labor pain with minimal depression of the parturient or fetus. Common neuraxial anesthetics include epidural, combined spinal-epidural (CSE), and spinal techniques.

Absolute contraindications to neuraxial anesthesia include patient refusal, uncorrected severe hypovolemia, uncorrected coagulopathy, elevated intracranial pressure, infection at the site of insertion, untreated bacteremia, severe stenotic valvular heart lesions, and a documented allergy to local anesthetics. There are many relative contraindications such as stable preexisting CNS disease, chronic severe headaches and back pain, or poorly controlled chronic hypertension. Patients with these and other preexisting conditions should undergo careful preanesthetic evaluation and consultation that takes into consideration the risks and benefits of the proposed procedure.

Historically, the platelet count at which a neuraxial anesthetic could be safely administered has been considered to be greater than $100{,}000 \times 10^9$/L. However, contemporary practice surveys indicate that most practitioners are comfortable providing a regional anesthetic with the platelet count as low as $80{,}000 \times 10^9$/L.[80] Careful consideration of thrombocytopenic parturients should include a thorough history and physical examination for signs and symptoms of coagulopathy with an emphasis on previously administered medications including herbal supplements. A review of laboratory findings should clearly include all prior platelet counts (to establish any trends) as well as other relevant laboratory findings. The ACOG offers guidelines for assessing the obstetric patient (Box 46-2).

Patients receiving prenatal and/or intrapartum antithrombotic or thrombolytic therapy require special consideration. Normal

BOX **46-2**

American College of Obstetricians and Gynecologists (ACOG) Guidelines for Assessment of the Obstetric Patient

Major Recommendations

The following recommendations are based on good and consistent scientific evidence (Level A):

- Regional anesthesia provides a superior level of pain relief during labor when compared with systemic drugs and therefore should be available to all women.
- Parenteral pain medications for labor pain decrease fetal heart rate variability and may limit the obstetrician-gynecologist's ability to interpret the fetal heart rate tracing. Consideration should be given to other drugs in the setting of diminished short- or long-term heart rate variability.

The following recommendations are based on limited or inconsistent scientific evidence (Level B):

- Patients with platelet counts of 50,000 to 100,000/μL may be considered potential candidates for regional analgesia.
- Regional anesthesia is preferred in women with preeclampsia unless a contraindication to regional analgesia is present.
- Breastfeeding does not appear to be affected by the choice of anesthesia; therefore, the choice should be based on other considerations.

The following recommendations are based primarily on consensus and expert opinion (Level C):

- It is not necessary to routinely obtain a platelet count before administration of regional anesthesia in a pregnant patient without complications.
- Clear liquid intake may be allowed in patients in labor without complications.
- Sodium citrate should be administered promptly to neutralize gastric contents following the decision to perform a cesarean delivery.
- Identifying women with risk factors for failed intubation or other complications of anesthesia and referring them for antepartum anesthesia consultation may reduce this risk.
- To avoid respiratory depression, close monitoring of the cumulative narcotic dosage given to a patient antepartum, intrapartum, and postpartum is essential.
- The decision of when to place epidural analgesia should be made individually with each patient, with other factors, such as parity, taken into consideration. Women in labor should not be required to reach 4 to 5 cm of cervical dilation before receiving analgesia.

From American College of Obstetricians and Gynecologists (ACOG). *Guidelines for Assessment of the Obstetric Patient: Obstetric Analgesia and Anesthesia,* ACOG Practice Bulletin No. 36. Washington, DC: ACOG; 2002:15.

pregnancy is associated with a hypercoagulable state that, alone or in combination with certain pathologic conditions, can predispose parturients to thromboembolic events. Conditions that may require anticoagulation therapy in the obstetric population include deep vein thrombosis, antiphospholipid antibody syndrome, factor V Leiden mutations, and protein S and C deficiencies. The concern with neuraxial anesthetics is the potentially catastrophic complication of epidural hematoma. Epidural hematoma results from uncontrolled bleeding in the non-distendable epidural space, which, if untreated, can cause ischemic injury to the cord resulting in persistent neurologic dysfunction. Epidural hematoma is a rare complication that is estimated to occur in less than 1 in 150,000 epidural and 1 in 220,000 spinal anesthetics.[81] The American Society of Regional Anesthesia and Pain Medicine (ASRA) has published consensus statements in an effort to guide practitioners in the management of these often complex patients.[82]

Preprocedure Preparation

History and Physical. It is optimal to complete the history and physical for every patient whose plan includes an epidural anesthetic early in the labor process, often long before the regional anesthetic is indicated. Maternal patience and cooperation is easier to obtain in the absence of significant labor pain. An early history and physical also allows for recognition of potential problems and provides the time for additional work-up when necessary. Valuable time also can be saved with a previously completed history and physical if an anesthetic intervention becomes urgently necessary.

The history should include questions regarding pertinent systemic diseases as well as the obstetric history and course of the current pregnancy. Particular attention should be directed toward problems with previous pregnancies, deliveries, or anesthetics. A review of the patient's medical record to include previous analgesic interventions, such as intravenous narcotics, should be performed. The physical examination should include an inspection of the back, heart, and lungs, as well as an airway examination. It has been recently demonstrated that the airway examination can change during the course of labor.[32] Therefore, a repeat examination is indicated immediately before administering anesthesia in labor regardless of prior examination results.

The maternal vital signs and fetal condition should be documented. This includes dilation, effacement, station, FHR, membrane status, and variability. The obstetric history includes gestational age and the parturient's gravidity (i.e., number of conceptions) and parity (i.e., number of live births). Obtaining a platelet count before the institution of neuraxial anesthesia in healthy patients with uncomplicated pregnancies has not been shown to reduce overall complication rates.[46] However, in the presence of hypertensive disorders or coagulopathies with anesthetic implications, the elective anesthetic should generally be delayed until appropriate laboratory results (e.g., coagulation studies, platelet count) are available. In circumstances of little or no prenatal care, obtaining baseline laboratory values may be indicated due to the possibility of undiagnosed medical conditions.

Informed Consent. Those who provide anesthesia to laboring women have an obligation to obtain informed consent prior to the procedure. The elements of informed consent include a description of the procedure, the risks, benefits, potential complications, and alternatives. However, there are several issues unique to obstetric anesthesia that can complicate informed consent. The first involves capacity and whether a woman in great pain and distress has the ability to understand and reason.[83] Despite the pain of labor, women feel they retain the ability to assimilate information and make good decisions. Jackson et al.[84] found that most women in active labor were able to voluntarily consent and that their ability to understand was not affected by pain, premedication, or duration of labor. Affleck et al.[85] determined that recall of risks by parturients is similar to the recall of risks by other patients and does not appear to be affected by parity or the reported level of pain.

A second confounding issue is caring for the pregnant minor. Competence describes the legal authority to make a decision and is recognized in the United States as occurring at 18 years of age. However, various state laws make exceptions (emancipation) for minors who are free of parental care, control, and custody. This may occur when a minor is married, a member of the military,

or a high school graduate. Becoming pregnant does not necessarily constitute emancipation. With respect to obstetric anesthesia, it is best to include the legal guardian of a minor patient in the informed consent process. Anesthesia providers must have a working knowledge of various local, state, and federal guidelines as well as their institutions' applicable policies and procedures.

Informed consent should include those risks that are reasonably foreseeable, but it does not have to include every possible risk. Material risks are those that a reasonable person would want to be made aware of before deciding on a recommended therapy.[86] They include risks that commonly occur as well as those risks that are rare but may result in severe morbidity and mortality. There exists no distinct and inclusive list of potential risks and complications; however, several recent surveys of practitioners demonstrate some consensus regarding what should be disclosed.[87,88]

Drugs and Equipment. It is the provider's responsibility to ensure that the anesthesia equipment available in the obstetric area is consistent with other anesthetizing locations in the facility.[89]An oxygen source, a positive pressure apparatus capable of delivering 100% oxygen, and an appropriate suction assembly must be present at every location where neuraxial anesthesia is provided. Emergency airway supplies as well as resuscitation drugs need to be immediately available. Emergency drugs include atropine, an induction drug (for terminating a local anesthetic–induced seizure), succinylcholine, ephedrine, epinephrine, calcium chloride (for treating magnesium sulfate overdose), and sodium bicarbonate. Equipment should be checked prior to each anesthetic.

As services are often provided in multiple locations, an "epidural" cart that contains routine supplies as well as emergency equipment is preferred. A standard "crash cart" with defibrillator and a supply of intralipid 20% to treat intravascular injection of local anesthetics should be readily available (see Seizures Related to Local Anesthetics section). Noninvasive automatic blood pressure monitoring and pulse oximetry are required in each labor and delivery room. In addition to proper drugs and equipment, a knowledgeable assistant is essential for the safe insertion of a neuraxial anesthetic. An obstetric nurse who can assist with fetal heart rate monitoring and positioning is desirable. Intravenous (IV) access is required prior to initiating a neuraxial anesthetic and should be maintained throughout its duration. IV insertion sites should take into consideration the vigorous arm movement that can occur during second-stage labor. The dilute concentrations of local anesthetic commonly used in labor analgesia today result in significantly less sympathetic blockade and hypotension compared with traditional high-dose blocks.[90] As a result, the administration of a fixed volume of intravenous fluid is not required before neuraxial analgesia is initiated.[46]

Local Anesthetics

Bupivacaine. Bupivacaine is an amino-amide local anesthetic with a relatively long duration of action and the ability to produce a differential block whereby sensory fibers are blocked more readily than motor fibers. When compared with lidocaine, there is less tachyphylaxis during long-term administration. In lower doses, it has limited placental transfer as well as minimal neonatal effects. These characteristics have made it the most commonly used local anesthetic in obstetric anesthesia. Bupivacaine is marketed as a racemic mixture of the S^- and R^+ isomers. Refractory cardiac arrest has been associated with high concentrations of bupivacaine inadvertently administered intravascularly. It is more difficult to resuscitate patients from bupivacaine-induced cardiac arrest when compared with other local anesthetics. The exact cause remains unclear; however, evidence suggests that toxicity occurs primarily at sodium channels, and there may be qualitative differences in cardiotoxicity caused by low- and high-potency local anesthetics.[91] The epidural administration of 0.75% bupivacaine has been prohibited for use in obstetric anesthesia by the Food and Drug Administration (FDA). Clinical techniques to reduce the incidence of cardiac toxicity include fractional dosing (less than 5 mL), frequent aspiration for blood during injection, and use of a test dose. The use of low concentrations for continuous epidural infusion and low doses (less than 15 mg) for spinal anesthesia are not associated with cardiac toxicity.[92]

Lidocaine. Lidocaine is an amino-amide local anesthetic that has been used extensively in obstetric anesthesia for decades. It has a rapid onset and an intermediate duration of action. When given in the epidural space, it produces a dense motor block when combined with epinephrine, which makes it well suited for epidural anesthesia for cesarean section. This dense motor block, however, makes it less desirable for labor analgesia. Lidocaine administered in the subarachnoid space is potentially neurotoxic.[93] In 1991 four cases of cauda equina syndrome were reported after the use of lidocaine in small-diameter catheters designed for continuous spinal anesthesia. In all four cases, there was initial evidence of a focal sensory block, and to achieve adequate analgesia, a dose of local anesthetic was given that was greater than that usually administered with a single-injection technique. The authors postulated, and subsequent data substantiated, that the combination of maldistribution and a relatively high dose of local anesthetic resulted in neuronal injury.[94] Transient neurologic symptoms consisting primarily of lower extremity pain also have been attributed to 5% hyperbaric lidocaine.[95] (see Chapter 10) For this reason, obstetric anesthesia providers do not use lidocaine in the subarachnoid space.

2-Chloroprocaine. Chloroprocaine is an amino-ester local anesthetic that is rapidly metabolized by ester hydrolysis. As such, its potential to produce cardiac and CNS toxicity after inadvertent intravenous administration is low. It has a rapid onset and brief duration of action. Chloroprocaine is used primarily in obstetric anesthesia to rapidly produce a surgical block in the presence of a preexisting epidural in the case of an emergency cesarean section. The epidural administration of chloroprocaine has been shown to reduce the effectiveness of subsequently administered epidural morphine, possibly by antagonism at the opioid receptors.[96] Neurotoxicity has been reported after inadvertent spinal administration of large doses intended for the epidural space but was likely a result of the low pH and/or the preservatives.[97]

Ropivacaine. Ropivacaine is an amino-amide local anesthetic that is produced as the pure levorotatory enantiomer. It has a propyl group attached to the pipechol ring as opposed to bupivacaine, which has a butyl group attached to the ring. Ropivacaine was developed largely to address the cardiac toxicity associated with bupivacaine. Minimum local anesthetic concentration (MLAC) is defined as the concentration that produces an effective response in 50% of subjects. Studies that address MLAC have found that ropivacaine is approximately 60% to 75% as potent as bupivacaine, which may explain the reduced motor block some studies have found with ropivacaine.[98] At a more clinically relevant dose, to achieve analgesia in 90% of women, bupivacaine and ropivacaine were equipotent.[99] Although equipotent doses of ropivacaine have been shown to produce less motor block when compared with bupivacaine, it has not been shown to influence the mode of delivery, the duration of labor, or neonatal outcome.[100]

Studies to address the potential cardiotoxicity of ropivacaine are obviously limited to animal models and in vitro preparations, and they have found either an advantage for ropivacaine in regard

to toxicity or no difference between ropivacaine and bupivacaine. It is possible that ropivacaine is less cardiotoxic than bupivacaine at high doses, but at the more dilute concentrations clinically relevant to obstetric anesthesia, this difference is less likely important.[101]

Neuraxial Anesthetic Placement

Aseptic technique must always be used during the insertion of neuraxial anesthetics. This includes preprocedure hand hygiene, wearing of sterile gloves, cap and mask (new for each case), removal of rings and watches, and sterile draping of the back.[102] A newly opened single-use container of preparation solution should be used for skin surface disinfection. Chlorhexidine gluconate in an alcohol base should be considered the antiseptic of choice. When compared with other commonly used antiseptic solutions, it is effective against a wider array of pathogens, has a greater degree of potency, shows a more rapid onset of action with an extended duration of effect, and has fewer and less severe localized skin reactions.[103] In addition, the efficacy of chlorhexidine gluconate is maintained in the presence of protein-based organic compounds such as blood and other body fluids. A sterile occlusive dressing should be placed over the catheter insertion site.

Baseline blood pressure and pulse oximetry should be measured and checked at regular intervals once the epidural anesthetic is begun. Typically, blood pressure is monitored every 2 minutes for 15 minutes, then every 5 minutes for another 15 minutes, thereby enabling the early detection and treatment of neuraxial anesthesia–induced hypotension. It is preferable to remain in the anesthetizing location during this time not only to assess the onset and progression of the neuraxial block but also to be in a setting where prompt recognition and treatment of potentially catastrophic complications such as total spinal block can be attended.

The sitting position is often easiest for the patient to maintain and usually offers the anesthetist the maximum interspace width. On the other hand, the use of the lateral position has been found to reduce the incidence of intravascular catheter placement.[104] However, the lateral position can make identification of the midline more difficult due to skin shifting. The lateral position also requires meticulous attention to shoulder position, because the upper shoulder naturally rotates anteriorly, resulting in a concomitant rotation of the vertebral column. The lateral position may help limit movement if the patient is having a difficult time cooperating with positioning. Some obstetric situations that often require rapid neuraxial block placement, such as fetal head entrapment, prolapsed umbilical cord, and footling breech presentation, preclude the use of the sitting position. For this reason, anesthetists must practice and be proficient in both the sitting and lateral positions.

It has long been observed that the failure rate of epidural anesthetics is greater in the obese patient. At the same time, neuraxial anesthetics are particularly desirable in obese parturients because of the increased cesarean section rates and concern surrounding a potentially difficult airway. The distance between the skin and the epidural space increases as the body mass index (BMI) increases, which can make epidural insertion more difficult.[105] However, morbid obesity, when considered alone, is not a predictor of difficult block placement. In a study of 427 morbidly obese patients receiving neuraxial anesthetics, four variables were evaluated to determine whether they could predict difficult insertion. The authors found that only the ability to palpate bony landmarks and the patient's ability to flex her back were significant predictors of difficulty, whereas BMI and the practitioners experience level were not predictive.[106]

The use of ultrasound imaging as an aid in the placement of neuraxial anesthetics is a relatively new and growing technique. The placement of neuraxial anesthetics relies primarily on palpation of underlying anatomy and visualization of surface landmarks and is therefore an essentially blind technique. Preprocedure imaging and, eventually, real-time ultrasound guidance, may ultimately improve clinical practice and the ability to teach these techniques.[107] Ultrasound imaging is particularly useful in determining the skin to epidural space depth, the location of the midline, and the precise interspace. Palpation alone, regardless of BMI, is a relatively ineffective method for determining vertebral interspace, which is of particular importance when performing techniques that involve dural puncture.[108] Morbidly obese patients or those with a history of difficult block placement may benefit from this technique.[109]

The type of epidural catheter used influences the anesthetic. Spiral wire-embedded flexible polyurethane catheters with a soft tip have been shown to result in fewer paresthesias and intravascular placements when compared with nylon catheters.[110] Previous comparisons between multiple- and single-orifice catheters focused on standard nylon (stiff) designs and found an advantage favoring multiple-orifice catheters. Recent work comparing both versions (single orifice and multiple orifice) of soft catheters has found no difference.[111] Multiple-orifice closed-end catheters are less prone to obstruction and likely result in better spread of local anesthetic in the epidural space.[112]

Historically, when larger doses of local anesthetic were used, a bolus of intravenous fluids was given prior to placement of the regional analgesic in an effort to reduce the incidence and magnitude of hypotension. However, when dilute concentrations of local anesthetics combined with lipid-soluble narcotics are used to initiate neuraxial analgesia for labor and are combined with efforts to reduce aortocaval compression, the incidence of hypotension is approximately 5%.[113] Zamora et al.[114] found that a 1-liter preload did not provide any added protection against hypotension but likely resulted in decreasing contraction frequency and was associated with delays in providing pain relief.

Test Doses

It is essential to aspirate for blood or cerebrospinal fluid (CSF) after placement of the epidural catheter and before each subsequent manually administered dose. Negative aspiration does not, however, conclusively indicate that the catheter is not in the subarachnoid or intravascular space. Therefore, the epidural test dose is designed to reveal inadvertent subarachnoid or intravascular injection of local anesthetic without producing systemic toxicity or widespread subarachnoid block. The key is to think of the test dose as the minimum amount of drug required to produce a modestly detectable effect either intrathecally or systemically. As such, the overall volume has little to do with its effectiveness. A commonly administered test dose is 3 mL of lidocaine 1.5% with epinephrine 1:200,000. This 45-mg dose of lidocaine, if unexpectedly administered in the subarachnoid space, will produce a noticeable, but manageable, spinal anesthetic within 3 to 5 minutes while having no appreciable effect when given in the epidural space.

When administered intravascularly, lidocaine 45 mg will often result in early signs and symptoms of modest systemic toxicity such as circumoral numbness, lightheadedness, or auditory changes. The above mentioned test dose also includes 15 mcg of epinephrine that, when given intravascularly into an epidural vein, has been shown to reliably increase HR in nonpregnant patients. The maternal HR should be monitored continuously using either pulse oximetry or electrocardiogram (ECG) during administration of

the test dose to detect these HR changes. In the laboring parturient, increases in HR are a less specific indicator of intravascular injection because of the changes in HR that normally occur during uterine contractions. Even when a test dose is carefully timed to be administered between contractions, it lacks both sensitivity and specificity. As a result, it is not universally accepted for use in obstetric anesthesia. Furthermore, concern exists that epinephrine may cause significant uterine artery constriction in a few patients, resulting in a decrease in fetal O_2 delivery.[115]

Some practitioners believe that by using multiple-orifice catheters in combination with incrementally administered (every 3-5 min) small doses (less than 5 mL) of dilute (less than 0.125%) local anesthetic, an epinephrine test dose is unjustified for labor analgesia. Careful aspiration of the epidural catheter for blood or CSF alone, without the administration of a test dose, may be effective in revealing an intrathecal or intravascular catheter.[116] If a parturient receiving a continuous epidural infusion of dilute local anesthetic remains comfortable, the catheter must, by default, be in the epidural space. On the other hand, if the catheter was intravascular, the parturient would have inadequate analgesia, and if it were intrathecal, a significant motor block would ensue.[117]

Observing for blood or CSF while aspirating the epidural catheter had a 0% false-positive rate and a 0.2% false-negative rate in over 1000 women in whom 60 intravascular or subarachnoid catheter placements were performed.[118] However, a test dose with epinephrine is necessary when administering larger and more concentrated doses such as those given in an epidural for cesarean delivery.[116] Ideally, the administration of every epidural dose should be considered a "test dose" in which the catheter is carefully aspirated and incrementally injected. In summary, every precaution to ensure proper placement of the epidural catheter should be employed including the use of minimum effective doses, careful aspiration, and incremental injection, coupled with the use of intravascular markers when large doses are used. Epinephrine remains the most widely used and studied marker, but its reliability is impaired in the face of beta-blockade, anesthesia, advanced age, and active labor. As an alternative, the use of subtoxic doses of local anesthetics themselves can produce subjective symptoms in unpremedicated patients. Fentanyl has also been confirmed to produce sedation in pregnant women when used as an alternative. The use of ultrasound observation of needle placement and injection may be useful, but has also been reported as not completely reliable. Constant vigilance and suspicion are still needed along with a combination of as many of these safety steps as practical.[119]

Anesthetic Effects on the Progress of Labor

There has been considerable controversy surrounding whether neuraxial analgesics prolong labor or increase the need for assisted or operative delivery. Randomized controlled trials designed to evaluate the effects of neuraxial anesthetics on the outcome of labor are notoriously difficult to design and implement due to ethical considerations and unacceptably high protocol failures. The number of variables involved and the diversity of both patients and study methods make this a difficult topic about which to draw valid conclusions.

It is likely that women who request early labor analgesia have more pain than women who do not, and pain is a marker for risk of cesarean delivery.[120] In a systematic review of 10 trials that enrolled over 2300 patients in which the effects of epidural versus parenteral opioids in labor were examined, Halpern et al.[121] found that epidural labor analgesia was not associated with increased rates of instrumented vaginal delivery or cesarean section. Not surprisingly, patient satisfaction and neonatal outcomes were better after epidural when compared with parenteral opioid analgesia. Another systematic review of seven existing trials found that epidural analgesia using low concentrations of bupivicaine and fentanyl was unlikely to increase the risk of cesarean section but may increase the risk of instrumented vaginal delivery.[122] Although women in those studies had a longer second-stage labor, they had better pain relief. It could be argued that the increased risk of instrumented vaginal delivery was the result of obstetricians choosing this method more frequently because of the presence of a functioning epidural.[123] It has been thought that early initiation of neuraxial analgesia (less than 4 cm) may increase the incidence of labor dystocia and cesarean section. However, a recent large study from China involving almost 13,000 patients found no difference in the duration of labor or cesarean section rate when primiparous women were randomized to receive epidural analgesia at 1 cm dilation versus 4 cm or more dilation.[124] Overall, the use of epidural analgesia does not increase the risk of cesarean section. It may affect the incidence of forceps delivery, but it depends on the medications used. Epidural analgesia does prolong labor, although the clinical significance of this prolongation has not been shown.[125]

Epidural Analgesia for Labor

Epidural analgesia remains a popular, safe, and effective means of providing analgesia for labor. The use of an indwelling epidural catheter gives the anesthetist the ability to produce a segmental block of varying density that can be adapted to the patient's requirements. This is accomplished by changing the volume and concentration of local anesthetic administered. Dosing an epidural with dilute concentrations of local anesthetic often results in satisfactory labor analgesia without producing significant motor block. When necessary, the same labor epidural can be converted to a surgical anesthetic by administering a larger volume of a more concentrated local anesthetic.

Combining a lipid-soluble opioid allows a decrease in concentration of local anesthetic without compromising analgesia while at the same time preserving motor function. Decreasing the dose of both drugs minimizes the potential complications and side effects of each. An epidural for labor analgesia is optimally inserted at the L2 to L3 interspace to allow for effective blockade of the T10 to L1 dermatomes necessary for analgesia in first-stage labor. Analgesia for second-stage labor and subsequent repair, if needed, requires an extension of the block to include the S2 to S4 dermatomes that innervate the perineum and vagina. Adequate analgesia must be balanced against loss of the sensation of labor, which is not desirable during the second stage, and motor block, which is bothersome to the mother during labor and prevents effective pushing during second stage.

Although the small amount of epinephrine present in a test dose should be safe for a healthy fetus, the larger amounts present in the volume of local anesthetic used in epidural infusions carry some risk of umbilical artery constriction in some parturients.[126] Epinephrine-containing local anesthetics also result in significantly enhanced motor block. For these reasons, routine use of epinephrine-containing solutions is not recommended, especially in the preeclamptic patient.

To avoid aortocaval syndrome, after epidural analgesia has been instituted, the patient should be instructed to avoid the supine position. A hip roll, wedge, or pillow should be used to maintain a left or right lateral position. Following the initial and all subsequent doses, the patient should not be left unattended for at least 20 minutes. The anesthetist should remain aware of cervical dilation and the progress of labor after the epidural catheter has been placed. Communication with the obstetric personnel is important

to prevent the use of a drug, dose, or concentration of local anesthetic that is inappropriate for the patient's circumstances.

Maintaining Epidural Analgesia for Labor and Delivery

Although it is possible to maintain epidural analgesia with intermittent bolus administration, this technique is associated with frequent provider interventions as well as periods of analgesia alternating with periods of pain. Hypotension occurs less often when a continuous infusion is used as a result of fewer changes in the level of sympathetic blockade. Continuous infusion results in less total local anesthetic administered (when compared with intermittent boluses), more effective analgesia, and significantly reduced workload. There is also no need for the careful incremental administration of local anesthetic associated with bolus doses.

The parturient's analgesia level and degree of motor block should be frequently assessed and changes in the infusion rate and/or concentration made as needed. An epidural catheter originally sited in the epidural space can potentially migrate into the subarachnoid or intravascular space. If the epidural catheter enters the subarachnoid space some time after placement during a continuous infusion, the resulting gradual increase in motor block can be easily recognized. Alternatively, if the catheter enters the intravascular space, the patient will have a loss of analgesia without overt symptoms of systemic toxicity.

Infusions of bupivacaine (0.0625% to 0.125%) or ropivacaine (0.1% to 0.2%) with fentanyl (1 to 3 mcg/mL) or sufentanil (0.3 to 0.5 mcg/mL) at infusion rates of 8 to 12 mL/hr are commonly used. Lower concentrations may be effective as long as adequate spread is achieved. However, maintaining an adequate sensory level with lower concentrations may necessitate an infusion rate of 10 to 15 mL/hr. In the majority of women, this dilute concentration is associated with minimal motor block, although the block will become denser as the infusion is maintained over time. A higher concentration may be needed as labor intensifies or in women who experience greater pain.

The epidural infusion should be maintained as the parturient transitions to second-stage labor provided the block is stable and effective and adequate motor function has been preserved. The ideal block provides effective analgesia for uterine contractions, dense analgesia of the perineum for delivery, and little motor block. If motor block hinders pushing or if sensory block prevents the parturient from sensing contractions and therefore effectively prevents pushing, the epidural infusion may be decreased or changed to a more dilute solution. On the other hand, the block can be supplemented during second-stage labor if additional perineal analgesia is required. This can be accomplished by injecting a relatively large 6 to 10 mL volume of bupivacaine 0.25%, lidocaine 1% to 2%, or 2-chloroprocaine 2%. Fentanyl 50 to 100 mcg can be added to the aforementioned bolus to further enhance analgesia. Instrumented vaginal delivery generally requires a more dense block, in which case lidocaine 2% with epinephrine 1:200,000 can be used with or without the addition of fentanyl.

Patient-Controlled Epidural Analgesia

Patient-controlled epidural analgesia (PCEA) is an alternate technique that allows the parturient to self-administer bolus doses as needed. It is normally initiated after analgesia has been established with either an epidural of a combined spinal-epidural technique. When compared with continuous epidural infusion, PCEA has several distinct advantages.[127] It reduces the number of unscheduled interventions required by the anesthetist, the total dose of drug used, and lower extremity motor block, all without sacrificing effective analgesia.[128] Maternal satisfaction would be expected to be increased due to enhanced control, but this has not been consistently shown to be the case. The best combination of variables (e.g., background infusion rate, bolus dose, and lockout interval) has yet to be established. The use of a background infusion likely reduces breakthrough pain but has been shown to result in an increase in total local anesthetic used.[129] Background infusion rates of bupivacaine 0.125% or ropivacaine 0.2% between 2 and 10 mL/hr have been used effectively. Bolus doses greater than 5 mL may provide superior analgesia compared with smaller boluses.[130] PCEA also may presumably limit the number of epidural catheter disconnections and reconnections necessary to manually bolus a catheter, hence reducing the potential exposure to pathogens and catheter contamination.

Programmed Intermittent Epidural Boluses

There is evidence to indicate that there may be more widespread distribution of anesthetic solution within the epidural space when large volumes are injected as a bolus compared with a slow infusion.[131] Automated epidural infusion pumps capable of administering programmed intermittent boluses have been recently introduced. With this technique, a bolus dose is automatically administered at regular intervals as opposed to a continuous infusion. Optimal dosing regimens are being studied at this time, but some evidence indicates that larger boluses timed more widely apart appear to increase effectiveness. Wong et al.[132] found that extending the programmed intermittent bolus interval and volume from 15 minutes to 60 minutes, and 2.5 mL to 10 mL, respectively, decreased overall bupivacaine consumption without decreasing patient comfort or satisfaction.

Combined Spinal-Epidural

The combined spinal-epidural (CSE) is a commonly used technique that many practitioners feel provides the best analgesia for labor and vaginal delivery. A CSE combines the best attributes of both techniques while minimizing their respective disadvantages. Analgesia obtained from the spinal component is uniformly effective and has a rapid onset. The epidural catheter allows the analgesia to be prolonged as required and provides the ability to convert the block to a surgical level when operative delivery is indicated.

Several methods have been described for performing the block, including the early technique of spinal needle insertion and removal immediately followed by epidural insertion at the same or different level. Most practitioners now use the "needle through the needle" technique in which the epidural space is identified with an epidural needle followed by placement of a longer small-gauge spinal needle through the existing epidural needle. Care must be taken to avoid displacing the spinal needle during injection. The spinal needle is then withdrawn and an epidural catheter is placed. The "needle through the needle" technique provides the additional benefit of confirming proper epidural needle location. If the epidural needle is not inserted in the midline of the epidural space, the subsequently placed spinal needle will not likely penetrate the dura and CSF flow will not be obtained. Figure 46-7 shows the proper orientation of both the spinal and epidural needles during a CSE technique.

The spinal component of a CSE can be dosed with either a lipid-soluble narcotic alone or in combination with isobaric bupivacaine. Narcotics are commonly used alone in early first-stage labor. For example, fentanyl 15 to 25 mcg or sufentanil 10 mcg in the subarachnoid space can provide analgesia for up to 2 hours with no motor block. Local anesthetic is often combined with the narcotic in late first-stage labor to produce a rapid-onset analgesia

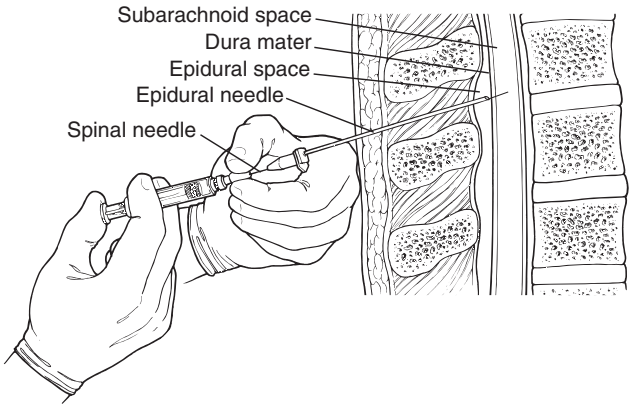

FIGURE **46-7** The proper orientation of both the spinal and epidural needles during the needle-through-needle CSE technique. (From Birnbach DJ, Gatt SP, Datta S. *Textbook of Obstetric Anesthesia*. Philadelphia: Churchill Livingstone; 2000:166.)

with minimal motor block. Isobaric bupivacaine 0.25% 1 mL (2.5 mg) combined with fentanyl or sufentanil provides a more dense analgesia than narcotic alone. Consideration should be given to initiating an epidural infusion before resolution of the spinal component to avoid the need for bolus dosing the epidural catheter.

Spinal Analgesia

In our contemporary practice, a single-shot spinal is rarely an appropriate anesthetic choice for a patient in labor due to its finite duration and lack of flexibility. Because the technique can often be performed quickly, it is generally reserved for multiparous patients in advanced second-stage labor when delivery is clearly imminent or for those exhibiting poor control who can then have an epidural placed with better cooperation. It is also suitable in parturients who have labored without anesthesia and require an instrumented vaginal delivery or those who have delivered without anesthesia and require an extensive repair. In rare cases, multiple single-shot spinal anesthetics, placed every 2 to 3 hours, have been used in parturients with conditions that preclude epidural placement such as a previous history of spinal surgery in which the epidural space has likely been surgically obliterated.

Continuous spinal anesthesia (CSA) using a macro-bore epidural catheter is an option in certain high-risk patients such as the extremely morbidly obese, those with previous spinal surgery or deformity, or those whose dura has been inadvertently punctured with the epidural needle. A CSA may be particularly indicated in a high-risk parturient after failed attempts at a conventional neuraxial anesthetic due to the increased morbidity and mortality associated with general anesthesia. The morbidly obese parturient is at greater risk for cesarean delivery as well as greater risk of failed regional technique.[133] To perform a CSA, an epidural needle is used to identify the subarachnoid space and the epidural catheter is then intentionally threaded into the subarachnoid space. This spinal catheter can then be dosed as a spinal anesthetic using isobaric bupivacaine 0.25% in 0.5-mL to 1-mL increments for labor analgesia. A CSA is not considered a first-line technique because it is clearly associated with an increased risk of postdural puncture headache. There is some evidence to indicate that a catheter left in situ in the subarachnoid space for at least 12 hours results in fewer postdural puncture headaches.[134] It is postulated that the epidural catheter creates a localized inflammatory response where it passes through the dura, which results in decreased CSF leakage when the catheter is ultimately removed. Block level must be carefully monitored when this technique is used. All caregivers in contact with these patients should be notified that the "epidural" catheter is actually subarachnoid to prevent accidental overdose. It is also best to clearly label the catheter as a spinal catheter.

Microcatheters (27-32 gauge) were developed for use in the early 1990s specifically for this purpose but were found to result in an unacceptably high incidence of cauda equina syndrome.[135] The low-flow velocity through the very small-diameter catheter resulted in poor mixing of the lidocaine local anesthetic that was used at the time, creating a pool of concentrated local anesthetic in close proximity to the nerve roots. Microcatheters were subsequently removed from the market by the FDA.[87]

Regional Opioids for Labor Analgesia

The combination of dilute local anesthetics with low-dose opioids allows for the reduced dose of both agents that ultimately results in decreased motor block while preserving acceptable analgesia and minimizing side effects. The agents work by binding to separate and distinct receptors. Local anesthetics work at the nerve axon while neuraxial opioids bind to receptors in the substantia gelatinosa within the dorsal horn of the spinal cord. These receptors are stimulated by the administration of opioids via the subarachnoid or epidural routes. Epidurally administered opioids are believed to be absorbed into the CSF, and ultimately the spinal cord, to exert their action on spinal opioid receptors. Neuraxially administered opioids are known to possess a "ceiling effect" whereby increasing the dose beyond conventional regimens does not result in an increased duration or quality of analgesia. Common side effects are, however, more severe and prolonged at the increased dose levels.

Side effects of epidural and subarachnoid opioid administration include respiratory depression, itching, urinary retention, nausea, and vomiting. IV doses of an opioid antagonist (naloxone) or agonist-antagonist (nalbuphine) are effective at reducing or eliminating the undesirable effects without antagonizing the analgesia and often are more effective against pruritus than an antihistamine.

Fentanyl. When used in combination with local anesthetics, fentanyl in epidural doses of 50 to 100 mcg and subarachnoid doses of 10 to 25 mcg produces good to excellent analgesia in 5 to 10 minutes. Administration of these doses, repeated as often as every 90 minutes in women in labor, has been shown not to affect Apgar scores, umbilical cord blood analysis, or neurobehavioral test results for up to 24 hours after delivery.[136-138] Fentanyl 100 mcg in the epidural space has been shown to be undetectable in breast milk.[139] When opioids are used alone, much higher doses are needed to provide labor analgesia, and even these higher doses are not entirely effective during the second stage of labor. When analgesia from fentanyl administration is at its peak, serum fentanyl levels are lower than those known to produce equivalent analgesia after IV administration. In fact, most women have undetectable plasma fentanyl levels after receiving 100 mcg of epidural fentanyl.[140]

The duration of action of fentanyl in the epidural space is 60 to 140 minutes. Because fentanyl is so much more lipid soluble than morphine, it is absorbed into neural tissue faster; therefore it has a faster onset and shorter duration of action when compared with morphine. As a result, the cephalad migration of fentanyl is much less than that of morphine; therefore fentanyl is associated with a significantly lower incidence of CNS side effects. This is likely why respiratory depression has rarely been reported following subarachnoid or epidural administration of fentanyl in conventional doses.

For continuous epidural infusion, fentanyl concentrations up to 2.5 mcg/mL of local anesthetic can be used without adversely affecting neonatal respiration or neurobehavioral scores.[141]

Bupivacaine (up to 0.125%) or ropivacaine (up to 0.2%) with 1 to 2 mcg/mL of fentanyl is a widely used combination.[142]

Sufentanil. Sufentanil is a highly lipid-soluble drug that enhances receptor affinity, resulting in increased potency. When injected into the epidural space, 98% of the dose is absorbed either by epidural fat or into epidural veins. Little sufentanil reaches the CSF. As a result, relatively higher plasma levels of sufentanil are achieved compared with those of fentanyl after the epidural injection of equipotent doses. When sufentanil is injected directly into the subarachnoid space, plasma levels of the drug are much lower than its CSF levels. One advantage of sufentanil is that it has a shorter plasma half-life than fentanyl; therefore, accumulation should be even less likely to occur when it is used instead of fentanyl.

Morphine. Morphine is relatively lipid insoluble compared with fentanyl or sufentanil. When administered in the epidural or subarachnoid space it has a slow onset of action of 30 to 60 minutes and, when used alone for labor analgesia, is not associated with a high degree of maternal satisfaction. It is this pharmacologic profile that makes it a poor choice for use in labor analgesia. However, morphine is uniquely suited for use as a postoperative analgesic when neuraxial anesthesia is utilized for cesarean section (see next section).

ANESTHESIA FOR CESAREAN SECTION

Birth by cesarean section now accounts for over 30% of all deliveries and is performed over 1.5 million times annually in the United States.[143,144] Common indications include cephalopelvic disproportion, nonreassuring fetal status, arrest of dilation, malpresentation, prematurity, prior cesarean delivery, and prior uterine surgery. The choice of anesthesia depends on maternal status, urgency of the surgery, condition of the fetus, and the patient's desires. This fact highlights the need for strong communication between the obstetrician, nursing staff, and anesthesia provider. The use of neuraxial anesthesia for cesarean section has increased dramatically along with a commensurate decrease in the use of general anesthesia.[145] Neuraxial anesthesia has significant advantages including decreased risk of mortality from failed intubation and aspiration of gastric contents, better neonatal outcomes from the use of less depressant agents, and the ability of the mother to be awake for the delivery. In fact, it has been shown that the risk of maternal death is 16.7 times greater with general anesthesia when compared with regional anesthesia. Recent evidence also suggests that general anesthetic agents are associated with apoptosis of fetal brain neurons in animal models.[146]

Regardless of the anesthetic technique used, left uterine displacement should be provided as soon as possible. The table should be rolled to the left or a wedge placed under the right hip of the patient in order to shift the uterus off the inferior vena cava and abdominal aorta, thereby preserving fetal oxygenation. Fetuses delivered of mothers with left uterine displacement have a lower incidence of CNS depression and acidosis than those delivered of mothers in the supine position.[147] In an awake parturient with a neuraxial anesthetic, it is not a requirement to secure the upper extremities to the armboards. The lower extremities, however, should be secured to prevent movement from the table.

Blood loss during cesarean section is usually between 500 mL and 1000 mL. However, the reported range of blood loss is great—in one study, from 164 to 1438 mL.[148] Many factors affect the volume of blood lost during cesarean section, including surgical time, surgical technique, blood pressure, fetal lie, fetal size, placental implantation, maternal coagulation status, and the ability of the uterus to contract after the placenta has been delivered. Visual estimation of blood loss is inaccurate and often complicated by the presence of large volumes of amniotic fluid and variably saturated sponges. Normal amniotic fluid volume is approximately 700 mL (range 300 mL to 1400 mL) and should be accounted for when estimating blood loss.[149]

Neuraxial Anesthesia for Cesarean Section

A dermatomal level of T4 is required to provide effective anesthesia for cesarean section. This level of block is associated with a rapid and extensive spread of anesthesia that can often result in maternal hypotension and, if untreated, fetal compromise. Common measures to minimize hypotension include left uterine displacement, intravenous fluid administration, and vasopressor use.

A nonparticulate antacid should be administered preoperatively for aspiration prophylaxis. An H_2-receptor antagonist and metoclopramide also can be used preoperatively to increase gastric pH and emptying. Anxiolytics are normally not administered preoperatively in order to minimize fetal depression. Prophylactically administered antibiotics have been traditionally withheld until cord clamping in an effort to prevent fetal transmission and the obscuring of any subsequent neonatal sepsis workup. However, antibiotics administered pre-incision have been shown to decrease the surgical site infection rate from 6.4% to 2.5%, making the practice much more common.[150] Requirements for standard monitoring remain the same as with any anesthetic; however, blood pressure should be assessed at least every 1 minute for the first 20 minutes or until the patient's condition has stabilized. Left uterine displacement is an essential aspect of positioning to preserve maternal cardiac output and, ultimately, utero-placental exchange.

The routine supplemental use of oxygen in the absence of preexisting fetal compromise has not been shown to be of any maternal or neonatal benefit in spite of its common practice.[151] Although supplemental oxygen may reduce postoperative nausea and vomiting after general anesthesia, its administration during cesarean section with neuraxial anesthesia does not decrease the incidence or severity of intraoperative or postoperative nausea or vomiting.[152] Oxygen administration during elective cesarean section appears to increase oxygen free radical activity in both the mother and fetus.[153] Consideration, however, should be given to the use of end-tidal CO_2 monitoring made possible by the use of sampling nasal cannula for those patients susceptible to intraoperative respiratory compromise or in those who have been provided IV sedation.

Spinal Anesthesia for Cesarean Section

Single-shot spinal anesthesia is probably the most commonly used anesthetic technique for cesarean delivery because it offers many distinct advantages. It is relatively simple, has a rapid onset, provides a more reliable block, and uses smaller and therefore less toxic doses of local anesthetic when compared with epidural anesthesia. Its simplicity and rapid onset make it suitable for all but the most emergent cesarean deliveries when compared with general anesthesia. It is considered an economical anesthetic insofar as its rapid onset functions to decrease overall operating room times. Drawbacks include its fixed duration of action and rapid onset of sympathectomy with resultant hypotension. Hyperbaric bupivacaine 0.75% 13 mg is effective in 95% of patients (ED_{95}) and provides 90 to 120 minutes of surgical anesthesia. In practice, neither the patient's height, weight, nor body mass index correlates to the ultimate block level obtained.[154] The compound curvature of the spine in the supine position serves to limit the upward spread of the block when hyperbaric local anesthetics are used. A series

of recent studies has determined that decreasing the bupivacaine dose results in less hypotension but is associated with an increased risk of intraoperative pain, a shorter duration of effective anesthesia, and a slower onset.[155]

When spinal anesthesia is used to produce the T4 block needed for cesarean section, hypotension has been shown to occur in up to 80% of patients despite left uterine displacement.[156] Maternal hypotension results mainly in nausea and vomiting but, if severe and untreated, may lead to cardiovascular collapse, a decreased level of consciousness, and uteroplacental hypoperfusion. The goal should be to prevent, to the greatest extent possible, and effectively treat hypotension before complications arise.

Crystalloid preloading has traditionally been used in an effort to prevent hypotension but has been shown to be minimally effective, possibly due to its rapid redistribution from the intravascular space.[157,158] On the other hand, colloid preloading (hydroxyethylstarch 6%) consistently reduces the incidence and severity of hypotension and may improve maternal cardiac output.[159] Despite these findings, the routine use of hydroxyethylstarch 6% (HES) continues to be debated because of its disadvantages including cost, potential allergic reactions, and pruritus.

The timing of the fluid administration also has been investigated comparing preloading (prior to anesthetic placement) with coloading (given rapidly at the time of intrathecal injection). It appears that crystalloid coloading is somewhat effective compared with crystalloid preloading (not effective), provided the infusion rate and volume are high enough during the first 5 to 7 minutes after spinal injection when the sympathetic block is established.[160] The timing of a colloid administration does not appear to change its degree of effectiveness.[161] Current evidence suggests that combining a prophylactic vasopressor regimen with HES preloading, HES coloading, or crystalloid coloading is the best method of preventing maternal hypotension after the initiation of spinal anesthesia. Crystalloid preloading is clinically ineffective and thus should no longer be used. Routine fluid loading is no longer advocated prior to spinal anesthesia for cesarean delivery in preeclampsia and should be used with caution in women with multiple gestations.[157]

Ephedrine and Neo-Synephrine are vasopressors commonly used to treat maternal hypotension. Ephedrine is a synthetic, nonselective, noncatecholamine sympathomimetic drug. Doses of 5 to 25 mg intravenously are used to treat acute decreases in blood pressure. The duration of ephedrine's cardiovascular effects varies with the dose given. The effect of a 5- or 10-mg IV dose usually persists for 5 minutes. Tachyphylaxis can occur with repeated administration of small doses, resulting in a noticeably reduced clinical effect after subsequent dosing. Ephedrine is metabolized in the liver, and up to 40% is excreted unchanged by the kidneys. It has an elimination half-life of 3 hours.

Ephedrine causes direct β stimulation and indirect α stimulation through the release of endogenous norepinephrine. It has long been used in obstetric anesthesia because it was thought to affect uterine artery blood flow less than other vasoactive drugs in pregnant ewes.[162] However, recent evidence suggests that ephedrine may cross the placenta and stimulate fetal β-adrenergic receptors, resulting in a depression of fetal acid-base status.[163] Although the ultimate clinical relevance of this effect has yet to be defined, many practitioners are now using phenylephrine as a first-line vasopressor to treat maternal hypotension.[48] Hypotension is a primary cause of intraoperative nausea and vomiting in the early period after spinal anesthesia. Hypotension may lead to cerebral hypoperfusion, which is thought to activate the vomiting center. It has also been suggested that hypotension results in gastrointestinal hypoperfusion with the subsequent release of emetogenic substances such as serotonin. Optimum use of vasopressors to prevent hypotension significantly reduces the incidence of intraoperative nausea and vomiting.[48,164]

Phenylephrine is a direct-acting α_1-adrenergic agonist that results in vasoconstriction and an increased peripheral vascular resistance. It can result in a reflex bradycardia with a subsequent decrease in cardiac output. Based on early animal studies, α-agonists were thought to decrease uterine artery blood flow,[162] but phenylephrine has been shown to be safe for the treatment of maternal hypotension during regional anesthesia when given in the conventional dose range.[165] Neonatal blood gas values and Apgar scores remain within normal limits in all healthy subjects after the administration of 80-mcg or 100-mcg bolus doses of phenylephrine.[166] Phenylephrine can be administered by either bolus dosing or continuous infusion; however, the optimal regimen for each has yet to be determined. Many practitioners now feel that the maternal HR should play a role in the selection of a vasopressor. There is evidence to indicate that during phenylephrine infusion there is a dose-dependent decrease in cardiac output that parallels a decrease in heart rate.[167] When the HR is at baseline or above, phenylephrine may be used. When the HR is below baseline, ephedrine will increase the blood pressure and HR without further reductions in CO. Phenylephrine is now established as a first-line vasopressor for maternal hypotension and can be used with ephedrine for heart rate management.

It is common practice to add opioids to hyperbaric bupivacaine for cesarean section spinal anesthesia because they provide additional intraoperative and postoperative analgesia without affecting the block height. Maternal complaints of nausea, vomiting, and visceral pain occur occasionally even in the presence of an adequate T4 block. Intraoperative block quality can be significantly improved with the addition of fentanyl 10 to 20 mcg or sufentanil 2.5 to 5 mcg. The onset of these lipid-soluble opioids is 5 to 10 minutes with an effective duration of 60 to 90 minutes. Morphine can be added in addition to either fentanyl or sufentanil to provide long-acting postoperative analgesia. Morphine has an onset of action (60 to 90 minutes) that coincides with the effective duration of fentanyl or sufentanil so that, when used in combination, the patient has uninterrupted opioid analgesia intraoperatively and for 12 to 18 hours postoperatively.

After the placenta has been delivered, oxytocin should be given at the direction of the obstetrician. Pitocin is the clinically available synthetic equivalent of oxytocin, a naturally occurring hormone synthesized in the supraoptic and paraventricular nuclei of the hypothalamus. In the mature uterus of a pregnant woman, oxytocin causes an increase in the frequency and strength of uterine contractions. Endogenous oxytocin release occurs with stimulation of the cervix, vagina, and breasts.

The half-life of oxytocin varies from 4 to 17 minutes. It is metabolized by liver, kidney, and plasma enzyme pathways in the parturient. Commercially available preparations of oxytocin contain a preservative that may cause systolic and especially diastolic hypotension, flushing, and tachycardia when infused at high doses.[168] The amount of oxytocin added to the IV solution should be tailored to the volume of solution remaining in the bag, the flow rate of the IV, and the patient's condition. If an unusually large blood loss results in hypotension, and fluid resuscitation is required, it may be helpful to infuse the oxytocin at an appropriate rate and to start a second IV line for administering fluid volume at a rapid rate. If the solution with the added oxytocin is infused fast enough to replace volume, it is possible that the high dose of oxytocin may cause further hypotension. In some cases the obstetrician may choose to administer oxytocin directly into the uterine

muscle to maximize its effect. Carbetocin, a long-acting oxytocin agonist, appears to be a promising agent for the prevention of PPH and is currently being widely studied.

If oxytocin does not adequately stimulate uterine contraction, the next drug used is usually an ergot alkaloid (e.g., Methergine, Ergotrate). Because of their potent vascular effects, ergot alkaloids are not administered intravenously. Ergot alkaloids normally cause an increase in blood pressure, central venous pressure, and pulmonary capillary wedge pressure. An intramuscular dose of Methergine 0.2 mg is commonly administered for stimulating uterine contractions. Intravenous administration, which is avoided, may result in arterial and venous constriction, coronary artery constriction, severe hypertension, cerebral bleeding, headache, nausea, and vomiting. Ergot alkaloids are metabolized and eliminated chiefly by the liver. The plasma half-life is approximately 2 hours, but uterine effects last much longer.

When the uterus does not contract well despite the use of oxytocin and ergot alkaloids, prostaglandin F_{2a} (e.g., Carboprost, Hemabate; 250 mcg) can be administered either intramuscularly or directly into the uterine muscle. Prostaglandins are potent stimulators of uterine contractions. The contractions induced by prostaglandins are strong and painful. Nausea, vomiting, and diarrhea are frequent side effects. In addition to causing uterine contractions, prostaglandins may cause hypotension by relaxing vascular smooth muscle; however, cases of severe hypertension after prostaglandin administration also have been reported.[169]

Transversus abdominal plane (TAP) blocks can be used to provide postoperative analgesia in patients who are not candidates for intrathecal morphine, when neuraxial anesthesia is contraindicated, or in those who receive general anesthesia.[170] The sensory nerves that supply the anterior abdominal wall course through the fascial plane between the internal oblique and the transversus abdominis muscles. Local anesthetics injected into this plane block sensory impulses from the anterior abdominal wall and are effective in relieving the pain associated with a Pfannenstiel incision.[171] A suggested technique for spinal anesthesia for cesarean section is outlined in Box 46-3.

BOX 46-3

Spinal Anesthesia Technique for Cesarean Section

- Nonparticulate oral antacid no more than 1 hour prior to surgery
- Administer an IV preload (colloid) or coload (crystalloid or colloid)
- Apply standard monitors and record preprocedure vital signs
- Record preprocedure fetal heart tones
- Consider oxygen administration
- Perform lumbar puncture at L3-L4
  - Sitting or lateral position
  - Small-gauge (24- or 25-gauge) non-cutting needle (e.g., Sprotte, Whitacre, Pencan)
  - Hyperbaric bupivacaine 15 mg in 8.25% dextrose (7.5-15 mg.)
    - Add fentanyl 20 mcg for intraoperative analgesia
    - Add preservative-free morphine 150 mcg for postoperative analgesia
- Supine position with left uterine displacement
- Monitor blood pressure every 1 minute at least until birth
- Confirm block level (T4) prior to surgical start
- Treat hypotension with phenylephrine; if maternal heart rate decreases below baseline or blood pressure is not increased, use ephedrine
- Administer oxytocin as directed at delivery

Epidural Anesthesia for Cesarean Section

An epidural inserted in the operating room for an elective cesarean section is not often the technique of choice because it has a slower onset and requires a much higher dose of local anesthetic to achieve a surgical level of anesthesia when compared with a spinal anesthetic. However, an epidural catheter does provide the flexibility to extend the duration of the block when a long surgical time is anticipated. The slower-onset sympathectomy associated with an epidural may make treating the resultant hypotension easier and can be of value in patients who are particularly susceptible to abrupt changes in blood pressure. Meticulous attention to correct catheter placement and dosing safety is required when this technique is used due to the increased volume and concentration of local anesthetic needed to obtain a surgical block. After a negative test dose and careful aspiration for blood and CSF, lidocaine 2% with epinephrine 1:200,000 can be used when dosed in 3- to 5-mL increments. A total volume of approximately 20 to 25 mL is required to obtain a T4 level. Bupivacaine is generally avoided due to the increased maternal mortality associated with it when toxicity occurs.

When a parturient with an epidural in place for labor analgesia requires a cesarean section, the indwelling epidural catheter should be used to provide surgical anesthesia. Because larger volumes of more concentrated local anesthetic are required to produce surgical anesthesia and unrecognized epidural catheter movement into either the intrathecal or intravascular space is always a possibility, careful aspiration and incremental dosing is again important. After discontinuation of the analgesic infusion, the selection of local anesthetic is largely determined by the urgency required for delivery. The addition of sodium bicarbonate 1 mEq/10 mL to lidocaine 2% with epinephrine 1:200,000 will hasten the onset of anesthesia when a rapid conversion to surgical anesthesia is necessary. Commercially prepared lidocaine containing epinephrine has a low pH in order to preserve the epinephrine. The addition of sodium bicarbonate immediately prior to use increases the biologically active non-ionized fraction of drug.[172] This combination normally results in approximately 90 to 120 minutes of surgical anesthesia. Sodium bicarbonate cannot be added to bupivacaine because it results in precipitation when the pH is raised. 2-Chloroprocaine is rapidly metabolized by ester hydrolysis and, as a result, is associated with a very low incidence of toxicity; it can be used to rapidly convert a labor epidural to a surgical anesthetic with little concern of toxicity but will likely require intraoperative augmentation because it has an effective duration of approximately 45 minutes. The efficacy and duration of epidural morphine analgesia is diminished when administered after 2-chloroprocaine. The precise mechanism of this interaction is unknown but may be the result of opioid receptor antagonism.[96]

In the presence of a well-functioning labor analgesic, the total volume required to raise the block level from the existing T10 to the required T4 is approximately 10 to 15 mL. Although controversial, conversion of a labor epidural to a surgical anesthetic can be initiated in the labor room in an emergency. Careful attention should be directed toward the existing analgesia level, incremental dosing, and maternal vital signs while in the labor room. On arrival to the operating room, the block level can then be assessed and additional doses given as required during the surgical preparation.

Breakthrough pain in labor requiring multiple epidural doses is a significant predictor of subsequent failure of epidural anesthesia and highlights the need to replace inadequate catheters before an unplanned cesarean is required.[173] Efforts should be directed toward avoiding the situation of a failed epidural in the operating room. This includes early recognition and replacement of poorly performing labor epidurals. However, if an inadequate

epidural is identified in the operating room, and the fetal status allows, consideration should be given toward replacing the epidural to a different interspace or the use of a combined spinal-epidural technique in which the spinal is dosed lightly and the epidural is subsequently used to augment the level as needed. In the scenario of a recently dosed inadequate epidural, a superimposed single-shot spinal anesthetic can often produce an unpredictable, and frequently higher than expected, block level. Alternatively, the inadequate epidural can be given time to absorb and resolve before a single-shot spinal. Ultimately, a general anesthetic may be required. A suggested technique for converting an epidural in use for labor analgesia to a cesarean anesthetic is given in Box 46-4.

Combined Spinal-Epidural for Cesarean Section

As with labor analgesia, the combined spinal-epidural (CSE) technique can provide several advantages over either technique when used alone. A lower spinal dose can be used, resulting in decreased hypotension, whereas the block can be augmented to increase the block height or prolong the duration if necessary. The technique, however, is not without its disadvantages. Because the spinal component is injected prior to placement of the epidural catheter, if difficulty is encountered with catheter placement, the patient could remain in the sitting position for a prolonged time, resulting in lower block height. The presence of a dense spinal block makes evaluating subsequent test doses for subarachnoid injection difficult. If a lower spinal dose is used and the block is not adequate for surgery, subsequent epidural dosing will ultimately delay the start of surgery. Some practitioners advocate the CSE technique after attempts with a spinal have been unsuccessful. An epidural needle has a larger diameter and may be less likely to deflect from its intended direction around dense ligaments or bone.

BOX 46-4

Converting an Epidural in Use for Labor Analgesia to a Cesarean Anesthetic

- Administer nonparticulate oral antacid no more than 1 hour prior to surgery.
- Discontinue continuous epidural infusion.
- Administer an IV coload (crystalloid).
- Apply standard monitors and record preprocedure vital signs.
- Record preprocedure fetal heart tones.
- Consider oxygen administration.
- Place in supine position with left uterine displacement.
- Carefully aspirate epidural catheter for blood and cerebrospinal fluid.
- Administer lidocaine 2% with epinephrine 1:200,000 and sodium bicarbonate 1 mEq/10 mL local anesthetic (total dose 10 to 15 mL).
  - Administer 3 mL and observe maternal heart rate (HR) for 60 seconds and level of block for 3 to 5 minutes.
  - If no sign of subarachnoid or intravascular injection, administer 3 to 5 mL and observe for 3 to 5 minutes.
- Treat hypotension with phenylephrine; if maternal HR decreases below baseline or blood pressure is not increased, use ephedrine.
- Confirm block level (T4) prior to surgical start.
- Administer 3 to 4 mg preservative-free morphine (0.5 mg/mL 6 to 8 mL) via the epidural catheter after cord is clamped for postoperative analgesia.
- Administer oxytocin as directed at delivery.

General Anesthesia for Cesarean Section

General anesthesia (GA) may be indicated despite the numerous disadvantages of the technique when compared with regional anesthesia. GA allows for better control of the airway and improved hemodynamic control, making it useful in cases of existing or expected hypovolemic shock. GA is a necessary choice when a neuraxial anesthetic is not in place and a surgical delivery is urgent enough to preclude its placement or when contraindications, such as patient refusal or coagulopathy, are present. It is also an alternative in the presence of a failed neuraxial technique. Neuraxial techniques have progressively eclipsed GA for use in cesarean section primarily in an effort to reduce maternal mortality.[145] Practical steps to decrease the use of GA include referral and evaluation of high-risk parturients early in pregnancy to optimize their medical condition and plan for anesthetic management, considering early neuraxial anesthetic placement to ensure proper functioning, and promptly replacing epidural catheters that are providing suboptimal labor analgesia.[174]

The Difficult Airway. An airway evaluation is an important part of the preparation for anesthesia in any patient and even more so in the parturient. Airway problems tend to occur more frequently in obstetric patients than in other healthy patients; failure to intubate has been reported to occur as frequently as 1 in 250 obstetric patients.[175] This is true at least in part because of the soft-tissue edema often present in the hypopharynx. A patient's airway may significantly change also during the course of her labor and, as such, should be evaluated again prior to an operative delivery. Breast enlargement and cephalad displacement of the thorax can make maneuvering the laryngoscope into the mouth difficult, necessitating the use of a short-handled laryngoscope. Placement of a rolled towel lengthwise along the thoracic spine or widthwise under the shoulders helps to elevate the chest off the operating table. This makes it possible to extend the neck and position the head more optimally, facilitating insertion of the laryngoscope blade and improving visualization of the glottis. Positioning for the obese parturient for laryngoscopy is shown in Figure 46-8.

Airway problems resulting in a failure to oxygenate and ventilate remain the leading cause of anesthesia-related mortality in the obstetric population.[176]Although rapid-sequence induction is the technique most commonly used to minimize the risk of gastric aspiration during induction of general anesthesia, it is *not* indicated if the laryngoscopist has doubts about his or her ability to intubate the patient. In such a case, an alternative method, such as awake intubation, may be necessary. Blind nasal intubation should be performed cautiously, if at all, in the parturient, who commonly has swollen nasal mucosa that are prone to bleeding. The anesthetist should be familiar with and able to perform the steps in an obstetric failed intubation algorithm (Figure 46-9).

Induction. Induction of general anesthesia requires a rapid-sequence technique using cricoid pressure after denitrogenation and preoxygenation for 3 minutes. The standard induction agent in the healthy parturient is propofol (2 to 2.5 mg/kg). As expected, propofol produces neonatal depression but is rapidly redistributed and cleared from the neonate, resulting in a rapid emergence.[177,178] Ketamine (1 mg/kg) or etomidate (0.3 mg/kg) are especially useful in patients who have airway disease or are hemodynamically unstable. Ketamine has been associated with lower analgesic demands during the first 24 hours postoperatively.[179] The indirect sympathomimetic effect of ketamine helps support blood pressure until adequate intravascular volume can be replaced.

The induction of anesthesia should be delayed until all preparation for surgery is complete and the surgical staff indicates they are ready. The operating surgeon should be instructed to delay

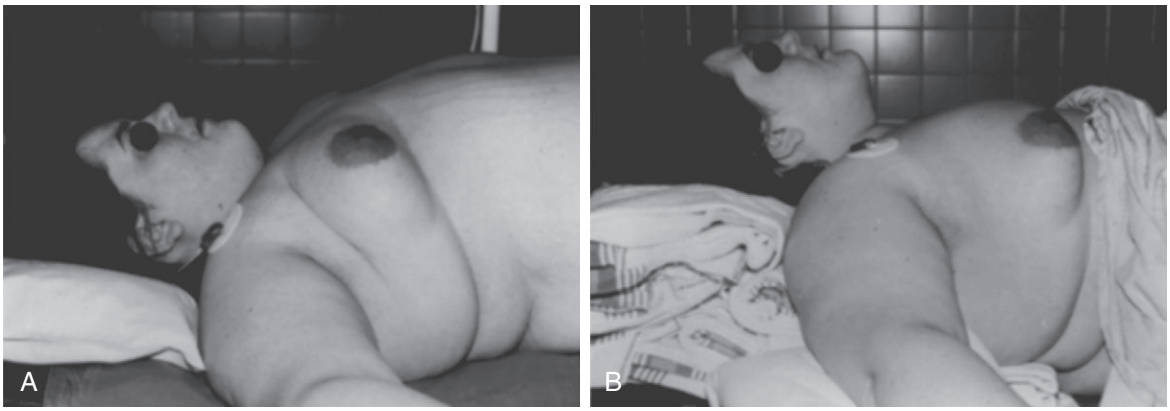

FIGURE **46-8** Positioning for the obese parturient for laryngoscopy. **A,** Standard positioning. **B,** Improved positioning with the elevation of the torso and head. (From Hagberg CA. *Benumof's Airway Management*. 2nd ed. Philadelphia: Mosby; 2007:844.)

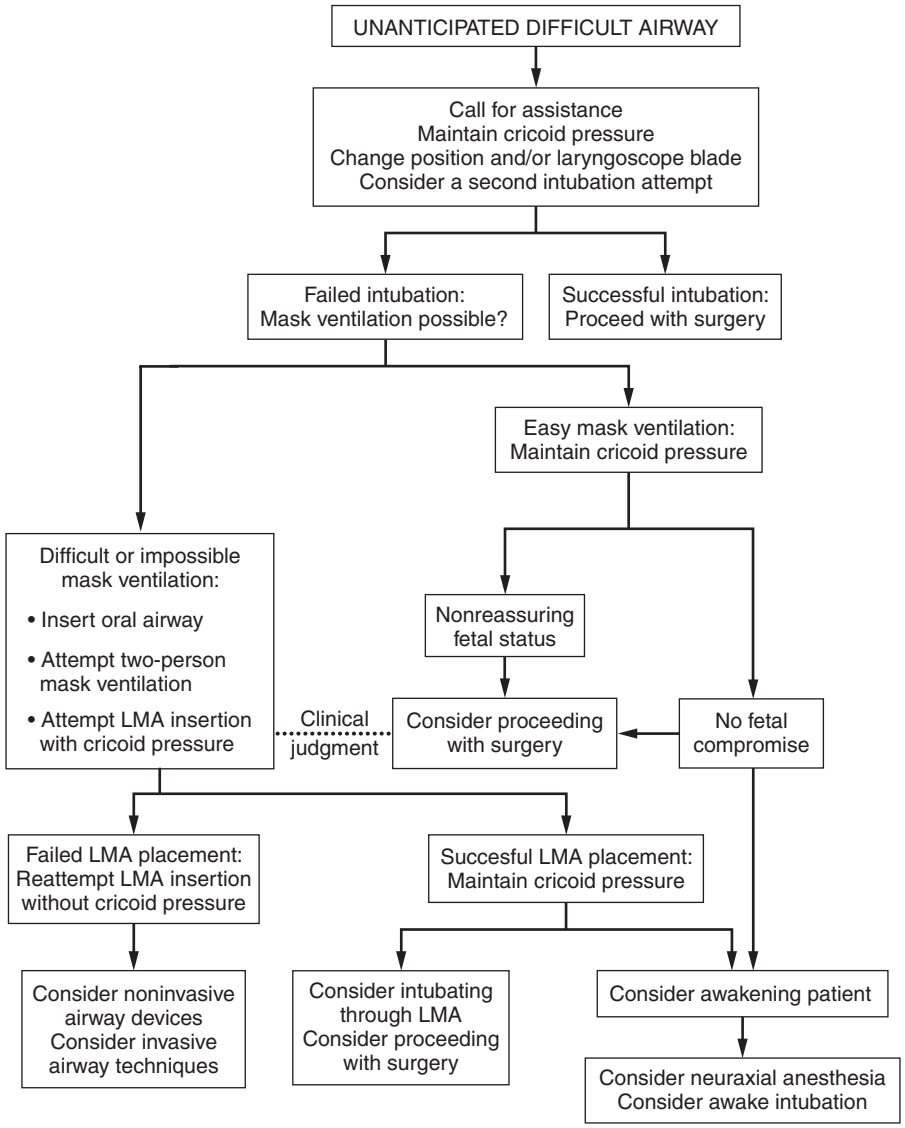

FIGURE **46-9** Unanticipated difficult airway algorithm adapted for use in obstetric anesthesia. It is intended as a guide only. Practitioner's skill set and judgment should guide clinical decisions. (From Chestnut DH, et al. *Chestnut's Obstetric Anesthesia: Principles and Practice*. 4th ed. St. Louis: Mosby; 2009).

incision until confirmation of endotracheal tube placement is made. The incision is made after verification by capnography, auscultation of breath sounds over the chest and abdomen, and bilateral chest expansion. The reasoning behind this practice is to minimize fetal exposure to depressant drugs.

Succinylcholine (1 to 1.5 mg/kg) remains the muscle relaxant of choice during induction of general anesthesia in the parturient. When succinylcholine is contraindicated, a fast-acting nondepolarizer may be judiciously administered, or an awake intubation may be attempted. Rocuronium 0.5 to 1.0 mg/kg can be used. Although intubation can be accomplished quickly with a fast-onset nondepolarizing muscle relaxant, the duration of action will be longer than with succinylcholine. Pregnancy is associated with fewer fasciculations and less succinylcholine-related muscle pain, therefore, a defasciculating dose of a nondepolarizing muscle relaxant may not be required.

Maintenance of Anesthesia. General anesthesia can be maintained with a volatile inhalational agent and nitrous oxide. The predelivery goal of at least 0.80 MAC should be delivered with a relatively high fresh-gas flow rate consisting of 50% oxygen/50% nitrous oxide to ensure adequate anesthesia and minimize intraoperative awareness. If fetal distress is present or if maternal O_2 saturation is below 97%, high concentrations of O_2 may be used without nitrous oxide. Administering 100% O_2 does result in improved fetal oxygenation compared with 50% O_2, but questions have been raised about the danger of free radical activity in neonates born to women administered greater than 50% O_2.[180] Comparisons of Apgar scores, umbilical venous O_2 tension, time to breathing, and resuscitation efforts in neonates has revealed that infants born to women given 100% O_2 before delivery have slightly better outcomes.[181] Maternal hyperventilation should be avoided during mechanical ventilation because a Pa_{CO_2} less than 20 mmHg can result in decreased uterine blood flow and a shift of the oxyhemoglobin dissociation curve to the left. Maternal Pa_{CO_2} should be maintained at the normal term pregnancy range of 30 to 32 mmHg.

The use of bispectral index (BIS) monitoring remains controversial in that even the most rapid application before an emergency cesarean section takes some time, and its use has not been shown to conclusively prevent recall in all cases.[182] When used, a target BIS score of less than 60 can be obtained at a MAC of approximately 0.8 or above.

Volatile inhalational agents are tocolytic and result in decreased uterine contractility and tone that can result in increased postdelivery blood loss. The uterus continues to contract in response to oxytocin provided the MAC is less than 1.0.[183] In the presence of uterine atony and hemorrhage, their concentration can be decreased at delivery and anesthesia supplemented with narcotics and benzodiazepines as needed. The routine use of intraoperative muscle relaxation is generally not necessary and can be left to the surgeon's preference. Immediately after delivery, the recently distended abdominal musculature is quite flaccid and the surgical team should be accustomed to performing cesarean sections on spontaneously ventilating patients. In the absence of neuromuscular relaxation, the anesthetic depth can be better adjusted to the patient's requirements according to respiratory rate and depth. Intraoperative awareness from inadequate anesthesia may be less likely to occur in a patient who is not surgically relaxed.

Infants delivered by cesarean section under GA are more likely to be depressed and to require active resuscitation compared with those delivered with a neuraxial anesthetic and therefore an individual (other than the anesthesia provider) trained in neonatal resuscitation should be present at delivery.[184] The length of time from uterine incision to delivery has been shown to correlate with the degree of neonatal acidosis.[185] The interval should be recorded. An interval of 3 minutes seems to be the critical value;[186] neonates delivered later than 3 minutes after uterine incision are more likely to be depressed. At the completion of surgery, the patient is extubated awake (i.e., following commands) after full recovery of neuromuscular function has been confirmed and extubation criteria have been met. A suggested method for providing general anesthesia for cesarean section is given in Box 46-5.

BOX 46-5

General Anesthesia for Cesarean Section

- Histamine$_2$-receptor antagonist or proton pump inhibitor and/or metoclopramide intravenously
- Nonparticulate oral antacid no more than 1 hour prior to surgery
- Left uterine displacement
- Apply standard monitors and record preprocedure vital signs
- Record preprocedure fetal heart tones
- Denitrogenation/preoxygenation with 100% oxygen for 3 minutes
- When abdominal preparation is complete and surgical drapes are in place, confirm the surgical team is ready to begin
- Intravenous rapid sequence induction:
  - Cricoid pressure
  - Propofol, ketamine, or etomidate
  - Succinylcholine (rocuronium or vecuronium if succinylcholine is contraindicated)
- Intubation with a 6.0- to 7.0-mm cuffed endotracheal tube
- Pre-delivery maintenance with 50% oxygen/50% nitrous oxide and volatile halogenated agent with a goal of 0.8 minimum alveolar concentration
- After delivery:
  - Increased concentration of nitrous oxide, consider reducing concentration of volatile halogenated agent
  - Opioid titrated as needed
  - Consider a benzodiazepine (midazolam)
  - Muscle relaxant as needed
  - Administer oxytocin as directed
- Extubation awake with intact airway reflexes

Modified from Tsen LC. Anesthesia for cesarean delivery. In: Chestnut DH, et al, eds. *Chestnut's Obstetric Anesthesia: Principles and Practice*. 4th ed. St. Louis: Mosby; 2009:521.

COMPLICATIONS OF REGIONAL ANESTHESIA

Hypotension

Hypotension is a frequent complication of obstetric neuraxial anesthesia and results from a rapid-onset sympathectomy and subsequent decreased venous return and decreased cardiac output. Hypotension commonly manifests as maternal nausea and vomiting and can impair uterine perfusion. Maternal hypotension of sufficient magnitude and duration results in uteroplacental hypoperfusion and ultimately fetal acidemia. It is defined as a 20% decrease from baseline or a systolic pressure less than 100 mmHg. Efforts to reduce the incidence of hypotension include left uterine displacement, bolus intravenous fluid administration, and the use of vasopressors.

Nausea and Vomiting

Nausea and vomiting is not uncommon during labor and delivery. The causes are often multifactorial and include delayed gastric emptying, administration of opioids, exteriorization of the

uterus, and motion during transport. The aggressive treatment of hypotension can prevent much vomiting. Some clinicians believe that a sympathetic block results in unopposed gastrointestinal vagal stimulation, which predisposes the patient to nausea. The administration of an antimuscarinic agent (glycopyrrolate) before the institution of either an epidural or subarachnoid block may prevent nausea by this mechanism. Opioids administered in either the epidural or subarachnoid space improve block quality and do not increase intraoperative nausea.

Multimodal approaches combining antiemetics with different mechanisms of action may be more effective than single drugs when treating nausea and vomiting.[187] Metoclopramide (10 mg IV) is a frequently given prokinetic that likely reduces the incidence of intraoperative nausea and vomiting. It can be given preoperatively or at cord clamp.[188] The serotonin receptor antagonist ondansetron (4 mg IV) may be somewhat more effective compared with metoclopramide in preventing intraoperative nausea.[189] Scopolamine transdermal patches have been shown to significantly reduce the incidence of post–cesarean section nausea and vomiting resulting from regional anesthesia.[190] Transdermal scopolamine patch begins to be effective in 2 to 4 hours. Although this onset time is long, the duration of action and simplicity of the scopolamine patch (48 hours or longer) make it an attractive choice for parturients with a strong history of PONV. Side effects include dry mouth and dizziness, which, for some patients, will outweigh the benefits of scopolamine.

Postdural Puncture Headache

Postdural puncture headache (PDPH) is a result of a loss of CSF from the subarachnoid space. The total volume of CSF normally present within the subarachnoid space is approximately 150 mL; 75 mL above the foramen magnum, 75 mL caudad to the foramen. Production is approximately 0.35 mL/min or 500 mL/day. PDPH occurs when CSF loss exceeds production. CSF loss occurs through a hole in the dura made during the performance of a subarachnoid block or accidentally during the attempted performance of an epidural block. Because the needle used to place an epidural catheter has a larger diameter (17 to 18 gauge) relative to spinal needles used in contemporary practice, puncture of the dura with an epidural needle can result in the loss of a significant volume of CSF. Loss of CSF is not the only cause of headache after regional anesthesia in the obstetric patient. In a retrospective review of 95 women who had a headache more than 24 hours after delivery, Stella et al.[191] found that tension/migraine and preeclampsia/eclampsia accounted for over 70% of reported headaches whereas a diagnosis of PDPH was made in 16%. More serious causes of postpartum maternal headache include meningitis and intracranial pathology such as cortical vein thrombosis and subarachnoid hemorrhage.

The incidence and severity of PDPH vary with factors thought to be related to the volume and rate of CSF leakage from the subarachnoid space. The incidence of PDPH is inversely related to age and seen infrequently in those older than 70 and younger than 10 years old. Women appear to be slightly more susceptible than men, and pregnancy may increase the incidence. In general, large-diameter needles are more likely to be associated with PDPH when compared with small-diameter needles. A dural puncture with a 17-gauge epidural needle has a 70% PDPH rate compared with less than 1% with a pencil-point spinal needle. With respect to spinal needles, the incidence of PDPH is significantly reduced with the use of pencil-point needles (e.g., Pencan, Sprotte, Whitacre) compared with beveled cutting needles (e.g., Quincke) (Figure 46-10). In a retrospective study of 366 obstetric patients, the incidence of PDPH after the use of a Sprotte needle was 1.5%, compared with 9% after the use of a beveled Quincke needle of similar gauge.[192]

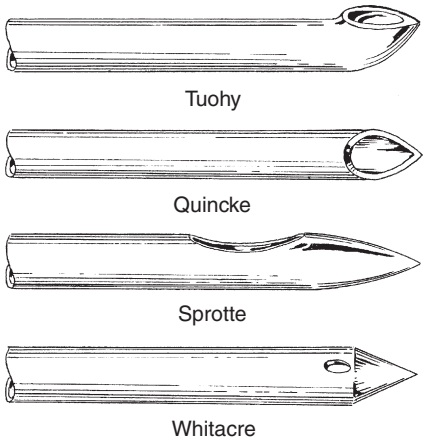

FIGURE **46-10** Physical characteristics of four different types of spinal and epidural needles. Needle diameters are not to scale.

Some evidence indicates that the bevel's orientation as it punctures the dural fibers plays a role. Electron microscopy has confirmed that the collagen fibers composing the dura are oriented primarily longitudinally.[193] Penetrating the dural fibers along their vertical axis may result in less CSF leakage compared with horizontal bevel orientation. The angle at which the needle approaches the dura may also modify the amount of CSF leakage and therefore the incidence of PDPH; however, the angle of approach most often is dictated by anatomy and therefore is difficult for the anesthetist to modify effectively. When inadvertent dural puncture occurs during epidural placement, there is evidence to indicate that placing a subarachnoid catheter reduces the incidence of PDPH.[134] The use of air as opposed to saline in the loss of resistance technique may also be associated with greater PDPH rates. Aida et al.[194] studied 3700 patients who received epidural anesthesia and found that 100 had an inadvertent dural puncture. PDPH occurred in 67% of the patients in the air group as opposed to 10% in the saline group. A head computed tomography (CT) scan was done in all 100 PDPH patients that identified supraspinal intrathecal air bubbles in 78% of those with PDPH.

The hallmark of a PDPH is its postural component. The headache is relieved when supine and returns on sitting or standing. It is commonly fronto-occipital and sometimes is associated with neck and shoulder stiffness. Photophobia may be present in patients with severe headaches, whereas double vision occurs less frequently. Temporary deafness has occurred rarely. The onset of the headache is usually not immediate, but may take 1 to 2 days to become bothersome. It can be mild to severe, and often becomes worse if the patient feels sick and does not consume liquids.

Treatment

Patients should be given a choice of treatments ranging from the most conservative to the most aggressive. PDPH may be a mild irritation for a few days, or it may be debilitating. Conservative treatment is appropriate for mild headaches and includes bed rest, hydration, and oral analgesics. In hospitalized patients who are not taking fluids by mouth, IV hydration is warranted. Liberal hydration does not increase the production of CSF; however, it is important that the patient not be allowed to become dehydrated, because dehydration does decrease CSF production.

Caffeine is a cerebral vasoconstrictor that can be transiently effective in relieving the symptoms of PDPH in some patients.

Serotonin also causes cerebral vasoconstriction. Case reports of serotonin type-1 δ-receptor agonists (sumatriptan) successfully relieving PDPH have also been published.[195]

Severe PDPH that is unresponsive to conservative therapy for 24 hours should be treated with an epidural blood patch. The usual contraindications to an epidural procedure apply as well to this treatment. After resolution of the neural blockade has been confirmed, a blood patch is performed by placing an epidural needle in the epidural space, preferably at the same interspace as the dural puncture or one interspace below. Once the needle is in place, an assistant performs a peripheral venipuncture and draws 20 mL autologous blood using strict aseptic technique. The blood is then slowly injected into the epidural space. The ideal volume for injection appears to be between 15 and 20 mL. If discomfort develops in the back or neck, the injection is temporarily stopped. If the discomfort passes quickly, slow injection of the target volume of 15 to 20 mL may continue (unless discomfort returns). After the desired volume is injected, the Tuohy needle is withdrawn, and the patient should lie quietly for at least 1 hour.[196]

The mechanism of action appears to be two-fold. First, the epidural blood covers the dural defect with a fibrin clot, and second, the injected volume of blood applies pressure to the dura, decreasing the relative total volume of CSF. An epidural blood patch is effective in more than 90% of patients when it is performed 24 hours or more after the dural puncture. A second patch is effective in approximately half of those who do not obtain relief from the first; this brings the total success rate to approximately 95%. Placing further patches does not increase the success rate significantly. A prophylactic blood patch is a technique in which autologous blood is injected through the epidural catheter immediately prior to its removal. However, the patient likely has yet to develop a headache and may then be treated unnecessarily. The absolute sterility and precise location of an indwelling epidural catheter cannot be easily assured. In addition, prophylactic blood patches do not appear to reliably influence the incidence or severity of PDPH.[197]

Seizures Related to Local Anesthetics

Local anesthetic–induced seizures during epidural anesthesia can result from inadvertent direct vascular injection into an epidural vein or accumulation from repeated dosing. The signs and symptoms of local anesthetic toxicity are directly related to their serum concentration and increase in severity as the concentration rises. Early signs of systemic toxicity include circumoral numbness, lightheadedness, and visual and auditory disturbances although both neurologic and cardiovascular signs may occur simultaneously. Unconsciousness, seizures, and cardiovascular depression/collapse follow as plasma concentrations increase further.

Necessary measures to prevent local anesthetic toxicity during epidural anesthesia include aspiration of the catheter for blood prior to injection, use of an appropriate test dose, fractionated dosing, and vigilance for signs of toxicity. The incidence of venous cannulation with an epidural catheter is approximately 6% in the obstetric population. In a recent review of randomized controlled trials, Mhyre et al.[198] identified effective strategies to reduce the incidence of venous cannulation that included insertion in the lateral as opposed to the sitting position, using single-orifice rather than multi-orifice catheters, using wire-embedded polyurethane (soft) rather than nylon (hard) catheters, and limiting the depth of insertion to less than 6 cm.

Clearly, the first step to be taken when any of these signs or symptoms occurs is discontinuation of the injection of local anesthetic. Early recognition of a positive response to a test dose often halts the progression of symptoms. If a seizure occurs, both mother and fetus are at risk of hypoxia. Quick action involves the administration of small doses of a benzodiazepine to end the seizure and support of ventilation and oxygenation. The seizures are not necessarily lethal, but the resultant anoxia and acidosis are. Emergency drugs, a self-inflating breathing bag, masks, laryngoscopes, oral and nasal airways, endotracheal tubes, and stylets should be on all epidural insertion carts. Cardiovascular support is provided symptomatically, when needed. Careful evaluation of the maternal and fetal status should dictate decisions regarding obstetric management. The American Society of Regional Anesthesia and Pain Medicine has recently issued a new practice advisory on local anesthetic systemic toxicity, and it is presented in detail in Chapter 10.[199]

Rescue treatment with 20% lipid emulsion has been shown to be effective in treating local anesthetic–induced cardiotoxicity. The precise mechanism of action remains unknown but may involve the exogenous lipid providing an alternate binding site for the lipid-soluble local anesthetic, often referred to as the lipid sink theory. Although the timing, dose, and duration has yet to be firmly established, its low cost, simplicity of use, and apparent lack of significant side effects leads to the recommendation that 20% lipid emulsion be available wherever regional anesthesia is used. [200]

Total Spinal Block

Total spinal anesthesia is a complication that results from the excessive and unintended cephalic spread of local anesthetic. It can follow the inadvertent injection of a large "epidural" dose of local anesthetic into the subarachnoid space after unrecognized subarachnoid catheter placement or migration of a previously placed epidural catheter into the subarachnoid space. Unintentionally high or total spinal block also can result from a single-shot spinal anesthetic performed after a failed epidural block. It is thought that the large amount of previously placed epidural local anesthetic migrates through the dural hole made by the spinal needle. A total spinal block is normally rapid in onset and preceded by complaints of dyspnea, difficult phonation, and hypotension. In the presence of these symptoms, consideration should be given to alternative diagnoses that include anaphylactic shock, eclampsia, or amniotic fluid embolus.

Accidental Subdural Injection

Occasionally the epidural catheter may be placed inadvertently in the subdural space between the dura and arachnoid membranes. After a negative test dose for intravascular and subarachnoid injection, local anesthetic is administered through the supposed epidural catheter in the normal fashion. After a delay of 10 to 25 minutes, a sudden excessive spread of the block is noted,[187] primarily in the cephalad direction.[201] The magnitude of the spread of the local anesthetic block is significantly greater than would be anticipated if the catheter were in the epidural space and very similar to what would be expected with a subarachnoid injection. Hypotension caused by extensive sympathetic block is usually the primary problem and is treated with ephedrine or other vasopressors as needed. If the block is sufficiently extensive to compromise respiration or airway maintenance, endotracheal intubation is necessary. This complication is uncommon and likely unpreventable. The possibility of respiratory compromise emphasizes the necessity of being prepared to manage such a complication as well as the need for close monitoring after epidural administration.

Cardiopulmonary Resuscitation of the Pregnant Patient

Cardiopulmonary resuscitation (CPR) has been accomplished successfully early in pregnancy, but use of the technique is problematic at best in the near-term parturient. The fetus does not tolerate

decreases in maternal oxygenation and blood pressure well. The mother has a high O_2 demand and a small O_2 reservoir (residual volume). Most importantly, the term or near-term uterus obstructs central venous return in the supine parturient.[202,203] It follows that left uterine displacement is important to the success of CPR in pregnant women. However, lateral tilt has been shown to decrease the force of cardiac compressions and presumably their effectiveness.[204] When the near-term parturient does not respond to resuscitative efforts within 5 minutes, emergent cesarean section is often indicated. This makes possible direct oxygenation of the neonate and has resulted in substantially improved venous return in the mother,[203] ultimately allowing for successful resuscitation.

Neurologic Injuries

Neurologic complications are fortunately rare but may be associated with labor and delivery or neuraxial anesthesia. In a retrospective review of observational studies, Ruppen et al.[204] found the incidence of persistent neurologic injury in obstetric patients who received epidural anesthesia or analgesia to be 1 in 240,000 and the rate of transient (less than 1 year duration) neurologic injury to be 1 in 6700. Obstetric injuries related to childbirth involve pressure and stretching of peripheral nerves by the descending fetus and are identified by the appearance of a single neuropathy. On the other hand, neuraxial anesthesia–related injuries involve a spinal nerve root and, hence, follow a dermatomal distribution. Although neuraxial anesthesia is often cited as the cause of all obstetric nerve injuries, careful identification and evaluation of the defect can indicate otherwise. The American Society of Regional Anesthesia and Pain Medicine has published a practice advisory on neurologic complications that discusses this topic further.[193] Figure 46-11 illustrates the distribution of both peripheral nerve sensory innervation and spinal dermatomes.

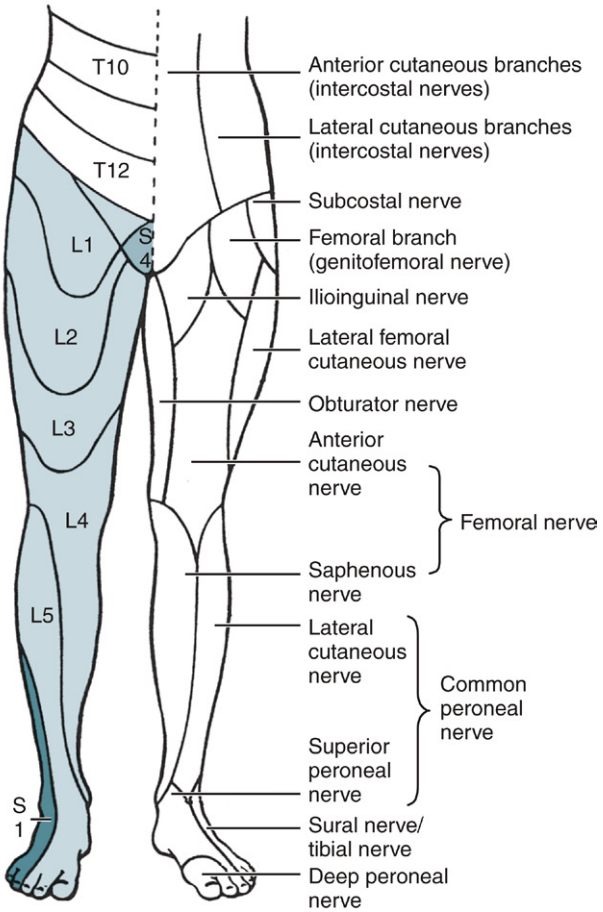

FIGURE **46-11** The dermatomal (right leg) and peripheral (left leg) sensory nerve distributions useful in distinguishing central from peripheral nerve injury. (From Redick LF. Maternal perinatal nerve palsies. *Postgrad Obstet Gynecol.* 1992;12:1-6. In: Chestnut DH, et al, eds. *Chestnut's Obstetric Anesthesia: Principles and Practice*. 4th ed. St. Louis: Mosby; 2009:705.)

OBSTETRIC COMPLICATIONS

Maternal morbidity and mortality continue to remain a problem in the United States. Using the 2003 to 2006 Nationwide Inpatient Sample, approximately 1.3 per 1000 hospitalizations for delivery was complicated by near-miss morbidity or mortality. The majority of these events (58.3%) occurred in 11.8% of the delivering population. Most of the women have important medical comorbidities or obstetric complications identified prior to admission for delivery. The highest rates were noted among women with pulmonary hypertension (98.0 cases per 1000 deliveries), malignancy (23.4 per 1000), and systemic lupus erythematosus (21.1 per 1000).

Common causes of maternal death include hemorrhage, embolism, preeclampsia, infection, and congestive heart failure.[205]

Prematurity

Premature delivery is a leading cause of perinatal morbidity and mortality. Premature delivery is implicated in more than 50% of all perinatal deaths. Premature labor is defined as regular uterine contractions that occur before 37 weeks of gestation or before 259 days from the last menstrual cycle and that result in dilation or effacement of the cervix. Late preterm births, defined as those of 34 to 36 weeks' gestation, compose approximately 70% of all preterm births.

Fetal size is categorized as: low birth weight, referring to births weighing 500 to 2500 g; very low birth weight, referring to births of 500 to 1500 g; and extremely low birth weight, referring to births of 500 to 1000 g. Preterm labor diagnosis is facilitated by measuring fetal fibronectin and maternal cervical ultrasonography.[206]

The ability to stop premature labor can allow the fetus additional time to mature. It is often given for 48 hours to allow for corticosteroid and latency antibiotic administration, which promote fetal maturation and decrease maternal chorioamnionitis. Stopping labor is termed *tocolysis* (from the Greek *tokos*, meaning "childbirth," and *lysis*, meaning "breaking up"). The cause of preterm labor is not well understood; however, four pathways are supported by a considerable body of clinical and experimental evidence: myometrial and fetal membrane overdistention, decidual hemorrhage, precocious fetal endocrine activation, and intrauterine infection or inflammation. The processes leading to preterm parturition may originate from one or more of these pathways. Common risk factors include multifetal pregnancies and preterm rupture of membranes.[207,208]

Methods of Tocolysis

Although more than 80% of women with preterm labor who are treated with tocolytics have their pregnancies maintained for 24 to 48 hours, few data suggest that tocolysis maintains pregnancy for a longer period. A critical goal of tocolysis is to delay delivery long enough to allow for the administration of corticosteroids, which reduces the risks of the neonatal respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, and overall perinatal death. The initial benefit of corticosteroid therapy occurs approximately 18 hours after administration of the first dose with maximal benefit at about 48 hours. Thus treatment

of acute preterm labor may allow time for the onset of the therapeutic effect of corticosteroids. As a general rule, if tocolytics are given, they should be given concomitantly with corticosteroids. The gestational age range for their use is debatable, but because corticosteroids are not generally used after 33 weeks, most practitioners do not recommend use of tocolytics at or after 33 weeks.[207] Some obstetricians are questioning the use of tocolytics. They cite growing evidence that bacterial colonization of fetal membranes and amniotic fluid triggers an inflammatory response in the mother and fetus and this leads to preterm labor and long-term neurologic and respiratory complications in the neonate. This raises questions about the desirability of prolonging pregnancy in this context. Combined with recent meta-analyses that fail to demonstrate improvements in neonatal outcome with tocolytic use, and a poor maternal/fetal side-effect profile, the case for continued use of these drugs needs to be questioned.[208-210]

A variety of agents are used as tocolytics. These include β-adrenergic receptor agonists, nitric oxide donors, magnesium sulfate, calcium channel blockers, prostaglandin synthesis inhibitors, and oxytocin antagonists. Labor-inhibiting drugs are only marginally effective. Tocolytics act by two primary mechanisms: through generation or alteration of intracellular messengers or by inhibiting the synthesis or blocking the action of a known myometrial stimulant.

Magnesium Sulfate. Magnesium sulfate has been used for decades as a tocolytic, but recent evidence questions its efficacy.[210] Magnesium causes relaxation of vascular, bronchial, and uterine smooth muscle by altering calcium transport and availability. Motor end plate sensitivity and muscle membrane excitability also are depressed. Magnesium hyperpolarizes the plasma membrane and inhibits myosin light-chain kinase activity by competing with intracellular calcium, which in turn reduces myometrial contractility.

The normal serum magnesium level during pregnancy is 1.8 to 3 mg/dL. A serum magnesium level of 4 to 8 mg/dL is therapeutic as a tocolytic, but even toxic levels do not eliminate uterine contractility. At 10 to 12 mg/dL, the patellar reflex is eliminated. Levels above 12 mg/dL cause respiratory depression; at approximately 18 mg/dL, respiratory depression progresses to apnea. The presence of higher levels (25 mg/dL) can cause cardiac arrest. Women given magnesium sulfate must be monitored closely for evidence of hypermagnesemia.

The side effects of magnesium sulfate administration are dose dependent. The most frequent serious side effect is pulmonary edema.[207] As magnesium levels increase, skeletal muscle weakness increases and CNS depression and vascular dilation occur. Magnesium sulfate infusion commonly results in a slight decrease in blood pressure during epidural anesthesia. Magnesium antagonizes the vasoconstrictive effect of α-agonists, so ephedrine and phenylephrine are likely to less effectively increase maternal blood pressure when administered concomitantly with magnesium. Cardiac muscle is not affected to a clinically evident degree when magnesium is administered at therapeutic levels, although magnesium can have profound myocardial effects during a gross overdose. Magnesium is eliminated unchanged by the kidneys.

Patients on magnesium sulfate therapy have partial, if subclinical, neuromuscular blockade. Both depolarizing and nondepolarizing neuromuscular blocking drugs are potentiated by magnesium.[211] Administration of priming or defasciculating doses of neuromuscular blocking drugs may cause significant paralysis when combined with magnesium therapy. The neuromuscular-blocking effects of magnesium can be at least partially antagonized by calcium.

Magnesium sulfate overdose is treatable. In an excellent case report, a 23-year-old gravida received a 20-g bolus of magnesium sulfate superimposed on a therapeutic magnesium (Mg^{2+}) level. She attained a magnesium level of 38.7 mg/dL. She had a respiratory arrest, became hypotensive and bradycardic, and developed a prolonged QRS complex. Resuscitation was successfully accomplished with discontinuation of the magnesium administration, endotracheal intubation and ventilation, IV administration of calcium chloride, and diuresis to facilitate the elimination of magnesium. Vital signs improved dramatically with ventilation and calcium administration, and the woman was extubated 8 hours later after her magnesium level had declined to a therapeutic level.[212]

Neonatal side effects after maternal magnesium administration are rare. A few cases of hypotonia and respiratory depression in neonates after prolonged high-dose maternal magnesium administration have been reported; however, in general, magnesium administration is safe for the neonate. Magnesium is also used in the treatment of preeclampsia, a vasospastic disease of pregnancy that can result in severe hypertension, coagulopathy, and seizure. Magnesium sulfate causes relaxation of vascular smooth muscle, a decrease in SVR, and a decrease in blood pressure. At serum levels of 7 to 9.5 mg/dL, it is an anticonvulsant. It also decreases fibrin deposition, improving circulation to visceral organs that are vulnerable to vasospasm and failure.

β-Agonists. Stimulation of the β_2-receptor system causes smooth muscle relaxation, including relaxation of the uterus. The myometrium has β_2-receptors in cell membranes. Stimulation of these receptors triggers a cascade of biochemical effects, resulting in inhibition of myometrial contractility at the cellular level. β_2 stimulation also causes an increase in progesterone production. Progesterone in turn causes histologic changes in myometrial cells that limit the spread of contractile impulses. The β-adrenergic receptor agonists cause myometrial relaxation by binding to β_2-adrenergic receptors and subsequently increasing the levels of intracellular cyclic adenosine monophosphate (AMP), which activates protein kinase, inactivating myosin light-chain kinase, thus diminishing myometrial contractility.

β_2 stimulation increases blood glucose and insulin levels. When a β-agonist infusion is started, the blood glucose level increases within a few hours and returns to baseline within 72 hours without treatment. Potassium is redistributed from the extracellular to intracellular compartments. This results in a decrease in serum potassium level, sometimes to less than 3 mEq/L. As with glucose levels, serum potassium levels return to normal within 72 hours after initiation of β-agonist therapy.

Clinically used β-agonists cross the placenta and have fetal and neonatal effects. Fetal tachycardia (FHR greater than 160 bpm) is common. Neonatal hypoglycemia may result, especially if maternal serum glucose is elevated at delivery. When maternal and therefore fetal blood glucose levels are elevated, the fetus increases insulin release in response. After delivery the neonate continues to release insulin at an increased rate, even though it is no longer receiving a glucose load from the mother, which can result in a rebound hypoglycemia.

Terbutaline (Brethine, Bricanyl, others) is a synthetic, relatively β_2 receptor–selective, noncatecholamine sympathomimetic amine. Due to the high incidence of tachycardia and other significant side effects and its lack of efficacy, terbutaline use is currently discouraged.[207,209]

Nitric Oxide Donors. Nitric oxide is a vasodilator that is essential for the maintenance of normal smooth-muscle tone and is produced in a variety of cells. Nitric oxide increases cyclic guanosine

monophosphate (cGMP) content in smooth-muscle cells that inactivates myosin light-chain kinases, leading to smooth-muscle relaxation. In a comparison of nitroglycerin (a nitric oxide donor) and magnesium sulfate, the latter was more likely to delay delivery for at least 12 hours. However, transdermal nitroglycerin was superior to placebo in prolonging pregnancy. Maternal hypotension is common, and nitroglycerin is rarely used.[207,209]

Calcium Channel Blockers. Nifedipine is the most commonly used calcium channel blocker agent because it can be administered orally. Calcium channel blockers inhibit the influx of calcium ions through the cell membrane and the release of intracellular calcium from the sarcoplasmic reticulum. This decreases intracellular free calcium, leading to inhibition of calcium-dependent myosin light-chain kinase–mediated phosphorylation, which results in myometrial relaxation. The combination of nifedipine with magnesium for tocolysis is potentially dangerous due to neuromuscular blocking effects that can interfere with pulmonary and cardiac function.[207]

Cyclooxygenase Inhibitors. Cyclooxygenase converts arachidonic acid to prostaglandin H_2. Prostaglandin H_2 serves as a substrate for tissue-specific enzymes, which are critical to parturition. Prostaglandins enhance the formation of myometrial gap junctions and increase available intracellular calcium by raising transmembrane influx and sarcolemmal release of calcium. Indomethacin is the most commonly used tocolytic agent in this class.[207]

Oxytocin Receptor Antagonists. Atosiban is an oxytocin receptor antagonist that blocks the normal effects of oxytocin in the uterus. Normally, oxytocin stimulates contractions by inducing the conversion of phosphatidyl inositol triphosphate to inositol triphosphate, which binds to a protein in the sarcoplasmic reticulum and causes the release of calcium into the cytoplasm. Reports of fetal deaths with the administration of atosiban before 28 weeks of gestation have limited the use of this agent. The FDA has not approved atosiban for use in the United States as a tocolytic.[207]

Anesthetic Considerations

When an anesthetic intervention is planned for a patient who is receiving a tocolytic agent, knowledge of maternal and fetal physiology and of the pharmacology of the tocolytic agent must be integrated.

Regional Anesthesia

When tocolysis fails, preterm deliveries are often accomplished by cesarean section. In this situation, 1- and 5-minute Apgar scores have been shown to be higher in neonates delivered with epidural anesthesia than in those delivered with general anesthesia.[213] Patients on magnesium therapy are often candidates for subarachnoid or epidural blocks as long as careful attention is devoted to volume status. Magnesium causes vasodilation, and maternal hemorrhage is tolerated poorly by parturients on magnesium.[214-215]

General Anesthesia

Succinylcholine is the muscle relaxant of choice during the rapid-sequence induction of an obstetric patient. In patients on magnesium therapy, defasciculation with a small dose of a nondepolarizing neuromuscular blocking agent is not recommended because significant paralysis may result, increasing the risk of aspiration of gastric contents. Magnesium potentiates depolarizing and, especially, nondepolarizing relaxants.[211]

Embolism

Thromboembolism

Thrombotic pulmonary embolism occurs in pregnant individuals five times more often than in nonpregnant individuals and is more likely to occur postpartum than antepartum. It is associated with prolonged inactivity, cesarean delivery, obesity, and increasing age and parity. The patient with pulmonary embolism may have a few minor complaints or a massive cardiovascular collapse. Pleuritic chest pain, dyspnea, hyperventilation, hypocapnia, coughing, hemoptysis, and distention of neck veins are associated with the disorder.

Venous Air Embolism

Venous air embolism can occur during labor, spontaneous vaginal delivery, and operative delivery and is frequently associated with placenta previa. During cesarean section most venous air emboli are detected between the time of delivery and uterine repair.[216,217] Air is entrained into open maternal venous sinuses in the uterine wall when the placenta separates or at the site of a surgical incision. As air accumulates in the pulmonary bed, the resultant increase in pulmonary vascular resistance causes an increase in central venous pressure. A heavy, nonradiating, retrosternal chest pain may persist for 10 minutes after even a small venous air embolism, and dyspnea is common. End-tidal CO_2 drops, because CO_2 cannot return to the lungs. A mill-wheel murmur may be heard over the precordium as a frothy air-blood mixture moves through the heart. This murmur is most pronounced when a large volume of air becomes trapped in the right ventricle. If a sufficient number of pulmonary arteries are affected, cardiovascular collapse can occur.

Amniotic Fluid Embolism

Amniotic fluid embolism is rare and may occur during labor, vaginal, or operative delivery and is occasionally associated with placental abruption. The pathogenesis is almost identical to that of venous air embolism except that patients who develop amniotic fluid embolism are prone to develop disseminated intravascular coagulation (DIC) if they survive the initial insult. Signs and symptoms of amniotic fluid embolism include chills, anxiety, cough, dyspnea, cyanosis, tachypnea, pulmonary edema, and cardiovascular collapse. O_2 saturation has been reported to decrease quickly.[216]

Anesthetic Implications

The incidence of postpartum thromboembolism can be affected by anesthetic interventions. Cesarean sections performed with general anesthesia are associated with accelerated maternal coagulation compared with those performed with regional anesthesia. The anesthetist can help prevent prolonged inactivity in those who have had a cesarean section by providing analgesia sufficient to allow comfortable ambulation. Use of epidural opioid analgesia is often an appropriate solution to this problem.

Because air embolism occurs when open veins are above the level of the heart, raising the head of the bed in order to position the uterus below the heart would seem to be useful for preventing embolization. However, a head-up tilt of between 5 and 10 degrees does not appear to decrease the incidence of venous air embolism during cesarean section and has increased the incidence of hypotension.[218] If embolism is suspected during spontaneous or operative delivery, the obstetrician should be informed immediately. The obstetrician can take steps to stop the entrainment of air or amniotic fluid, which include flooding the surgical field with saline, returning the uterus to within the abdomen, and stimulating uterine contractions.

One hundred percent O_2 should be administered and nitrous oxide, if in use, should be discontinued because it rapidly expands the volume of an air embolus and prevents the delivery of

100% O_2. An arterial line may be needed for monitoring of oxygenation and blood pressure. If the fetus has not been delivered, left uterine displacement improves uterine blood flow and facilitates hemodynamic stability. Pharmacologic support of the cardiovascular system is likely to be needed.

Patient position has been suggested to hinder the movement of the foreign substance into the pulmonary arteries. A slight reverse Trendelenburg (head-up) position with left lateral tilt of at least 15 degrees is designed to trap air in the right atrium, from which it can be aspirated via a central venous catheter.

In the case of amniotic fluid embolism, prompt recognition and action is necessary to prevent maternal mortality. Immediate support of maternal respiration and circulation is required. Treatment for coagulopathy must also begin immediately and ideally with the consultation of a hematologist.

Placenta Previa

Placenta previa is present when the placenta has implanted on the lower uterine segment and either partially or completely covers the opening of the cervix. Placenta previa has an incidence of up to 1%, and the mortality rate for those with it approaches 1%. Placenta previa is more common in women who have had it during a prior pregnancy. It most often results in painless vaginal bleeding before the onset of labor that may stop without intervention or hemodynamically significant blood loss. The potential exists, however, for *sudden* loss of large amounts of blood. The risk of bleeding increases if the placenta is disturbed by manual examination of the cervix. Postpartum bleeding is often increased as well because the lower uterine segment, where the placenta previa was implanted, does not contract as well as the remainder of the uterus. Three variations of placenta previa are shown in Figure 46-12.

Anesthetic Implications

The diagnosis of placenta previa normally indicates an operative delivery. The anesthetist should prepare for increased blood loss and may choose either a general or regional anesthetic technique. Consideration should be given to the parturient's existing volume status and potential for blood loss.

Abnormal Placental Implantation

The placenta normally implants into the endometrium. A placenta implanted on or in the myometrium, the underlying muscular layer of the uterus, is termed *placenta accreta* (on the myometrium), *placenta increta* (into the myometrium), or *placenta percreta* (completely through the myometrium). Abnormal placental implantation likely precludes complete separation of the placenta from the uterine wall resulting in hemorrhage at delivery.

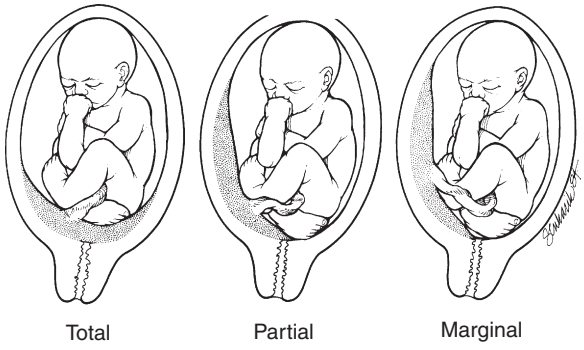

FIGURE **46-12** Three variations of placenta previa. (From Gabbe SG, et al. *Obstetrics: Normal and Problem Pregnancies*. 6th ed. Philadelphia: Saunders; 2012:422.)

Placenta accreta, placenta increta, and placenta percreta (Figure 46-13) are associated with placenta previa and are more common in women who have had a previous cesarean section.

Placental Abruption

Abruption occurs when the placenta begins to separate from the uterus before delivery; this allows bleeding behind the placenta and jeopardizes fetal blood supply. Placental abruption results in hemorrhage, uterine irritability, abdominal pain, and fetal hypoperfusion. Open venous sinuses in the uterine wall may allow amniotic fluid to enter the maternal circulation, resulting in an increased incidence of DIC. The reported incidence of abruption in the general population varies widely but is much higher in women with hypertension (up to 23% among women with preeclampsia).

Anesthetic Implications

In cases of placental abruption without fetal distress, vaginal delivery may still be possible. Because fetal distress can occur without warning, the anesthetist should be prepared to administer anesthesia for an emergency cesarean section. Performing a preanesthetic evaluation as soon as the diagnosis of placental abruption becomes known and confirming adequate IV access is recommended. If the mother is unstable or if fetal distress is present, operative delivery is necessary. Although placental abruption does not usually result in sudden blood loss, a large volume of trapped blood may become apparent at delivery.

Postpartum Hemorrhage

Approximately 4% of all parturients who deliver vaginally experience postpartum hemorrhage (PPH), and the incidence appears to be increasing over time.[218] Often, blood loss is hidden inside the women's body, soaked in laparotomy sponges, absorbed by drapes, or spilled onto the floor. Efforts should be made to objectively quantify blood loss at delivery because clinicians typically underestimate true blood loss.[219] Aggressive treatment has the potential to prevent the development of serious PPH.[220]

PPH may occur because of uterine atony (accounting for 80% of all postpartum bleeding), placental retention, abnormalities of the uterus, lacerations of the cervix or vaginal wall, uterine inversion, and abnormalities of coagulation. Uterine atony is associated with multiparity, prolonged infusions of oxytocin before delivery, polyhydramnios, and multiple gestation. A retained placenta or retained placental fragments must be removed manually. Nitroglycerin, a potent uterine relaxant with a relatively short duration

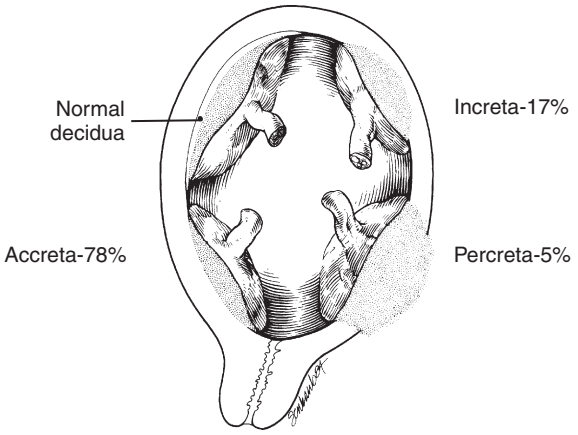

FIGURE **46-13** An example of placenta increta, percreta, and accreta. (From Gabbe SG, et al. *Obstetrics: Normal and Problem Pregnancies*. 6th ed. Philadelphia: Saunders; 2012:424.)

of action, can be used to provide uterine relaxation adequate for placental extraction. Sublingual nitroglycerin spray has been used effectively and offers the added benefits of long shelf life and a ready-to-use preparation.[221] Because nitroglycerin is a potent smooth muscle relaxant and vasodilator, care should be taken to ensure that intravascular volume is adequate before administration.

When hemostasis is not achieved despite the use of vigorous fundal massage and pharmacologic adjuncts such as oxytocin, ergot alkaloids, and prostaglandin, the obstetric staff may elect to attempt the use of an intrauterine balloon. The device is specifically designed for this purpose and is placed in the uterine cavity and normally filled with saline in order to exert a tamponade effect. Balloon tamponade is a minimally invasive and rapidly applied approach that can be used as a temporizing measure while other resources are being mobilized.[222]

Institution-specific massive transfusion protocols and policies can be invaluable in coordinating communication between anesthesia, blood bank, and intensive care staff. Regardless of the approach, planning for the management of PPH is an integral part of an obstetric anesthesia practice.

An atonic uterus, especially an incised uterus, can lose several liters of blood within a few minutes, outpacing the ability of even the most prepared anesthesia providers to replace intravascular volume. Anesthesia at this point becomes trauma anesthesia, the primary purpose of which is the maintenance of vital organ perfusion and oxygenation. Maternal analgesia and amnesia are important but, nonetheless, secondary concerns. Etomidate, ketamine, benzodiazepines, and opioids are useful insofar as they result in minimal hemodynamic depression. If rapid blood loss begins during cesarean section with regional anesthesia, the anesthetist should consider the rapid-sequence induction of general anesthesia. It is difficult to manage volume resuscitation and keep an awake patient both mentally and physically comfortable.

Anesthetic Implications

Anesthesia for uterine exploration can be accomplished with a variety of methods including the use of an already established epidural catheter, a single-shot spinal "saddle block," or a general anesthetic. The choice of technique is ultimately driven by the patient's condition and the urgency of the proposed procedure. The continuous epidural infusion is routinely discontinued at completion of delivery and repair; however, the epidural catheter should always be left in place until the maternal condition has stabilized. In this manner, if a postpartum surgical intervention becomes necessary, reestablishing epidural anesthesia is an option.

Uterine Rupture and Dehiscence

Uterine rupture (complete) is the nonsurgical disruption of all uterine layers. It involves the entire thickness of the uterine wall and the fetal membranes resulting in communication between the uterine and peritoneal cavities. Uterine dehiscence (incomplete) does not include the entire thickness and the maternal peritoneum remains intact. These conditions are most commonly associated with labor in the presence of a previous uterine incision (*t*rial *o*f *l*abor *a*fter *c*esarean or TOLAC) but may occur in an unscarred uterus.[223] The classic description of complete uterine rupture includes sudden, severe, tearing abdominal pain in a multiparous woman in active labor. The pain may suddenly break through a previously adequate labor epidural. Fetal distress often rapidly develops. Unfortunately, uterine rupture does not always present classically. For example, some ruptures occur during periods of mild labor.[224] The clinical finding most commonly associated with uterine rupture is an abnormal FHR tracing.[225] Regardless of presentation, bleeding is often severe. The uterus receives approximately 800 mL of blood per minute (approximately 10% of the cardiac output); therefore, a tear in this organ holds the potential for rapid exsanguination. Mortality from uterine rupture accounts for half of the maternal deaths attributed to blood loss each year. Fetal mortality after uterine rupture is nearly 80%.

Anesthetic Implications

TOLAC is most often successful in those who have had a prior low-transverse uterine incision and in those who have also had a previous vaginal delivery. Labor dystocia, maternal obesity, and the need for induction reduce the likelihood of successful vaginal birth after cesarean section (VBAC). The American College of Obstetricians and Gynecologists has stated that anesthesia providers and physicians must be *immediately available* to provide emergency care during TOLAC.[226] Neuraxial analgesia is not only appropriate during TOLAC but may enhance safety by affording the ability to rapidly provide surgical anesthesia if necessary.

Disseminated Intravascular Coagulation

DIC is a generalized activation of the clotting system. It can occur when a large portion of the vascular system suffers damage or when thromboplastic material enters the general circulation. DIC is frequently associated with three obstetric problems: intrauterine fetal demise, placental abruption, and amniotic fluid embolism. Circulatory shock, which often accompanies DIC, worsens the problem by decreasing peripheral and hepatic blood flow and causing further cell damage. Renal failure may result from the deposit of fibrin and cellular debris in the microvasculature. The consumption of clotting factors results in uncontrolled bleeding. Laboratory studies show decreased levels of fibrinogen and platelets, increased prothrombin and partial thromboplastin times, and excessive amounts of fibrin degradation products.

Anesthetic Implications

Definitive treatment of DIC requires elimination of the cause, which, in the obstetric patient, often requires evacuating the uterus. When a surgical intervention is required, a general anesthetic is often indicated due to the coagulation disorder. Replacing the specifically depleted clotting factors and intensive support of the accompanying multiple organ system involvement is required. There remains no universally accepted treatment for DIC. Platelets, cryoprecipitate, and fresh frozen plasma should be administered to support the platelet count and fibrinogen level. The patient with DIC will require fluid resuscitation as a result of hemorrhage. Increased peripheral and hepatic perfusion limits cellular damage and improves clearance of activated clotting factors.

Breech Presentation

Many obstetricians now choose to deliver breech presentations by cesarean section. In this case, cesarean section usually is elective, and either a regional or a general anesthetic can be used. If the baby is to be delivered vaginally, a neuraxial technique may be requested and, in fact, is strongly indicated at some centers. The pelvic muscle relaxation that is provided may aid in the delivery of the fetal head.

Multiple Gestation

Multiple-gestation pregnancies carry greater risks for both mother and fetuses compared with singleton pregnancies. Many of the risk factors affect anesthetic management. Multiple-gestation pregnancies, especially rare monoamniotic pregnancies, are associated with complications requiring emergent surgical intervention more

often than singleton pregnancies. The multiple fetuses are often small and premature. The large uterus compounds the problems of aortocaval compression; therefore, left uterine displacement should be maintained at all times when the parturient is not lying on her side. If the fetuses are to be delivered vaginally, an epidural is valuable for maternal analgesia and neonatal safety. Because the neonate often is small and premature, a slow, controlled delivery through a well-relaxed birth canal makes birth trauma less likely. The epidural provides pelvic relaxation and reduces maternal discomfort, decreasing the likelihood that pain will induce a forceful reflexive expulsion of the fetus. Either regional or general anesthesia is appropriate for a cesarean section.

Prolapsed Umbilical Cord

A prolapsed cord is present when the cord protrudes through the cervix ahead of the presenting part. The cord may then be compressed against the cervix resulting in impaired flow. Maneuvers to restore blood flow include manual pressure against the presenting part to restore flow. Uterine relaxation or emergency cesarean section may be required. The choice of anesthetic technique is directed by the urgency of the fetal condition.

Preeclampsia

Description

Preeclampsia is a pregnancy-specific multisystem disorder of unknown etiology. The disorder affects approximately 5% to 7% of pregnancies and is a significant cause of maternal and fetal morbidity and mortality. The incidence of preeclampsia is highest in primigravidas younger than 20 years or older than 35 years of age and in women who have had preeclampsia during a previous pregnancy. An imbalance of prostacyclins and thromboxanes, both of which are produced by the placenta, has been demonstrated in preeclampsia.[227]

Preeclampsia is defined as new-onset hypertension and proteinuria after 20 weeks' gestation and is described as mild or severe. Mild preeclampsia exists when the blood pressure (BP) is higher than 140/90 and proteinuria is at least 300 mg/24 hr. Severe preeclampsia is defined as a BP higher than 160/110 and proteinuria is greater than 5 g/24 hr. It is considered severe if blood pressure and proteinuria are increased substantially or symptoms of end-organ damage (including fetal growth restriction) occur. Additional symptoms of severe preeclampsia may include: oliguria (less than 500 mL of urine in 24 hours), cerebral or visual disturbances, pulmonary edema or cyanosis, epigastric or right upper quadrant pain, impaired liver function, thrombocytopenia, and intrauterine growth restriction. Management before the onset of labor includes close monitoring of maternal and fetal status. Management during delivery includes seizure prophylaxis with magnesium sulfate and, if necessary, medical management of hypertension. Delivery remains the ultimate treatment.[228]

Preeclampsia results in increased maternal, fetal, and neonatal morbidity and mortality. The chief cause of maternal mortality is cerebral hemorrhage caused by hypertension. Pulmonary edema, renal failure, hepatic rupture, cerebral edema, and DIC are also associated with preeclampsia. Eclampsia is the onset of seizures in a patient with signs and symptoms of preeclampsia.

Pathophysiology

The precise pathogenesis of preeclampsia is complex and not well understood but likely involves a failure in normal placental angiogenesis resulting in decreased placental perfusion and placental infarcts. Placental ischemia worsens as pregnancy progresses, often causing intrauterine growth restriction. The hypoperfused placenta releases factors into the maternal circulation that damage the maternal endothelium, resulting in system-wide manifestations.

The upper airway edema normally associated with pregnancy can be more pronounced in the preeclamptic patient. The decreased colloid osmotic pressure associated with urinary protein loss combined with increased vascular permeability predisposes the parturient to pulmonary edema and respiratory distress syndrome. Central nervous system effects include headache, hyperexcitability, and hyperreflexia. Thrombocytopenia occurs in up to 20% of women and is related to the severity of the disease process. Increased vascular tone results from hypersensitivity to endogenous catecholamines. Systemic vascular resistance is increased, ultimately resulting in end organ ischemia. Plasma volume is normal in mild disease but may be reduced by up to 40% in severe disease.[229] Hepatocellular necrosis results in hepatic enlargement, which ultimately can lead to hepatic capsule rupture. The hallmark diagnostic sign of proteinuria occurs as a result of glomerular capillary endothelial destruction.

Obstetric Management

Delivery is at present the only definitive way of ending the disease process of preeclampsia. When a fetus is at a gestational age of more than 37 weeks, obstetricians generally proceed with delivery. In the presence of mild preeclampsia prior to 37 weeks' gestation, delivery is delayed while the maternal condition is carefully monitored. If preeclampsia is severe or fetal distress occurs, delivery is usually accomplished expeditiously. Corticosteroids are often administered to enhance fetal lung maturity. In any case, obstetric treatment is aimed at preventing eclampsia (seizures), avoiding decreases in uteroplacental blood flow, and maximizing organ perfusion. Magnesium sulfate is routinely used to prevent seizures in severe preeclampsia both before and after delivery. Magnesium sulfate (which is also used as a tocolytic) causes venodilation, mild CNS depression, a decrease in the rate of hepatic fibrin deposition, and a reduction in uterine activity. Decreasing fibrin deposition prevents further decay in organ perfusion and often greatly decreases liver pain. Hypertension can be treated to prevent maternal complications such as intracranial hemorrhage and hypertensive myocardial ischemia. There is no evidence to indicate that treating the hypertension changes the underlying maternal disease process.

Regional Anesthesia and Preeclampsia

Regional analgesia and anesthesia are generally preferred for both spontaneous vaginal delivery and cesarean section in the preeclampsia patient when they are not contraindicated. A carefully initiated epidural infusion helps control maternal hypertension and may improve organ blood flow. During a cesarean section, regional anesthesia avoids stimulation of the airway, which can aggravate hypertension and possibly cause cerebral bleeding. During a premature vaginal delivery, epidural analgesia allows a slower, more controlled delivery of the infant and decreases the likelihood of trauma to the fetal head.

Because thrombocytopenia and other coagulation problems are associated with severe preeclampsia, careful consideration should be given to the patient's coagulation status before regional anesthesia is initiated. A careful bleeding history should be taken and all prior platelet counts evaluated before insertion of a neuraxial anesthetic in a patient with a diagnosis of preeclampsia. A bleeding time is no longer considered an adequate method of assessing the risk of bleeding.[230] There has, however, been considerable discussion regarding what constitutes an adequate platelet

count. Regional anesthesia is generally not contraindicated in mildly preeclamptic parturients with platelet counts greater than 100,000/mm^3. In parturients with a platelet count between 80,000/mm^3 and 100,000/mm^3, further laboratory studies to include prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen level, and international normalized ratio (INR) are indicated. The provision of a neuraxial anesthetic to a patient with a platelet count below 80,000/mm^3 should take into careful consideration the risks involved.[231]

General Anesthesia and Preeclampsia

Coagulopathy, or a serious deterioration in the maternal or fetal condition, is the most common indication for general anesthesia in the patient with preeclampsia. Laryngoscopy results in an exaggerated hypertensive response, and the concomitant upper airway edema may make intubation more difficult. Difficulty in intubation increases the duration of airway stimulation and potentially worsens hypertension. The challenge during induction of general anesthesia is prevention of a further increase in blood pressure, which may result in intracranial hemorrhage.

Labetalol is generally considered to be the first-line drug in treating the hypertension during anesthesia. Treatment of systolic blood pressures above 160 mmHg should be a guide in order to avoid intracranial bleeding.[232] Esmolol also has been safely used at induction without significant neonatal effects.[233] Opioids administered prior to delivery are normally avoided because they can result in undesirable neonatal and maternal respiratory depression. Maternal respiratory depression can become a significant issue in the event of a failed intubation. Remifentanil has been shown to blunt the hypertensive response to laryngoscopy in healthy pregnant patients but resulted in significant fetal respiratory depression.[234] Control of blood pressure during induction of general anesthesia demands both careful planning and skill.

Nondepolarizing muscle relaxants are markedly potentiated in women with preeclampsia who have therapeutic levels of magnesium. Magnesium sulfate reduces the onset time of rocuronium and prolongs the total recovery time by about 25%.[235] If a nondepolarizing muscle relaxant must be used, small doses should be used and the response should be carefully monitored with a peripheral nerve stimulator.

HELLP *Syndrome*

HELLP syndrome consists of *h*emolysis, *e*levated *l*iver enzymes, and a *l*ow *p*latelet count. From 5% to 10% of women with preeclampsia develop HELLP syndrome. Clinical signs of HELLP syndrome include epigastric pain, upper abdominal tenderness, proteinuria, hypertension, jaundice, nausea, and vomiting. Rarely, HELLP syndrome may result in liver rupture. Some experts believe that a degree of compensated DIC is present in all patients with HELLP syndrome.

ANESTHESIA FOR THE PREGNANT PATIENT UNDERGOING A NONOBSTETRIC PROCEDURE

Occasionally anesthetists must provide anesthesia care for a pregnant woman having nonobstetric emergency procedures. Some key points are noted in Box 46-6.

BOX 46-6

Key Points for the Pregnant Patient Undergoing Nonobstetric Procedure

- A significant number of women undergo anesthesia and surgery during pregnancy for procedures unrelated to delivery.
- Maternal risks are associated with the anatomic and physiologic changes of pregnancy (e.g., difficult intubation, aspiration) and with the underlying maternal disease.
- The diagnosis of abdominal conditions often is delayed during pregnancy, which increases the risk of maternal and fetal morbidity.
- Maternal catastrophes involving severe hypoxia, hypotension, and acidosis pose the greatest acute risk to the fetus.
- Other fetal risks associated with surgery include increased fetal loss, increased incidence of preterm labor, growth restriction, and low birth weight. Clinical studies suggest that anesthesia and surgery during pregnancy do not increase the risk of congenital anomalies.
- It is unclear whether adverse fetal outcomes result from the anesthetic, the operation, or the underlying maternal disease.
- No anesthetic agent is a proven teratogen in humans, although some anesthetic agents, specifically nitrous oxide, are teratogenic in animals under certain conditions.
- Many anesthetic agents have been used for anesthesia during pregnancy, with no demonstrable differences in maternal or fetal outcome.
- The anesthesia management of the pregnant surgical patient should focus on the avoidance of hypoxemia, hypotension, acidosis, and hyperventilation.
- When performing a maternal laparoscopy, use an open technique to enter the abdomen when possible.
- Monitor maternal end-tidal P_{CO_2} with or without arterial blood gas to avoid fetal hypercarbia and acidosis.
- Maintain low pneumoperitoneum pressures or use a gasless technique.
- Limit the extent of Trendelenburg or reverse Trendelenburg positions and initiate any position slowly.
- Monitor fetal heart rate and uterine tone when feasible.

Adapted from Van de Velde M. Nonobstetric surgery during pregnancy. In: Chestnut DH, et al, eds. *Chestnut's Obstetric Anesthesia: Principles and Practice*. 4th ed. St. Louis: Mosby; 2009:337; Reitman E, Flood P. Anaesthetic considerations for non-obstetric surgery during pregnancy. *Br J Anaesth*. 2011;107(suppl 1):i72- i78.

NEONATAL RESUSCITATION

All labor and delivery personnel should be trained in basic neonatal resuscitation, including anesthetists. The necessary drugs and equipment must be readily available for all deliveries (Box 46-7). The anesthetist in clinical practice may participate in neonatal resuscitation, but a single anesthetist is responsible for attending to the care of the mother.

Approximately 15% of newborns require resuscitation, but this can generally be predicted from the known risk factors (Box 46-8). Tactile stimulation of the newborn will often result in spontaneous respiration. If spontaneous respiration is delayed after stimulation, initiation of assisted ventilation should begin.

The Apgar scoring system is widely used to assess newborns. The score is derived from five parameters including heart rate, respiratory rate, muscle tone, reflex irritability, and color. The assessment is performed at 1 minute and again at 5 minutes. The score is used to guide resuscitation. A score of 8 to 10 is considered normal, 4 to 7 indicates moderate distress or impairment, and 0 to 3 indicates the need for immediate resuscitation.

If the parturient has received prenatal care, there may be previous knowledge or suspicions of a congenital anomaly that may be used to guide resuscitation. In the event of little or no prenatal care, this information may be unavailable.

BOX **46-7**

Equipment and Drugs Needed for Neonatal Resuscitation

Suction Equipment
- Bulb syringe
- Mechanical suction and tubing
- Suction catheters, 5F or 6F, 8F, and 10F or 12F
- 8F feeding tube and 20-mL syringe
- Meconium aspiration device

Bag-and-Mask Equipment
- Neonatal resuscitation bag with a pressure-release valve or pressure manometer (the bag must be capable of delivering 90% to 100% oxygen)
- Facemasks, newborn and preterm sizes (masks with cushioned rim preferred)
- Oxygen with flowmeter (flow rate up to 10 L/min) and tubing (including portable oxygen cylinders)

Intubation Equipment
- Laryngoscope with straight blades, No. 0 (preterm) and No. 1 (term)
- Extra bulbs and batteries for laryngoscope
- Tracheal tubes, 2.5, 3.0, 3.5, and 4.0 mm ID
- Stylet (optional)
- Scissors
- Tape or securing device for tracheal tube
- Alcohol sponges
- CO_2 detector (optional)
- Laryngeal mask airway (optional)

Medications
- Epinephrine 1:10,000 (0.1 mg/mL): 3- or 10-mL ampoules
- Isotonic crystalloid (normal saline or Ringer's lactate) for volume expansion: 100 or 250 mL
- Sodium bicarbonate 4.2% (5 mEq/10 mL): 10-mL ampoules
- Naloxone hydrochloride 0.4 mg/mL: 1-mL ampoules (or 1 mg/mL: 2-mL ampoules)
- Normal saline, 30 mL
- Dextrose 10%, 250 mL
- Normal saline "fish" or "bullet" (optional)
- Feeding tube, 5F (optional)
- Umbilical vessel catheterization supplies
  - Sterile gloves
  - Scalpel or scissors
  - Povidone-iodine solution
  - Umbilical tape
  - Umbilical catheters, 3.5F, 5F
  - Three-way stopcock
- Syringes, 1-, 3-, 5-, 10-, 20-, and 50-mL
- Needles, 25-, 21-, and 18-gauge, or puncture device for needleless system

Miscellaneous
- Gloves and appropriate personal protection
- Radiant warmer or other heat source
- Firm, padded resuscitation surface
- Clock (timer optional)
- Warmed linens
- Stethoscope
- Tape, ½- or ¾-inch
- Cardiac monitor and electrodes and/or pulse oximeter with probe (optional for delivery room)
- Oropharyngeal airways

From Aucott SW, Zuckerman RL. Neonatal assessment and resuscitation. In: Chestnut DH, et al, eds. *Chestnut's Obstetric Anesthesia: Principles and Practice*. 4th ed. St. Louis: Mosby; 2009:155.

BOX **46-8**

Risk Factors Suggesting an Increased Need for Neonatal Resuscitation

Antepartum Risk Factors
- Maternal diabetes
- Pregnancy-induced hypertension
- Chronic hypertension
- Chronic maternal illness (e.g., cardiovascular, thyroid, neurologic, pulmonary, renal)
- Anemia or isoimmunization
- Previous fetal or neonatal death
- Bleeding in second or third trimester
- Maternal infection
- Polyhydramnios
- Oligohydramnios
- Premature rupture of membranes
- Post-term gestation
- Multiple gestation
- Fetal size-date discrepancy
- Drug therapy (e.g., lithium carbonate, magnesium, adrenergic-blocking drugs)
- Maternal substance abuse
- Fetal malformation
- Diminished fetal activity
- No prenatal care
- Age younger than 16 or older than 35 years

Intrapartum Risk Factors
- Emergency cesarean section
- Forceps or vacuum-assisted delivery
- Breech or other abnormal presentation
- Premature labor
- Precipitous labor
- Chorioamnionitis
- Prolonged rupture of membranes (more than 18 hours before delivery)
- Prolonged labor (more than 24 hours)
- Prolonged second-stage labor (more than 2 hours)
- Fetal bradycardia
- Nonreassuring fetal heart rate patterns
- Use of general anesthesia
- Uterine tetany
- Narcotics administered to mother within 4 hours of delivery
- Meconium-stained amniotic fluid
- Prolapsed cord
- Abruptio placentae
- Placenta previa

From Aucott SW, Zuckerman RL. Neonatal assessment and resuscitation. In: Chestnut DH, et al, eds. *Chestnut's Obstetric Anesthesia: Principles and Practice*. 4th ed. St. Louis: Mosby; 2009:155.

BOX **46-9**

Neonatal Resuscitation Guidelines

- Initial evaluation of the newborn with emphasis on heart rate and respirations. Pulse oximetry should be used for evaluation of oxygenation because assessment of color is often unreliable.
- To avoid hypothermia, preterm babies less than 28 weeks' gestation should be wrapped immediately after birth, up to their neck and without drying, and kept wrapped under radiant heat until their temperature has been verified in the neonatal intensive care unit (NICU). For these infants, delivery room temperature should be maintained at least at 26° C.
- Ventilatory resuscitation should begin with air rather than 100% oxygen in term infants receiving resuscitation at birth with positive pressure ventilation. If despite effective ventilation there is no increase in heart rate or if oxygenation, best guided by pulse oximetry, remains unacceptable, a higher concentration of oxygen should be considered. Oxygen saturation during labor and just after birth is more or less 60% and will increase to ± 90% after 10 min.
- Positive pressure ventilation (PPV) is an extremely important and effective intervention that should be initiated if the infant is apneic or gasping or if the heart rate is less than 100 bpm after 30 seconds of administering the initial steps of resuscitation. Prompt improvement in heart rate is the best indicator of adequate ventilation. The T-piece resuscitator is specifically used for neonatal resuscitation and is the device of choice.
- In births with meconium-stained amniotic fluid, suctioning of the oropharynx and nasopharynx before delivery of the shoulders is no longer recommended. In babies born through meconium-stained fluid, available evidence does not support or refute the routine endotracheal intubation and suctioning, even if they are depressed at birth, and the current practice should not been changed.
- Detection of exhaled carbon dioxide, in association with clinical assessment, for example, increasing heart rate, is the most reliable method for confirming endotracheal tube placement in infants with spontaneous circulation. Colorimetric exhaled CO_2 detectors are useful in identifying airway obstruction during face-mask ventilation in preterm infants.
- Chest compressions are indicated when the heart rate is less than 60 beats per minute despite adequate ventilation for 30 seconds. In the newly born infant, the standard compression: ventilation ratio is 3:1.
- If the arrest is clearly due to a cardiac etiology, a higher compression: ventilation rate (e.g., 15:2) may be considered. Compressions should be delivered on the lower third of the sternum at a depth of one third of the anteroposterior diameter of the chest. The two thumb-circling hands method is recommended because it is less tiring and allows for better depth control.
- The use of drugs is rarely indicated because the most important and effective step is establishing adequate ventilation. If emergency drugs are required, they can be given by three possible routes: venous (e.g., umbilical vein), endotracheal tube, and intraosseous. If the heart rate remains less than 60 beats per minute despite adequate assisted ventilation for 30 seconds and chest compression for an additional 30 seconds, then the administration of epinephrine at the dose of 0.01 to 0.03 mg/kg, intravenously or 0.05 to 0.1 mg/kg via the tracheal route.
- The use of therapeutic hypothermia, both whole-body hypothermia and selective head-cooling, may reduce the risk of death and disability in infants with moderate-to-severe hypoxic-ischemic encephalopathy. Hypothermia is recommended as a treatment for neonates with suspected asphyxia. Hypothermia should be induced, lowering temperature to 33.5° C to 34.5° C within 6 hours of birth, continuing it for 72 hours, and then rewarming over at least 4 hours. Treated infants should be followed up on a long-term basis.
- Healthcare providers may consider not initiating neonatal resuscitation when there are factors associated with almost certain infant death or unacceptable morbidity, or both. The parents must be included in the decision-making process regarding initiating or withholding resuscitation of their infant, particularly in situations when the prognosis is uncertain and morbidity rate is very high. Discontinuing continuous and adequate resuscitation after 10 minutes, if there are no signs of life, is justifiable.

Adapted from Biban P, et al. New cardiopulmonary resuscitation guidelines 2010: managing the newly born in the delivery room. *Early Hum Dev.* 2011;87(suppl 1):S9-S11.

Most newborns do not require neonatal resuscitation. However, about 10% of newborns require some type of resuscitative assistance at birth. The vast majority will require just assisted lung aeration. Approximately 1% require major interventions such as intubation, chest compressions, or medications. The new 2010 guidelines released by the European Resuscitation Council (ERC), the American Heart Association (AHA), and the American Academy of Pediatrics (AAP) are given in Box 46-9.

SUMMARY

Nurse anesthetists play a major role in the provision of obstetric anesthesia care. The practice of obstetric anesthesia has the additional challenge of assuring the safety of the newborn. The satisfaction attained from successful maternal and fetal outcomes is like no other in medicine. Advances in monitoring and prenatal care have allowed for continuous refinements in regional and, when necessary, general anesthesia management of these patients.

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Neonatal Anesthesia

◆ *Sass Elisha*

CHAPTER 47

The neonatal period is generally regarded as the first 28 days of extrauterine life. Anesthesia for the neonate is often required as the result of an urgent or life-threatening illness that requires surgical intervention. The normal human neonate is remarkably resilient and well equipped to survive in this hostile environment. The differences between the baby and the adult, however, are clearly greatest in the neonatal period, especially if birth occurs before term. The neonate that is born prematurely and ill is not as resilient as the full-term infant. Therefore, the neonatal anesthetist must have a thorough understanding of normal growth and development, the anatomic and physiologic differences during various stages of maturation, and how immature organ systems affect anesthetic pharmacokinetics and pharmacodynamics. Anesthetic management of the neonate requires integration of this specialized knowledge and refinement of acquired technical skills.

In the past, neonates and in particular preterm, sick neonates were anesthetized with the "Liverpool Technique," which consisted of oxygen, nitrous oxide, and curare. Volatile anesthetics and opioids were not used, and the "stable" state that resulted was due to a sympathetic system in overdrive. However, in the last three decades, our understanding of neonatal physiology, particularly neurobiology, has led to an active program of research in the field of neonatal anesthesia. Neonates, term and preterm, respond to painful stimuli.[1] Signs of distress are clearly evident when neonates are exposed to stimuli that are painful. The behavioral, physiologic, and humoral signs are similar to those seen in older children and adults.[2] Therefore, all neonates require anesthesia for surgery except under extraordinary circumstances. Physiologic development is in a transitional state, and congenital anomalies may be present. Neonates and infants younger than 12 months old exhibit the highest rate of adverse events both intraoperatively and in the postanesthesia recovery room. Preterm infants are more prone to developing respiratory complications.[3]

DEVELOPMENTAL CONSIDERATIONS

Fetal Circulation

The fetal circulatory system relies on the placenta for delivery of oxygen and transport of carbon dioxide (CO_2). The chorionic villus is the functional unit of the placenta. Normally, fetal blood is separated from the maternal blood in the placenta by a thin layer of cells known as *syncytial trophocytes*. Oxygen, CO_2, and small nonionized particles readily pass through this layer, whereas substances with a larger molecular weight are prevented from diffusing across the syncytial trophocytes. Fetal circulation is characterized by high pulmonary vascular resistance (uninflated atelectatic lungs and hypoxic vasoconstriction) and low systemic circulatory resistance (high flow and low impedance of the placental vessels). Fetal deoxygenated blood travels down the aorta and through the internal iliac arteries, arriving in the placenta via paired umbilical arteries. The umbilical arteries divide, forming the arterioles, capillaries, and venules of the intervillous placental space. Oxygenated blood is delivered to the fetus from the placenta via a single umbilical vein. This oxygenated blood bypasses the lungs by flowing through extracardiac (ductus arteriosus, ductus venosus) and intracardiac (foramen ovale) shunts, forming a parallel circulation. The ductus venosus routes oxygenated blood away from the sinusoids of the liver. The oxygenated blood in the inferior vena cava is directed by the eustachian valve toward the atrial septum and passes through the foramen ovale to enter the left side of the circulation. Oxygenated blood passes into the left ventricle and exits the aorta, supplying the coronary arteries. Blood entering the pulmonary artery from the right ventricle flows to the aorta via the ductus arteriosus. Only 5% to 10% of the combined ventricular output flows through the pulmonary circulation.

Transitional Circulation

The transitional circulation is established at the time of birth. With the cessation of placental blood flow, aortic pressure increases. Clamping of the umbilical vein doubles systemic vascular resistance. Pulmonary vascular resistance falls with lung expansion, and increasing partial pressure of arterial oxygen (Pa_{O_2}) produces pulmonary vasodilation, resulting in further decreases in pulmonary resistance. These changes in systemic and pulmonary blood flow produce corresponding changes in intracardiac pressure. Decreases in right atrial pressure with accompanying increases in left atrial pressure change the direction of blood flow through the foramen ovale, resulting in the closure of the foramen ovale as left atrial pressure increases. The foramen ovale may reopen if right atrial pressure is greater than left atrial pressure (e.g., pulmonary hypertension), permitting venous blood to flow from right to left. Within a period of 2 to 3 months, the foramen ovale will be permanently closed. Up to 25% of adult patients may demonstrate a probe patent foramen ovale at autopsy.[4] Closure of the ductus arteriosus is precipitated in part by the increase in systemic vascular resistance and decrease in pulmonary vascular resistance. In utero prostaglandins maintain the patency of the ductus arteriosus. Within a few hours after birth, the muscular wall of the ductus arteriosus constricts, preventing the retrograde flow of blood from the aorta into the pulmonary artery. This functional closure (thrombosis) occurs within 1 to 8 days. Anatomic closure (fibrosis of the ductus arteriosus) requires 1 to 4 months. Ductus closure may be influenced by elevations in the systemic Pa_{O_2} that occur after birth. The majority of portal blood flow continues to enter the ductus venosus after interruption of umbilical vein blood flow. Although the cause of the initiating mechanisms of ductus venosus closure is unknown, the muscular wall of the ductus venosus begins to constrict 1 to 3 hours postnatally. Blood flow is directed into the liver, and portal venous pressure increases.

Persistent Pulmonary Hypertension of the Newborn

Persistent pulmonary hypertension of the newborn (PPHN) is the result of an abnormal early adaptation to the perinatal circulatory

transition. PPHN is characterized by a sustained elevation of pulmonary vascular resistance (PVR); decreased perfusion of the lungs; and continued right-to-left shunting of blood through the fetal channels (foramen ovale and ductus arteriosus). When PVR remains high after birth, right (and sometimes left) ventricular function and cardiac output are depressed. Moderate or severe PPHN is believed to affect up to 2 to 6 per 1000 live births, and complicates the course of 10% of all infants admitted to neonatal intensive care. These circulatory abnormalities are also responsible for an 8% to 10% risk of death and a 25% risk of long-term neurodevelopmental morbidity. Significant pulmonary hypertension also may develop in neonates and young infants as a result of bronchopulmonary dysplasia (BPD) or cardiac disease. Pulmonary hypertension affects roughly one third of infants with moderate-to-severe BPD.[5-7]

During fetal development, PVR is high but rapidly decreases at birth to near-normal levels, allowing the lungs to become a gas-exchanging organ. Before anatomic closure of the extracardiac and intracardiac shunts, fetal circulation may be reestablished and persist. Persistent PPHN is manifest by increases in PVR and accompanying pulmonary hypertension, which produces a right-to-left shunt across the foramen ovale and the ductus arteriosus, with resultant cyanosis. The presence of congenital cardiovascular or pulmonary disease inhibits functional and anatomic closure of these aforementioned fetal shunts. Persistent fetal circulation is common in preterm infants and infants with metabolic derangements (e.g., asphyxia, sepsis, meconium aspiration, congenital diaphragmatic hernia). Hypoxemia, acidosis, pneumonia, and hypothermia are primary precipitating factors of PPHN. Oxygenation, the avoidance of acidosis, and maintenance of normothermia will attenuate the increase in pulmonary vascular resistance. Continual increases in pulmonary vascular pressure and resistance will precipitate the development of right ventricular hypertrophy (cor pulmonale). Although pulmonary vasodilators may have some utility in decreasing pulmonary vascular resistance, concurrent reductions in systemic vascular resistance can occur and may worsen the shunt.

The primary aim of PPHN therapy is selective pulmonary vasodilation. Treatment of pulmonary hypertension includes optimization of lung function, oxygen delivery, and support of cardiac function. Optimal lung inflation is essential because PVR is increased when the lungs are underexpanded or overexpanded, independent of lung disease. The use of lung recruitment strategies, such as high-frequency ventilation and exogenous surfactant administration, is particularly important in infants with PPHN associated with parenchymal disease, but has limited impact in infants with primary vascular disease. Correction of severe acidosis and avoidance of hypoxemia are important because they both stimulate pulmonary vasoconstriction. Maintaining a normal hematocrit is also important to ensure adequate oxygen-carrying capacity while avoiding polycythemia, because hyperviscosity can increase PVR.

Treatment includes inhaled nitric oxide, sildenafil, milrinone, bosentan, and prostanoids such as prostacyclin, iloprost, or treprostinil.[5]

GROWTH AND DEVELOPMENT

Cardiovascular System

The myocardium of the newborn is immature. The neonatal heart contains the essential structural elements of the adult heart; however, there is cellular disorganization and fewer myofibrils. Although the ventricles are of equal size and shape, the contractile components (sarcoplasmic reticulum and T-tubule system) are immature. Accordingly, the neonatal heart is less capable of generating a response to an increase in resistive load (increase in stroke volume) and is dependent on free ionized calcium for contractility. Despite this immaturity, the neonatal heart is capable of limited increases in stroke volume up to left atrial pressures of 10 to 12 mmHg when afterload remains low. This information suggests that the neonatal heart is operating near the peak of the Frank-Starling curve because there is a limited reserve to increases in both preload and afterload.

During maturation, the left ventricle will hypertrophy through an increase in the number and size of myofibrils. This maturation is a consequence of left ventricular contraction against a higher postnatal systemic pressure. Acute increases in afterload (e.g., acidosis, hypothermia, pain) will produce further reductions in cardiac output. In the immediate postnatal period, left ventricular compliance is low. The neonate may develop congestive heart failure because the stiff left ventricle will not stretch to accommodate large fluid loads. Left ventricular distention from volume overload compresses the adjacent right ventricle, producing additional embarrassment to cardiac output. Likewise, ventilation with high peak pressure will produce left ventricular dysfunction and overload of the right ventricle.

Owing to the immaturity of the contractile elements of the neonatal myocardium, the belief is that pediatric cardiac output is solely dependent on heart rate. Atropine is frequently administered for the treatment of decreased cardiac output. However, marked increases in heart rate fail to a large extent to produce further increases in cardiac output. Although the neonatal myocardium will develop less stretch with volume loading than the older child or adult, volume expansion remains important, albeit to a smaller extent than in the adult, in increasing cardiac output. The combination of hypovolemia and bradycardia produce dramatic decreases in cardiac output that threaten organ perfusion. Epinephrine rather than atropine increases contractility and heart rate and is now advocated for the treatment of bradycardia and decreased cardiac output in pediatric patients. The baroreceptor reflex is not completely developed, limiting the neonate's ability to compensate for hypotension with the reflex tachycardia expected in the older child and adult.

Autonomic innervation of the neonatal heart is predominantly controlled by the parasympathetic nervous system; the sympathetic nervous system is immature at birth. Parasympathetic dominance produces bradycardia with minor clinical interventions such as pharyngeal suctioning and laryngoscopy. Marked variation in the newborn heart rate and rhythm occur secondary to changes in autonomic tone. The electrocardiogram (ECG) recording in the newborn reflects the immaturity of the conduction system. The ECG axis is shifted to the right but shifts to the left with maturation and accompanying hypertrophy of the left ventricle. The P wave is evident; the PR is less than 0.12 second and increases until adolescence. T waves are upright in the recorded chest leads, reflecting right ventricular domination. The newborn heart rate averages 120 beats per minute (bpm) during the first day of life, increasing to 160 bpm at 1 month of age, then steadily decreasing to an average of 75 beats by the adolescent period. Sleep may produce heart rates lower than 100 bpm, whereas pain increases the rate up 200 bpm.

Blood pressure increases immediately after birth, rising to a mean systolic pressure of 70 to 75 mmHg within the first 48 hours. Blood pressure is lower in the preterm infant. As the heart rate decreases with maturation, there is an accompanying increase in blood pressure. Hypotension in an anesthetized newborn is defined as a systolic blood pressure of less than 60 mmHg. In a 1-year-old child, hypotension is defined as systolic pressure less than 70 mmHg. In the older child, hypotension is determined as a systolic pressure of 70 mmHg plus twice the child's age in years. Table 47-1 shows values for heart rate and blood pressure at different ages.

TABLE 47-1 Age-Related Changes in the Cardiovascular System

Age	Heart Rate	Systolic BP	Diastolic BP
Neonate	140	70-75	40
12 mo	120	95	65
3 yr	100	100	70
12 yr	80	110	60

BP, Blood pressure.

Fetal hemoglobin is the predominant hemoglobin species in the newborn, contributing between 70% and 90% of the total. This amounts to a hemoglobin of between 18 and 20 g/dL at birth. Fetal hemoglobin has a higher affinity for oxygen than adult hemoglobin. In utero, this increased oxygen affinity facilitates oxygen uptake as fetal blood circulates through the placenta, increasing the binding of oxygen to fetal hemoglobin and allowing the fetus to exist in a relatively low Pa_{O_2} environment. There is a rapid change in the fetal hematopoietic physiology in the oxygen-rich extrauterine environment. The increased arterial oxygen content after birth results in a decrease in erythroid activity, and hematopoiesis ceases. A decrease in erythropoiesis and decreased life span of the newborn's red blood cells (RBCs) produces a progressive decrease in hemoglobin, reaching a nadir by age 3 months. This "physiologic anemia of infancy" does not compromise the delivery of oxygen, because the oxyhemoglobin dissociation curve shifts to the right and RBC concentrations of 2,3-diphosphoglycerate increase (Figure 47-1). Fetal hemoglobin is replaced by adult hemoglobin during the first 3 to 6 months, producing a rightward shift of the oxyhemoglobin dissociation curve.

It is important to note that the premature infant may experience a dramatic fall in hemoglobin because of insufficient body stores of iron. Newborns should receive vitamin K prophylaxis, because the concentration of vitamin K–dependent clotting factors (II, VII, IX, and X) are 20% to 50% of adult levels. Premature infants generally have lower levels of vitamin K–dependent clotting factors. Maternally ingested drugs such as warfarin and isoniazid may precipitate the development of a coagulopathy.

The newborn's blood volume is dependent on the time of cord clamping (transfusion from the placenta). Blood volume is approximately 80 to 90 mL/kg but may be as high as 100 mL/kg in the premature neonate. The intravascular volume decreases 25% in the immediate postnatal period with the loss of intravascular fluid. Blood volume increases over the next 2 months, peaking at 2 months of age. Table 47-2 provides an estimate of circulating blood volume development.

Respiratory System

In utero, fetal lung development beings with the formation of lung buds, which occurs during the first few weeks after conception. During organogenesis in the second trimester, distinct bronchi and bronchopulmonary segment proliferation that extends downward to the terminal bronchioles is created. There are 10 to 20 million terminal sacs, which, after elongation, begin to develop into alveoli after birth. The process of alveolar formation is accelerated between 12 to 18 months postnatally and increases to 200 to 300 million between 8 to 10 years of age.

Type II pneumocytes are responsible for the production and secretion of surfactant, which begins between 22 and 26 weeks, and concentrations peak between 35 and 36 weeks' gestation. Surfactant decreases surface tension within the alveoli to decrease

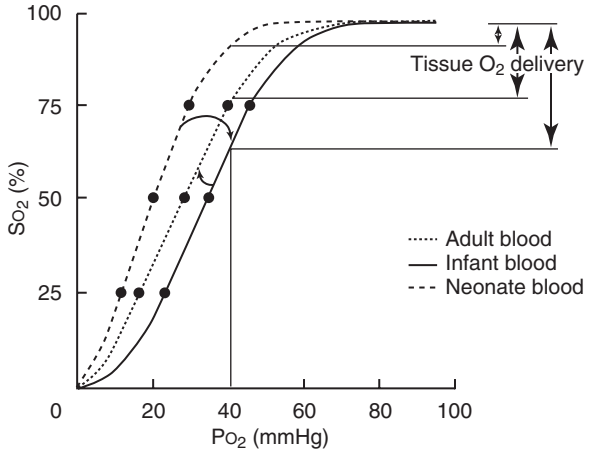

FIGURE 47-1 Schematic representation of oxyhemoglobin dissociation curves with different oxygen affinities. *Top arrows*, Direction of rightward shifting of the oxyhemoglobin dissociation curve (and P50) after birth. By 10 weeks of age, the adult position of the curve is reached. (From Davis PJ, Cladis FP, Motoyama EK. *Smith's Anesthesia for Infants and Children*. 8th ed. Philadelphia: Mosby; 2011:62.)

TABLE 47-2 Estimated Blood Volumes by Age

Age Group	Volume (mL/kg)
Premature	90-100
Newborn (less than 1 mo of age)	80-90
Infants 3 mo to 3 yr of age	75-80
Children older than 6 yr of age	65-70
Adults	65-70

alveolar collapse. This relationship can be explained by the Law of Laplace as shown below. In the absence of adequate pulmonary surfactant such as in a premature neonate, alveoli become stiff and noncompliant as depicted in Figure 47-2. Severe atelectasis decreases alveolar surface area available for oxygen and carbon dioxide exchange. Increased physiologic dead space and ventilation perfusion mismatch cause hypoxia and hypercarbia, necessitating mechanical ventilation. The treatment for infantile respiratory distress syndrome includes synthetic surfactant, continuous positive airway pressure, and mechanical ventilation.[8]

$$P = 2T/R$$

P = pressure within a sphere, T = surface tension, R = radius of the sphere

Anatomy

At birth the neonatal larynx is small compared with the mouth and pharynx. The epiglottis is short and small, and the vallecula is shallow so that the tongue approximates the epiglottis. The larynx is pointed toward the nasopharynx, facilitating nasal breathing. The arytenoids are large in proportion to the lumen of the larynx. The subglottic region is smaller than the glottic opening with the cartilages telescoping into one another, forming a conical shape.[9] The cricoid cartilage is the narrowest portion of the airway, and the cricoid lumen is not a round but mostly an ellipsoid structure. It is lined with a pseudostratified epithelium that is easily injured, resulting in significant edema and stridor. A recent study questions this traditional teaching. Video bronchoscopic images and magnetic

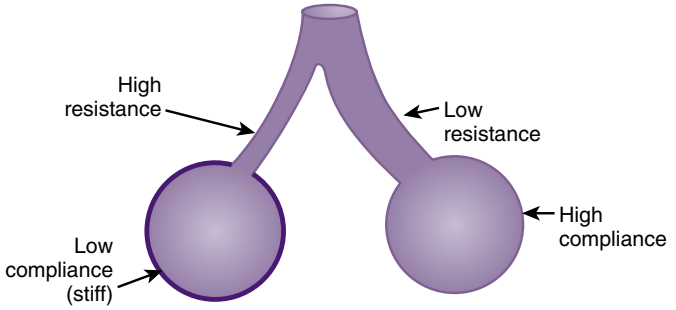

FIGURE **47-2** An idealized state showing the reciprocal relationship between resistance and compliance; gas flow is preferentially delivered to the most compliant regions, regardless of the rate of inflation. Static and dynamic compliance are equal. (From Davis PJ, Cladis FP, Motoyama EK. *Smith's Anesthesia for Infants and Children*. 8th ed. Philadelphia: Mosby; 2011:354.)

resonance spectrographs were obtained in 135 children, aged 6 months to 13 years. Measurement of laryngeal dimensions, including cross-sectional area, anteroposterior, and transverse diameters at the level of the glottis and the cricoid were performed. They found that the glottis rather than cricoid was the narrowest portion of the pediatric airway. They also noted that like adults, the pediatric airway is more cylindrical than funnel shaped.[10]

The newborn tongue is large and difficult to manipulate because of the position of the hyoid. In addition, a smaller potential submental space is present, in which it is possible to displace the tongue during laryngoscopy. The anterior position of the larynx and the large tongue increase the potential difficulty of mask ventilation.

The larynx is located more cephalad and anterior, extending from the second to the fourth cervical vertebrae (C2 to C4). The anesthetic implication of the more cephalad location is that placing a neonate in the "sniffing position" for laryngoscopy and intubation will only move the larynx in an anterior direction.

The occiput of the newborn's head is large and prominent. The placement of a rolled towel under the shoulders aids in the visual alignment of the oral, pharyngeal, and laryngeal axes during laryngoscopy (Figure 47-3 and Table 47-3).

Mechanics of Breathing

The neonate's chest wall is pliable for lack of developed musculature and a skeletal structure primarily composed of cartilage. The ribs are horizontal in orientation, providing minimal assistance in the expansion of the chest wall with inspiration. During inspiration the compliant chest wall is noted to collapse inward during respiration (paradoxical breathing). To maintain negative intrathoracic pressure in the face of a compliant chest wall, the neonate and infant actively recruit accessory muscles of respiration (i.e., intercostal muscles). Additionally, exhalation is limited by the adductor muscles of the larynx, which contract and serve as an expiratory valve or brake to maintain end-expiratory pressure. These structural differences are responsible for the decrease in functional residual capacity (FRC) with administration of general anesthesia in the neonate and infant. The previously cited muscular activity responsible for maintaining FRC is lost with the administration of sedatives, inhalation anesthetics, and neuromuscular relaxants. Rapid hypoxemia follows the loss of FRC. FRC may be restored with the application of continuous positive airway pressure or controlled ventilation. The premature infant has an even more pliable chest wall, and paradoxical chest movement may occur with breathing during rest.

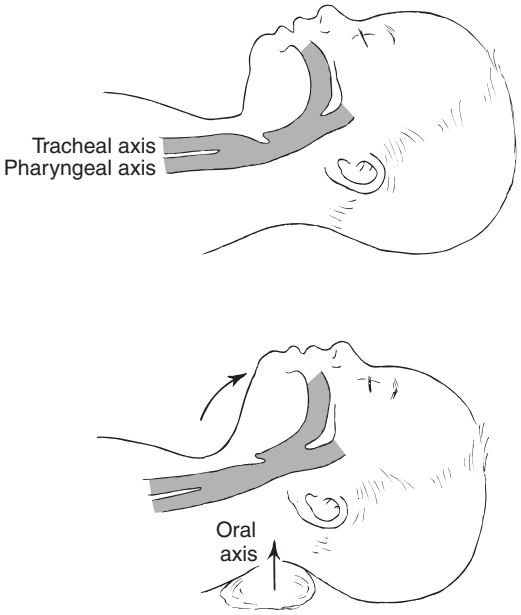

FIGURE **47-3** Alignments of visual, oral, and laryngeal axes during laryngoscopy.

TABLE **47-3** Differences Between the Adult Airway and the Pediatric Airway

	Pediatric	Adult
Laryngeal location	C2-C4	C3-C6
Narrowest location of airway	Cricoid	Glottis
Shape of epiglottis	Longer, more narrow	V-shaped
Right mainstem bronchus	Less vertical	More vertical

The diaphragm contributes to the differences in respiratory function of the neonate and infant. Unlike the adult diaphragm, which is dome shaped, the diaphragm of the neonate and infant is relatively flat. Accordingly, its anterior insertion on the chest wall fails to contribute any mechanical advantage with contraction. Primarily the diaphragm and to a lesser extent the intercostal muscles allow for expansion of the thoracic cavity and the associated increase in negative intrathoracic pressure. As a result, during inspiration, air is drawn into the lungs, and with relaxation of these muscles, air passively exits the lungs due to the elastic recoil. Two types of muscle fibers are present in muscle tissue—specifically, the diaphragm and intercostals. Type 1 muscle fibers are slow twitch muscle fibers and are resistant to fatigue. These fibers are essential for sustained ventilatory activity. Type 2 muscle fibers, also known as fast twitch muscle fibers, are fast twitch but fatigue rapidly. A newborn infant's diaphragm is composed of 25% type 1 muscle fibers as compared to 55% type 1 muscle fibers in the adult diaphragm. Also, type 2 muscle fibers are predominant within the intercostals. Therefore, newborns and young infants are at risk of muscle fatigue, respiratory distress, and respiratory arrest. The anesthetist must assess for respiratory compromise resulting from the depressant effects of residual anesthetic agents, airway obstruction, and postoperative pain. Assisting with respirations and relieving airway obstruction during the perioperative period will promote adequate gas exchange and decrease the degree of atelectasis.

Control of Breathing

The control of breathing is dependent on the Pa_{O_2} sensed via the peripheral chemoreceptors (carotid and aortic bodies), the partial pressure of arterial CO_2 (Pa_{CO_2}), and pH, which influence the central chemoreceptors within the respiratory control center of the medulla. Increases in Pa_{CO_2} produce corresponding increases in tidal volume and respiratory rate, although this response is not as vigorous as in the adult. Increases in Pa_{O_2} will depress the ventilatory response in the newborn, whereas a decreased Pa_{O_2} will increase the ventilatory response. The ventilatory response to hypoxemia produces two distinctly different responses. Initially hypoxemia stimulates an increase in ventilation for the first minute but produces ventilatory depression with a decreasing response for the next 3 to 5 minutes. This response is more robust in the premature infant than in the newborn. Ventilatory depression is more profound in the hypothermic, acidotic, or hypercarbic neonate.

Respiratory depression and/or apnea may develop in the newborn after stimulation of the carina and/or the superior laryngeal nerve, following upper airway obstruction or following lung inflation (Hering-Breuer reflex). The newborn may exhibit periodic breathing with inspiratory pauses lasting 10 seconds, followed by abrupt increases in ventilation. Periodic breathing is more common in the premature infant and occurs more often during rapid eye movement sleep. Apneic episodes are not uncommon in the premature infant; such episodes produce arterial desaturation. Bradycardia and cardiac arrest may follow these apneic episodes. The suspected causes of apnea in premature infants include immature responses of the respiratory control center to hypercarbia or hypoxic stimuli and respiratory fatigue. Infants who have experienced apneic or bradycardic episodes are at risk for these episodes after general anesthesia.

Lung Volumes

The mean values for pulmonary function in the newborn and adult are shown in Table 47-4. The infant's metabolic rate and oxygen consumption are approximately twice those of the adult. The decreased reservoir for oxygen (decreased FRC), coupled with the increased demand for oxygen (increased metabolic rate), results in rapid desaturation when ventilation is interrupted. Airway closure produces a mismatching of ventilation and perfusion. The volume of these poorly ventilated alveoli that contribute to intrapulmonary shunting is greater in neonates than in adults. In addition, increased pulmonary vascular resistance can produce a right-to-left shunt through the foramen ovale or a patent ductus arteriosus, resulting in the rapid development of cyanosis.

Airway Dynamics

Airway resistance is greater in neonates and declines markedly with growth from 19 to 28 cm H_2O/L/sec to less than 2 cm H_2O/L/sec in adults.[11-13] According to Poiseuille's law, airway resistance is inversely proportional to the fourth power of the radius of the airway during laminar flow. A neonate must overcome the resistance to airflow, as well as the elastic recoil of the lungs and chest wall. The rate of ventilation that uses the least amount of muscular energy and generates a satisfactory tidal volume has been found to be 37 breaths per minute in the healthy newborn.

The metabolic cost of breathing in the neonate is similar to an adult, approximately 0.5 mL per 0.5 L of ventilation. This is equivalent to 1% of their metabolic energy. The premature neonate's metabolic cost of breathing is 0.9 mL/0.5 L, almost double the metabolic price. If the neonate has pulmonary problems, the cost could go even higher.[14]

TABLE 47-4 Mean Values for Normal Pulmonary Function in the Newborn and the Adult

	Newborn	Adult
Body weight (kg)	3	70
Tidal volume (mL/kg)	6	6
Respiratory rate (bpm)	35	15
Alveolar ventilation (mL/kg/min)	130	60
Oxygen consumption (mL/kg/min)	6.4	3.5
Total lung capacity (mL/kg)	63	86
Functional residual capacity (mL/kg)	30	34
Vital capacity (mL/kg)	35	70
Residual volume (mL/kg)	23	16
Closing capacity (mL/kg)	35	23
Arterial pH	7.38-7.41	7.35-7.45
Pa_{CO_2}	30-35	35-45
Pa_{O_2}	60-90	90-100
Sa_{O_2} (%)	95-100	95-100

Pa_{CO_2}, Partial pressure of arterial carbon dioxide; *Pa_{O_2}*, partial pressure of arterial oxygen; *Sa_{O_2}*, oxygen saturation.

Airway resistance changes with age. Although the larger airway resistance remains constant, airway resistance in the smaller airways is increased. The increase in airway resistance increases the work of breathing in the neonate. Small airway disease (e.g., pneumonia) produces additional increases in the work of breathing.

Nervous System

The central nervous system in the newborn differs from the older child in the degree of myelination, muscle tone and reflexes, and development of the cerebral cortex. In the peripheral nervous system, myelination begins in the motor roots and progresses to the sensory roots. In contrast, the myelination in the cerebral sensory systems precedes that of the central motor systems. This incomplete myelination is associated with those reflexes that are used to measure neural development, the Moro and grasp reflexes. Myelination of the nervous system is not complete until age 3.

Development of Neuromuscular Junction

The neuromuscular junction (NMJ) undergoes developmental changes during the first 2 months of life. During the maturation process, the NMJ differs in several ways. There is a difference in the maturity, density, sensitivity, and distribution of the postsynaptic acetylcholine receptors; in the rapidity of neuromuscular transmission; and in muscle fiber type.[15] What differentiates the immature receptors from the developed ones is a functional difference that is due to a prolonged opening of the ionic channels. This prolonged channel opening allows the immature muscles to be more easily depolarized. These receptors also have a greater affinity for depolarizing agents and a lower affinity for nondepolarizing muscle relaxants (NDMRs). The clinical implication of these maturational changes is that neonates can have a greater variability in their responses to nondepolarizing muscle relaxants and in the monitoring of the NMJ via a peripheral nerve stimulator. Neuromuscular immaturity may be demonstrated with the appearance of fade after tetanic stimulation in the absence of neuromuscular blocking drugs. It is also worth noting that the type I fibers are more sensitive to NDMRs when compared with type II fibers. The clinical relevance of this difference is that the diaphragm of a neonate has fewer type I fibers as compared to a diaphragm of a

toddler or an adult. This makes the diaphragm of a neonate more responsive to NDMRs than his or her peripheral musculature.[16]

Pain Sensitivity

Pathways required for pain perception can be traced from sensory receptors in the skin to sensory areas in the cerebral cortex of newborn infants. These pain pathways have been demonstrated in the perioral area as early as 7 weeks' gestation. With positron emission tomography scans, neonates demonstrate maximal metabolic activity in the regions associated with sensory perception, such as the cortex, thalamus, and midbrain-brainstem regions. Neonatal anesthesia providers have seen newborns exhibit signs of increased sympathetic activity (e.g., tachycardia and hypertension) in response to surgical stimulation with inadequate anesthesia. The risks associated with inadequate or absent pain control expose the neonate to noxious stimulation that can have significant physiologic consequences. Those consequences in the presence of abnormal cerebral autoregulation could result in intraventricular hemorrhage and pulmonary hypertension.[17]

Lack of development of inhibitory tracts may actually increase the intensity and duration of the painful stimulus. It has been suggested that newborn infants may develop prolonged responses to painful procedures that far outlast the stimuli by hours or days. This is illustrated by several examples. Premature infants mount a metabolic stress response that can be blocked with opioids, increased crying, and interrupted sleep patterns; behavioral changes have been shown to occur for days after circumcision,[18] and with repeated heel lancing, there appeared to be a hyperalgesic response to injury.[19] Other physiologic alterations that have been demonstrated are increased right-to-left shunting, hypoxemia, acidosis, and intraventricular hemorrhage.[17]

Sensory nerve distribution is formed by 20 weeks' gestational age. Pain pathways and receptors are present within the central nervous system at birth. Physiologic stimulation from anesthesia management and surgery dramatically increase circulating catecholamines and other stress hormones. As in adults, during the perioperative experience, pediatric patients exhibit tachycardia and hypertension if light anesthesia is coupled with significant surgical stimulation. Due to the lack of cerebral vascular autoregulation, increased blood pressure can cause intracerebral bleeding, especially in premature neonates. The pain threshold for infants and children may be lower than in older children and adults, possibly because of increased pain sensitivity, behavioral factors, or both. Preoperative and postoperative signs of pain in patients that are preverbal include tachycardia, elevated blood pressure, crying, restlessness, and grimacing.

In recent years, the safety of anesthetic medications and their effect on the developing brain have been questioned. In animal studies, agents that either antagonize N-methyl-D-aspartate (NMDA) receptors or potentiate the neurotransmission of γ-aminobutyric acid (GABA) agents) have been implicated, and no safe doses or durations of exposure of these agents have been defined.[20] One proposed mechanism of action for these effects is by inhibition of brain-derived neurotrophic factor, which stimulates neural development.[21] Neurotoxicity resulting in neuroapoptosis, interference with nerve pathway, and nerve cell development can result in long-term neurocognitive deficits.[20,22-24] The most damage occurs during maturation periods when synaptogenesis rapidly occurs.[25] The Food and Drug Administration (FDA) is addressing this issue by forming a public-private partnership with the International Anesthesia Research Society called SmartTots (Strategies for Mitigating Anesthesia-Related Neuro-Toxicity in Tots). This partnership will seek to mobilize the scientific community, stimulate dialogue among thoughtful leaders in the anesthesia community, and work to raise funding for the necessary research. SmartTots is a multi-year collaborative effort designed to increase the safety of anesthetic drugs for the millions of infants and children who undergo anesthesia each year. Findings from these studies will help establish new practice guidelines. Data, outcomes, and best practices generated by SmartTots will be placed in the public domain.

Several major pediatric centers and subspecialty organizations with specific interest in this matter are part of this research consortium. Some ongoing clinical trials assessing the effects of anesthetics on neurocognitive development are noted in Table 47-5.

TABLE 47-5 Ongoing Clinical Trials Assessing the Effects of Anesthetics on Neurocognitive Development

Ongoing Clinical Trials	Study
Odense University Hospital (Denmark) and the Danish Registry Study Group	A nationwide epidemiologic study comparing the educational achievements of all children who have undergone a surgical procedure before the age of 1 year with that of a general-population control group
Columbia University	A prospective cohort study of children who have exposure to an anesthetic before the age of 3 years and their siblings who were not exposed; the two groups will be followed for neurodevelopmental outcomes
International Collaboration of Institutions from Australia, Canada, Italy, Netherlands, United Kingdom, and United States	Prospective, randomized, investigator-blinded, controlled clinical trial to assess the effects of general anesthesia using sevoflurane versus neuraxial anesthesia using bupivacaine on neurocognitive function in infants over 26 weeks' gestational age; children will be followed with evaluations of neurocognitive development at 2 and 5 years of age

Adapted from Rappaport B, et al. Defining safe use of anesthesia in children. *N Engl J Med.* 2011;364(15):1386-1390.

Cranium and Spinal Column

The most significant neurologic growth and development occurs in utero. The neural tube is nearly completely formed by 3 to 4 weeks' gestational age. It further differentiates over the next 4 to 12 weeks to create other anatomic structures that include the forebrain, facial bones, and spinal cord. Neurogenesis proceeds during weeks 12 to 20, followed by synaptogenesis and increased myelination. Increased density of synaptic connections and glial cells continues to develop until 2 years of age and is estimated to be 50% greater than in the adult brain.[26]

After birth, there is continued rapid functional and structural brain development. The brain doubles in weight within the first 6 months of life and triples in weight within 1 year. At 1 year of age, maturation of the cerebral cortex and brainstem is nearly complete. Myelination of nerve cells continues until 3 years of age. By age 2 years, the child's brain is 80% of the adult weight and 90% by age 5 years. Because of this rapid growth, fontanelles and supple cranial bones allow the skull to accommodate for this increased cerebral volume without increasing intracranial pressure. In 96% of children, the anterior fontanelle closes by 2 years of age. The posterior fontanelle closes at approximately 4 months. The anterior fontanelle can be used to assess increased intracranial pressure (bulging anterior fontanelle) and also

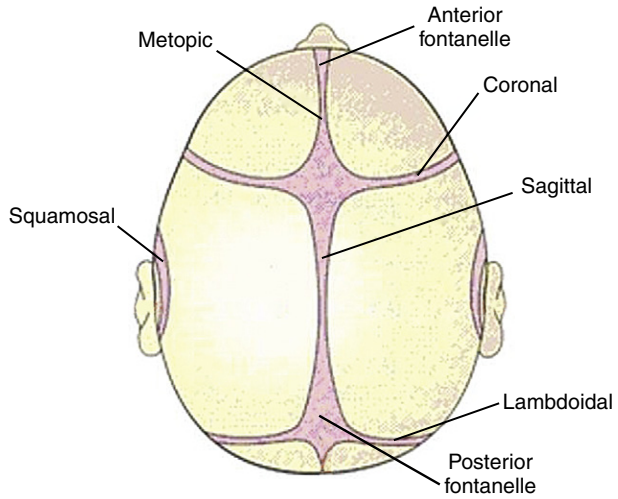

FIGURE **47-4** Cranial sutures and fontanelles in neonates and infants. (Modified from Davis PJ, Cladis FP, Motoyama EK. *Smith's Anesthesia for Infants and Children*. 8th ed. Philadelphia: Mosby; 2011:714.)

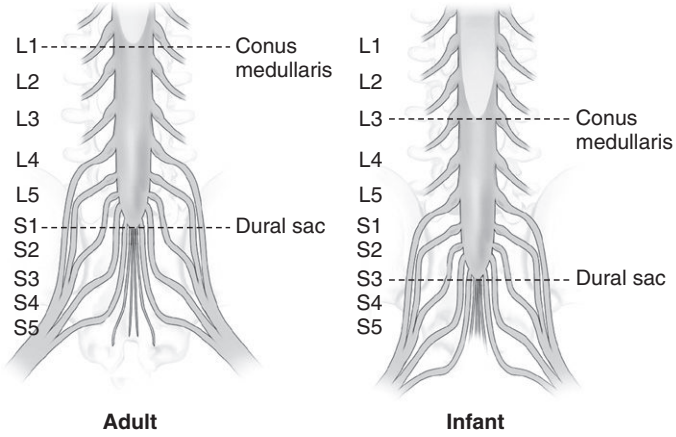

FIGURE **47-5** Comparison of levels of the conus medullaris and the dural sac in the infant and the older child or adult. (From Davis PJ, Cladis FP, Motoyama EK. *Smith's Anesthesia for Infants and Children*. 8th ed. Philadelphia: Mosby; 2011:463.)

dehydration (sunken anterior fontanelle). The blood-brain barrier is immature until approximately 1 year of age. Therefore, higher concentrations of medications and toxins that would be impermeable to the adult brain can result in higher cerebral concentrations throughout infancy. There are two major fontanelles, anterior and posterior, as shown in Figure 47-4.[27] Nerve cells within the spinal cord mature until completion at 6 to 7 years of age. As the pediatric patient grows, the conus medullaris and the dural sac migrates cephalad. Although the exact vertebral level of these structures varies slightly, the conus medullaris terminates between L2 and L3 in neonates. The dural sac ends between S2 and S3 until approximately 6 years of age. Being mindful of this information is imperative to providing safe anesthesia during placement of a spinal or caudal anesthetic. By age 8, the spinal cord approximates the adult and ends at L1.[27] Figure 47-5 depicts a comparison between the adult and infant spinal anatomy.

Cerebral Metabolic Requirement

Because of the rapid maturation of the central nervous system (CNS) during infancy and childhood, proper nutrition is essential to ensure normal development. With maturation, there is an increase in the metabolic demands of the CNS. The primary fuel for the brain is glucose, and in the neonate, there are decreased stores of glycogen, making hypoglycemia a major source of morbidity causing apnea, hypotension, bradycardia, convulsions, and brain injury.

Cerebral Blood Flow

Cerebral blood flow (CBF) is closely coupled with cerebral metabolic rate of oxygen consumption ($CMRO_2$). CBF in the premature infant is 40 mL/100 g/minute, and in older children approaches the adult level of 100 mL/100 g/minute. Autoregulation of CBF refers to the ability of the CNS to regulate CBF over a wide range of cerebral perfusion pressures. CBF autoregulation is thought to take place in the neonate, but the specific limits are unknown. Complete loss of cerebral autoregulation may occur with hypoxia, severe hypercapnia (greater than 80 mmHg), blood-brain barrier disruption after head trauma, subarachnoid or intracerebral hemorrhage, or cerebral ischemia, or after the administration of high concentrations of potent inhalation anesthetics and vasodilators (nitroprusside). Changes in CBF will parallel changes in cerebral blood volume, except when cerebral perfusion decreases and autoregulation produces vasodilation to maintain a constant flow. The cerebral vessels are very fragile in preterm and low-birth-weight infants. This fragility predisposes neonates to intracranial hemorrhage. Intracranial hemorrhage may be precipitated by hypoxia, hypercarbia, hyperglycemia, hypoglycemia, hypernatremia, and wide swings in arterial or venous pressure. The intravenous administration of hypertonic solutions may damage these fragile vessels. Therefore, adult-strength sodium bicarbonate should not be administered to neonates.

Autonomic Nervous System Immaturity

At birth, the autonomic nervous system is developed but not mature as in an adult. The sympathetic nervous system innervation to the heart and vasculature is less responsive compared with parasympathetic nervous system innervation. As a result, physiologic stress can cause severe and rapid cardiovascular collapse. As the pediatric patient ages, the child's sympathetic response becomes pronounced, and the child is able to compensate for stress by increasing heart rate and blood pressure. If bradycardia occurs, the anesthetist should focus first on hypoxia as possible cause. Rapid assessment and treatment is essential. Specific causes that could lead to bradycardia and cardiac arrest are included in Box 47-1.

Renal System

Fluid balance is not a concern for the fetus because water and electrolytes equilibrate across the placenta in response to growth and metabolic demands. The fetal kidneys make urine that passes into the amniotic cavity to compose one half of the amniotic fluid, which is then swallowed and absorbed in the gut. Structurally the kidney is different in the neonate. Nephrons are still being formed up to 35 weeks' gestation. The resulting glomerular filtration rate is much lower in a preterm (0.55 mL/min/kg) than a full-term baby (up to 1.6 mL/min/kg) or a 2-year-old child (2 mL/min/kg). Decreased systemic arterial pressure, increased renal vascular resistance, and decreased permeability of the glomerular capillaries contribute to the low glomerular filtration rate (GFR). In addition to the stiff, noncompliant myocardium, the neonate is unable to tolerate fluid overload because of the lower GFR. GFR reaches adult levels by 6 to 12 months of age. The renal medulla is not completely mature, and the potential effect of antidiuretic hormone is diminished. However, all of the hormones that affect the kidney are active even in a very immature infant, albeit with reduced potency. Neonates are *obligate sodium excreters* because of their inability to conserve sodium, even in cases of severe sodium depletion. The renin-angiotensin-aldosterone

BOX 47-1

Causes of Neonatal Bradycardia and Cardiac Arrest

Respiratory (any cause resulting in hypoxia)
- Airway obstruction (laryngospasm, postextubation croup)
  - Bronchospasm
  - Pulmonary aspiration
  - Inadequate oxygen delivery system
  - Pneumothorax

Pharmacologic
- Inhalation anesthetics
- Succinylcholine
- Anticholinesterases

Neurogenic
- Celiac reflex
- Oculocardiac reflex
- Superior/recurrent nerve stimulation (during intubation, airway manipulation)

Metabolic
- Hypoglycemia
- Anemia
- Hypothermia
- Acidosis

system (RAAS) acts to reduce sodium loss from the distal tubule, but the immature renal tubules fail to respond. In addition, the renal tubules have a limited ability to reabsorb glucose. Increasing plasma glucose concentrations may elicit an osmotic diuresis, depleting intravascular volume. Table 47-6 lists the daily electrolyte requirements for the newborn. Renal tubular function is immature until the age of 2 to 3 years. The neonate has a limited ability to concentrate urine compared with an adult (700 vs 1200 mOsm/L). Overall, the neonate has a tendency to accumulate sodium because it is essential for growth. Atrial natriuretic peptide is present, but its effects are blunted. In effect, the neonatal kidney is able to excrete water and sodium but cannot conserve them like the kidney of an older child.[28]

By the end of the first month of life, renal function is approximately 70% of adult levels and by the end of the first year, renal function reaches adult levels.

Fluid Balance

Neonates have a high turnover of fluid. After the first week, a baby needs 150 mL/kg/day of fluid (equivalent to 20 pints a day for an adult). This is because milk has a low concentration of energy compared with solid food, and the neonate cannot physiologically reduce urine output below 1 mL/kg/hr. Neonates also have high insensible losses, particularly from evaporation, as a result of a high surface area/body-weight ratio (four times higher than an adult) and immature skin. These problems are accentuated for the preterm baby. Thirst mechanisms are poorly developed and are affected by sepsis or respiratory distress syndrome. Also, a surge of antidiuretic hormone at birth causes oliguria over the first few days. Table 47-7 summarizes indicators of fluid balance.

Hepatic System

The liver begins to develop at 10 weeks' gestation, and by 12 weeks' gestation, it has already begun to function. Gluconeogenesis and protein synthesis are under way, and by 14 weeks glycogen is found in liver cells. The fetal liver has the ability to synthesize glycogen. Glycogen storage capacity is greatly increased just before birth. Approximately

TABLE 47-6 Daily Electrolyte Requirements of the Newborn

Electrolyte	Daily Requirement
Sodium	2-3 mEq/kg
Potassium	1-2 mEq/kg
Calcium	149-200 mg/kg

TABLE 47-7 Indicators of Fluid Balance

Parameter	Normal Range
Sodium	133-144 mmol/L
Body weight	Should fall by up to 10% below birth, by 1 week, then increase
Hematocrit	Increases (without transfusion) suggest dehydration
Creatinine	Should fall from maternal levels to less than 50 μmol/L after 5 days

98% of this stored glycogen is released from the liver within the first 48 hours of life, and glycogen levels are not restored to adult levels until the third week of life. Glycogen stores are not as large in preterm or small-for-gestational-age (SGA) infants. Therefore preterm and SGA infants should be monitored for the development of hypoglycemia.

The synthetic function of the liver is decreased, and the capability for biotransformation is decreased, with oxidative activities approximately one quarter to one half of adult values.[29] The capacity to enzymatically break down proteins is depressed at birth as a result of a decrement in quantity and quality of hepatic enzymes. Albumin, an essential protein that regulates colloidal osmotic pressure, is produced beginning at 3 to 4 months of gestation, approaching 75% to 80% of adult levels at the time of birth. Plasma levels of albumin and other necessary proteins for binding of drugs are lower in newborns and even lower in premature infants. The lower ability of the newborn to bind drug to plasma proteins results in greater levels of free drug. At approximately 1 year of age, its activity reaches adult levels.

There is little glucuronyl transferase activity in the fetal liver. This enzyme is responsible for the metabolic breakdown of bilirubin. Hyperbilirubinemia may develop in term infants within the first days of life. Bilirubin production as a result of the breakdown of RBCs and enterohepatic circulation is increased because of the aforementioned depressed activity of glucuronyl transferase that is required for hepatic conjugation. Bilirubin levels of 6 to 8 mg/100 mL are not uncommon in term infants. However, premature infants may have levels as high as 10 to 12 mg/mL on the third day of life. Phototherapy and, in rare cases, exchange transfusion are used to avoid the development of encephalopathy (kernicterus). In infants with hyperbilirubinemia, it is imperative that a determination of physiologic versus pathologic jaundice be determined.

Concentrations of clotting factors in the premature infant and the newborn are low; however, hepatic synthesis of essential clotting factors reaches adult levels during the first week after birth. In utero, the liver is the organ responsible for hematopoiesis, but by 4 to 6 weeks after birth, this function is assumed by the bone marrow.

Temperature Regulation

The neonate is decidedly disadvantaged in the ability to regulate body temperature. Large surface area, poor insulation, a small mass

from which heat is generated, and the inability to shiver all contribute to the problem of thermoregulation.

The neonate has a minimal ability to shiver, so sympathetic stimulation of brown fat metabolism (nonshivering thermogenesis [NST]) increases heat production. NST is the neonate's defense against hypothermia. It is metabolically driven heat production that does not involve muscular work. Brown fat stores located in the scapulae, axillae, the mediastinum, and in the retroperitoneal space surrounding the kidneys are metabolically active and contain a high density of mitochondria. Hypothermia stimulates the release of norepinephrine, which acts on brown fat to uncouple oxidative phosphorylation.[30] Heat production follows an increase in the basal metabolic rate stimulated through the release of anterior pituitary hormones.

Perioperative hypothermia has many contributing causes, including a cold operating room environment, anesthetic-induced vasodilation, the infusion of room-temperature intravenous fluids, evaporative heat loss from opened body cavities, use of cool irrigating solutions, and the inspiration of cool/dry anesthetic gases.

It is well recognized that the thermoregulatory response is inhibited by anesthetic agents. Core body temperature may decrease as much as 1° C to 3° C. Heat loss occurs as a result of the internal redistribution of heat, reduced metabolism and heat production, increased heat loss to the environment, and the effects of anesthetic agents on thermoregulatory control. Heat loss occurs more rapidly in neonates because of limited heat production (NST) and the body surface/body weight ratio. The skin (particularly of the premature neonate) is thinner and has less subcutaneous tissue, increasing the rate of evaporative heat loss.[31-34]

Radiant heat loss is responsible for the majority of heat loss.[28] It occurs with the transfer of heat to the environment and is dependent on the temperature differences between the neonate and the environment. Radiant heat loss may be minimized by wrapping the neonate in a warm blanket and isolating the skin from the cold operating table, effectively decreasing the transfer of heat. Radiant heat lamps may be used to maintain temperature during surgical positioning and preparation. Radiant heat lamps increase the temperature of the air between the neonate and the lamps, thereby minimizing radiant heat loss. However, radiant heat lamps are ineffective when operating room personnel or large objects are placed between the lamp and the patient. In addition, the placement of a radiant heat lamp in close proximity to the neonate may produce thermal injury.

An example of conductive heat loss includes placing the neonate on a cold operating table, resulting in heat transfer from the neonate to the table and thereby causing a decrease in core body temperature. Conductive heat loss is minimized with the use of warmed irrigating solutions, the use of warm blankets or heated forced-air blankets to cover the nonoperative areas of the patient, and the prewarming of the operating room. Covering the head with a stockinette or reflective cap dramatically decreases conductive heat loss. The neonate's head may account for up to 60% of the total heat loss during the perioperative period.

Convective heat loss is precipitated by moving air currents. The operating room air circulation is changed 6 to 12 times per hour and, in conjunction with cool ambient temperatures, increases heat loss. The air surrounding the body is warmed and subsequently rises, being replaced by the cooler ambient air. To minimize convective heat loss, the ambient air temperature must be increased. Prudent practice is to preheat the operating room to 26° C for premature and neonatal surgical patients. The premature infant or neonate arrives in the operating room in a heated Isolette and is immediately covered with a warm blanket before being transferred to the operating table. Convective heat loss may be increased when wet cloth is in contact with the infant. Wet diapers and blankets soiled with preparation solutions must be replaced and not allowed to remain in contact with the skin.

Evaporative heat loss occurs through the vaporization of liquid from body cavities and the respiratory tract. Evaporative heat loss is either sensible loss (the evaporation of sweat) or insensible loss (the evaporation of water through the skin). The thin-skinned premature infant is particularly susceptible to insensible evaporative heat loss. Sensible evaporative heat loss may be prevented by removing wet clothing or blankets and thoroughly drying the neonate. Insensible evaporative heat loss may be mitigated by increasing the relative humidity of the operating room, covering the patient with a plastic barrier, and using warmed irrigating solutions. Insensible respiratory tract evaporative heat loss may be prevented with humidification of the inspired gases, which requires attentive temperature monitoring to avoid superheating of airway gases and subsequent airway burns. The addition of in-line humidifiers to the patient breathing circuit adds to the complexity and weight, perhaps increasing the likelihood of unintended tracheal extubation. These humidifiers also may contribute to unintended increases in core body temperature during lengthy surgical procedures. The use of a passive heat and moisture exchanger, added between the patient circuit and endotracheal tube, has been of questionable efficacy.[35,36]

Iatrogenic increases in core body temperature also may occur. Attentiveness in covering the neonate may result in progressive increases in core temperature during prolonged surgical procedures. These steady increases in core temperature may be aggravated by the previous administration of atropine. Surgical procedures also may affect thermoregulation.

ANESTHETIC PHARMACOLOGIC CONSIDERATIONS IN THE NEONATE

Physiologic characteristics that modify the pharmacokinetic (what the body does to the drug) and pharmacodynamic (what the drug does to the body) activity in the neonate include differences in total body water (TBW) composition; immaturity of metabolic degradation pathways; reduced protein binding; immaturity of the blood-brain barrier; greater proportion of blood flow to the brain, heart, liver, and lungs; reduced glomerular filtration; smaller functional residual capacity; and increased minute ventilation.

Pharmacokinetics

Several age-related differences in absorption, distribution, metabolism, and elimination effect pharmacologic responses in the neonate. Absorption and distribution are increased via an increased cardiac output per kilogram of body weight, protein binding limits, body composition, and the immaturity of the blood-brain barrier. Elimination is decreased due to immature metabolic pathways and renal immaturity.

Cardiac Output

Resting cardiac output in the newborn is approximately 200 mL/kg/min. This means faster circulation times that are capable of delivering and removing drugs from their sites of action at a higher rate.

Body Composition

Total body water and extracellular fluid (ECF) are increased in neonates and fall proportionately with postnatal age. The percentage of body weight contributed by fat is 3% in a 1.5-kg premature neonate, 12% in a term neonate. The proportion of fat further doubles by 4 to 5 months of age. These body component changes

TABLE 47-8 Fluid Compartment Volumes

	Premature	Infant	Child	Adult
Total body water (TBW)	80%-90%	75%	65%-70%	55%-60%
Extracellular fluid (ECF)	50%-60%	40%	30%	20%
Intracellular fluid (ICF)	60%	35%	40%	40%

affect volumes of distribution of drugs. Water-soluble drugs such as neuromuscular blocking drugs (NMBDs) distribute rapidly into the ECF, but enter cells more slowly. The initial dose of water-soluble drugs is consequently higher in the neonate than in the child or adult. Delayed awakening occurs because central nervous system (CNS) concentration remains higher than that observed in older children as a consequence of this reduced redistribution.[37] Table 47-8 illustrates the changes in TBW, intracellular fluid (ICF), and extracellular fluid (ECF) during stages of maturation.

Protein Binding

Protein binding of parenterally administered drugs can be diminished in the neonate. Drugs that are normally highly protein bound can have a greater free fraction of the drug and theoretically a greater pharmacologic effect. Albumin and alpha-1 acid glycoprotein (AAG) concentrations are reduced in neonates, but are similar to those in adults by 5 to 6 months. Plasma albumin concentrations approximate adult values by 5 months of age and are lowest in preterm neonates. Binding capacity approaches adult values by 1 year of age.

Blood-Brain Barrier

The blood-brain barrier (BBB) restricts diffusion of compounds between blood and brain. It is immature in neonates, which can have clinical consequences. Small molecules access fetal and neonatal brains more easily than adult brains. BBB function improves gradually, possibly reaching maturity at term. Drugs bound to plasma proteins will not normally cross the BBB. However, the unbound lipophilic drugs passively diffuse across the BBB to achieve equilibrium very quickly. This may contribute to the tendency of drugs like the local anesthetics to produce seizures in neonates. Specific active transport systems across the BBB can be affected by CNS pathology, thereby changing the clinical effects of opioids and other compounds.[37,38]

Metabolism

Generally, due to a large proportion of the cardiac output that traverses the liver in the neonate, there is a more rapid clearance of drugs. However, phase I cytochrome P-450 (CYP) dependent reactions (e.g., oxidation, reduction, hydrolysis) are not fully developed, making some anesthetic-related drugs last longer than anticipated. These processes are fully developed within the first week of life, with remaining cytochrome-dependent metabolic pathways continuing to increase during the first 3 months of life.[39] Phase II reactions (conjugation reactions) increase water solubility to promote renal excretion, and this process is underdeveloped in neonates. Consequently, normal pediatric doses should not be given until the infant has reached the age of 1 month. Some cytochrome-dependent reactions can be induced prior to delivery when the mother is exposed to certain drugs and cigarette smoke.[40,41]

The neonate lacks the capacity to efficiently conjugate bilirubin (decreased glucuronyl transferase activity) and metabolize acetaminophen, chloramphenicol, and sulfonamides. Although the necessary enzyme systems are present at birth, enzyme activity is reduced, increasing drug elimination half-lives.[42-46]

Excretion

Most anesthesia-related drugs are eliminated by the kidney. In the neonate, GFR and tubular function is reduced, particularly in those infants born at less than 34 weeks. However, renal function reaches adult levels by 8 to 12 months of age. Healthy preterm and full-term neonates have relatively normal renal drug clearance by 3 to 4 weeks of age.

Pharmacodynamics

Pharmacodynamics describes the physiologic and pharmacologic mechanisms of drugs. The actions of a drug and its receptor are influenced by the number and type of receptors present and the action of the drug in the receptor population. Neonates can have significant differences in their dynamic response to drugs.

Nicotinic Acetylcholine Receptor

In its fetal form, the nicotinic acetylcholine receptor remains open longer after binding the acetylcholine, protecting or increasing the safety factor of neuromuscular transmission, and this could account for the neonate's resistance to muscle relaxants.[47] As it transitions into its adult form, the receptor open time is decreased after binding, resulting in less propensity for generation of an action potential, manifesting as less resistance to muscle relaxants. There is also a reduction in acetylcholine release in the neuromuscular junction in the neonate, which could account for the increased sensitivity to nondepolarizing muscle relaxants.[48] These opposing factors make a neonate's response to a neuromuscular blocking agent occasionally unpredictable.

Opioid Receptors

The mu (μ) and kappa (κ) receptors are responsible for the respiratory depression associated with opioids. In the neonate, changes in the number and affinity of these receptors may account for the increased respiratory depression that results when opioids are used.

γ-Aminobutyric Acid Receptor

Conventional thought is that the action of general anesthetics may be associated with activation of γ-aminobutyric acid (GABA) receptors.[49,50] The number of $GABA_A$ receptors in the neonate are only one third that of the adult, and half of these receptors have a high affinity for binding with benzodiazepines and other anesthetics.[51] The potency of anesthetics and benzodiazepines in neonates could be explained by the high affinity of these receptors.

DRUGS USED IN NEONATAL ANESTHESIA

Inhalation Agents

Inhaled anesthetic agents equilibrate more rapidly in neonates due to an increased level of ventilation in relation to FRC; increased cardiac output, which is directed mainly to the vessel-rich group of tissues; and reduced solubility of the inhaled anesthetics in blood. In addition, their decreased distribution of adipose tissue and decreased muscle mass affect the rate of equilibration among the alveoli, blood, and brain. The minimum alveolar concentration (MAC) of the inhalation anesthetics is less in neonates than in infants. Neonates have a somewhat lower MAC, which peaks at around 30 days of age and decreases thereafter (Figure 47-6). The anesthetic implication is that induction in this patient population is more rapid and the development of cardiovascular side effects occurs sooner. The margin of safety between adequate anesthesia

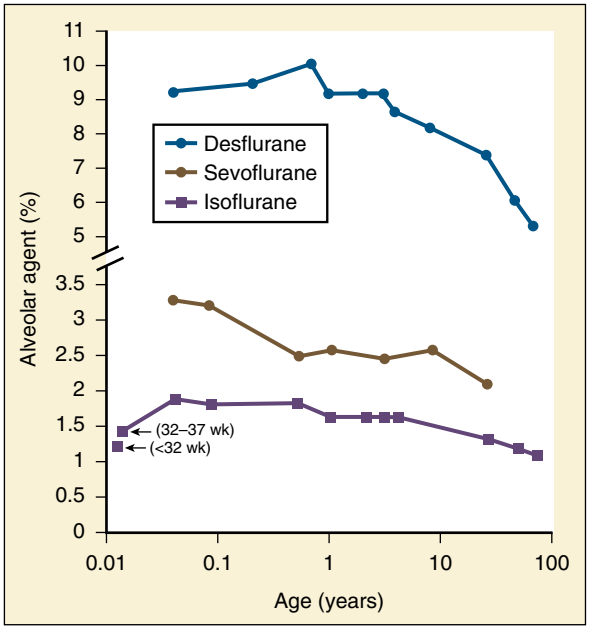

FIGURE **47-6** Effect of age on MAC of anesthetic gases. The MAC of anesthetic gases is dependent on age. MAC is higher at birth than in adults and increases until peaking at 3 to 6 months. The values at 1 year of age are closer to the adult values. (From Greeley WJ. Pediatric anesthesia. In Miller RD, ed. *Atlas of Anesthesia*. Vol 7. Philadelphia: Churchill Livingstone; 1999, 55.)

and significant cardiopulmonary depression is very narrow. Elimination of inhalation agents, and therefore recovery, is also rapid, provided that cardiopulmonary function is not depressed.

In neonates there is both left-to-right and right-to-left intracardiac shunting. In the presence of a left-to-right shunt, there is no increase in anesthetic uptake. However, when there is a right-to-left shunt, there is a slowing of the rate of rise of the alveolar concentration of inhaled agent due to the decrease in the anesthetic concentration in the blood of the arterial system. The clinical implication of a right-to-left intracardiac shunt is that these neonates could have a prolonged induction time.

Potent inhalation agents all depress ventilation in a dose-dependent manner and increase the risk of apnea. Likewise, they readily depress the myocardium and blood pressure because of immature compensatory mechanisms.

Intravenous Agents

Neonates and infants have a higher proportion of cardiac output delivered to vessel-rich tissues (i.e., heart, brain, kidneys, and liver). Intravenously administered drugs are readily taken up by these tissues and are subsequently redistributed to tissues less well perfused (muscle and fat). Intravenously administered drugs may have a prolonged duration of action in neonates and infants because of decreased percentages of muscle and fat. The CNS effects of opioids also may be prolonged because of the immaturity of the blood-brain barrier.[44] Anesthetists have historically been hesitant to use opioids because of their perceived toxicity profile in neonates, particularly morphine. Fentanyl is well tolerated even in the most critical neonates. It is now understood that appropriate anesthetic drugs are necessary for neonatal procedures.[52] Significant amounts of anesthetic drugs may be required for complex neonatal procedures.[53,54] Although some pharmacodynamic evidence suggests that intravenously administered anesthetic doses should be reduced, one must also recall the effect of increased body water. Increased doses of propofol and also ketamine are required, presumably because of a greater volume of distribution.[37,38,55] In most circumstances, when a neonate requires some type of surgical intervention, intravenous access is established prior to arrival in the operating room.

TABLE 47-9 Effective Doses (ED_{95}) of Clinical Neuromuscular Blocking Drugs (mcg/kg)

Neuromuscular Blocking Drugs	Neonate	Infant	Child	Adult
Succinylcholine*	620	729	423	290
Atracurium	120	156-175	170-350	110-280
Cisatracurium	—	43	41	50
Vecuronium	47	42-47	56-80	27-56
Rocuronium	600	600	600	300
Pancuronium	—	55	55-81	49-70

*Should be used for emergency airway stabilization in children younger than 12 years. Not for routine intubation.

Neuromuscular Blocking Drugs

Neonates have an increased sensitivity to the effects of NMBDs. The reason for this is both pharmacokinetic and pharmacodynamic. The increased volume of distribution means that a single NMBD dose for the neonate is the same as for the older child, but reduced clearance and increased sensitivity prolong duration. Neuromuscular blocking drugs are highly ionized and have a low lipophilicity, which limits their ability to cross the blood-brain barrier. These pharmacologic properties restrict the distribution of neuromuscular blockers to the ECF compartment, which is larger in the neonate and infant than in the child and adult (see Table 47-8). Increases in ECF volume and the ongoing maturation of neonatal skeletal muscle and acetylcholine receptors affect the pharmacokinetics and pharmacodynamics of neuromuscular blockers. Table 47-9 references the effective doses of neuromuscular blocking drugs in various age groups.

The neuromuscular junction is incompletely developed at birth. The presynaptic release of acetylcholine is slowed at birth compared with that in the adult, which explains the decreased margin of safety for neuromuscular transmission in the neonate. The acetylcholine receptors of the newborn are anatomically different from the adult receptors, which may explain the sensitivity of the neonate to the nondepolarizing class of neuromuscular blockers.

Neonates are more resistant to the effects of succinylcholine than children and adults. This is illustrated by the intravenous ED_{95} for neonates (620 mcg/kg), infants (729 mcg/kg), children (423 mcg/kg), and adults (290 mcg/kg) (see Table 47-9). The increase in dose requirement is in part a result of the increased volume of distribution within the large extracellular compartment. Plasma cholinesterase activity is reduced in neonates; however, the duration of action after a single dose is of expected duration (6 to 10 minutes). A much prolonged duration of action after a single bolus dose would suggest the presence of an inherited deficiency of plasma cholinesterase activity. Succinylcholine is only used for emergency airway control in children under 12 years of age due to the risk of severe hyperkalemia in patients with undiagnosed myopathies.[56]

The selection of a nondepolarizing neuromuscular blocker should take into consideration the desired degree and duration of skeletal muscle paralysis, the immaturity of organ systems, and the associated side effects of the selected relaxant. Interpatient variability in response to these drugs is greater, particularly

in premature infants and neonates. Monitoring of neuromuscular function must be used to guide repeated administration of these drugs in all neonatal patients, just as it should be used in any patient requiring neuromuscular blockade.

Reversal of Neuromuscular Blockade

The neonate is extremely vulnerable if respiration is impaired due to residual paralysis from a relaxant. Neuromuscular blockade should always be reversed unless mechanical ventilation in the postoperative period is planned. The safest treatment of prolonged apnea is sedation and controlled ventilation until the neuromuscular blocker is eliminated.

It can be difficult to judge adequacy of reversal in neonates. The rule of thumb is to observe flexion of the elbows and hips, knee to chest movements, return of abdominal muscle tone, and presence of facial grimacing. Another measurement is the ability to generate a maximum inspiratory force (MIF) greater than 25 cm of water or a crying capacity of more than 15 mL/kg.[57] Neonates are capable of generating an MIF of −70 cm H_2O with the first few breaths after birth.[58] An MIF of at least −32 cm H_2O has been found to correspond with leg lift, which is indicative of the adequacy of ventilatory reserve required before tracheal extubation.[59] If a peripheral nerve stimulator is used, the train-of-four should demonstrate the standard 90% recovery of the train-of-four.[60]

The two anticholinesterase drugs for reversal of neuromuscular blockade are neostigmine (0.05 to 0.07 mg/kg) and edrophonium (0.5 to 1.0 mg/kg). Neostigmine is routinely used. An anticholinergic agent, atropine (0.02 mg/kg) or glycopyrrolate (0.01 mg/kg), should be given prior to the anticholinesterase to prevent cholinergic side effects. Due to similarities in time to onset and duration of action, glycopyrrolate is usually combined with neostigmine and atropine with edrophonium.

Drug Preservatives

Premature neonates have a reduced ability to metabolize the preservatives benzyl alcohol and sodium benzoate. This accumulation of benzoic acid results in the "benzyl alcohol gasping syndrome," with deterioration of multiple organ systems, severe metabolic acidosis, and gasping respirations. These agents can produce severe CNS toxicity, seizures, and permanent brain damage. Use of preservative-free drugs and solutions is essential.[61]

FLUID MANAGEMENT

Neonatal fluid management varies based on gestational age, birth weight, rate of caloric expenditure and growth, ratio of evaporative surface area to body weight, the degree of renal functional maturation and reserve, and the TBW.[62] Total body water accounts for approximately 75% of body weight in the neonate. This high percentage of TBW results from expansion of the extracellular fluid compartment, which may account for 50% of the TBW. In the first few days of life, a term neonate can lose 5% to 15% of its body weight. Urine output is low, and if the neonate is kept warm and covered, fluid requirements are relatively low, as little as 40 to 60 mL/kg/day.[63,64] Box 47-2 shows the common electrolyte requirements in the newborn.

Assessing Fluid Requirements

In the neonatal period, several physiologic and physical factors can affect fluid requirements. Basically, the smaller the infant, the larger the percentage of body water to total body weight. With the smaller amount of body fat, the major part of body weight is water. The combination of uncontrollable renal loss and a large insensible water loss make the neonate prone to dehydration and hemodynamic instability. There are numerous physical observations that can assist in estimating the fluid status of the patient. Table 47-10 illustrates some of those clinical signs.[65]

Anesthesia and surgery have a significant effect on fluid homeostasis and renal function. The combination of vasodilation, myocardial depression, and blood pressure changes may alter fluid compartment dynamics, vascular capacitance, and/or organ blood flow. The renin-angiotensin system is inhibited as a result of anesthesia.

Water Requirements

Holliday published a seminal work identifying caloric requirements of the "average" hospitalized infant based on body weight. [63] A secondary finding was that the water requirement in milliliters was equivalent to the total energy expended in calories. Table 47-11 gives the water requirements of newborns.

Several things should be considered in planning the fluid management in the neonatal surgical patient:

- Dehydration present before preoperative fasting
- Fluid deficit due to fasting
- Maintenance requirements during anesthesia/surgery
- Estimated third-space loss
- Alterations in body temperature

BOX 47-2

Common Intravenous Fluid and Electrolyte Requirements in the Newborn

Glucose

- Most newborns require 2-4 mg/kg/min.
- SGA/LGA infants may require greater than 15 mg/kg/min on days 1 to 3 of life.
- Glucose tolerance may fluctuate significantly in very low- and extremely low-birth-weight (VLBW and ELBW) infants.

Sodium

- Most neonates require no sodium for the first 24 hours of life.
- On day 2 and beyond, most newborns receive 2 to 4 mEq/kg/day.
- Sodium requirement may change dramatically in response to gastrointestinal, genitourinary, or transcutaneous losses or drug or metabolic effects.
- The ELBW infant may have huge transcutaneous losses, requiring meticulous monitoring and replacement.

Potassium

- Requirements for potassium are minimal for the first 24 to 48 hours of life.
- Subsequently, maintenance delivery is about 1 to 3 mEq/kg/day, always in the presence of a normal urine output.
- Serum levels in the newborn, especially VLBW and ELBW, are higher than in older infants.
- Replace gastrointestinal, genitourinary, or iatrogenic losses cautiously.

Calcium

- Requirements for calcium range between 200 and 400 mg/kg/day (calcium gluconate).
- Requirements for calcium vary with gestational age, history of asphyxia, and growth disturbances (e.g., SGA, LGA).
- Serum levels can be obtained for total Ca^{2+} and/or ionized Ca^{2+}.

From Gregory GA, Brett C. Neonatology for anesthesiologists. In Davis PJ, Cladis FP, Motoyama EK, eds. *Smith's Anesthesia for Infants and Children*. 8th ed. Philadelphia: Mosby; 2011:515.
LGA, Large for gestational age; *SGA*, small for gestational age.

TABLE 47-10 Clinical Signs and Symptoms for Estimation of Severity of Dehydration in Infants

	DEGREE OF DEHYDRATION		
Clinical Signs	**Mild**	**Moderate**	**Severe**
Weight loss (%)	5	10	15
Behavior	Normal	Irritable	Hyperirritable to lethargic
Thirst	Slight	Moderate	Intense
Mucous membranes	May be normal	Dry	Parched
Tears	Present	±	Absent
Anterior fontanelle	Flat	±	Sunken
Skin turgor	Normal	±	Increased

From McClain CD, McManus ML. Fluid management. In Cote CJ, et al, eds. *A Practice of Anesthesia for Infants and Children*. 5th ed. Philadelphia: Saunders; 2013:170.

TABLE 47-11 Water Requirements of Newborns

	WATER REQUIREMENT (ML/KG/24 HR) BY AGE		
Birth Weight (g)	**1-2 Days Old**	**3-7 Days Old**	**7-30 Days Old**
<750	100-250	149-300	120-180
749-1000	80-150	100-150	120-180
1000-1500	60-100	80-150	120-180
>1500	60-80	100-150	120-180

From Merves MH. Neonatology. In Tschudy MM, Arcara KM, eds. *The Harriet Lane Handbook*. 19th ed. Philadelphia: Mosby; 2012, 455-475.

Because of the nature of the surgical interventions required by neonates, most will have had their fluid status managed in a neonatal unit. If that is not the case, during the time of preoperative evaluation, deficits should be determined and dehydration or electrolyte imbalance should be reversed. Other issues, such as acidosis, low hemoglobin, poor urine output, and poor perfusion should be resolved.[17]

There is no evidence that children who are denied oral fluids for more than 6 hours preoperatively benefit in terms of intraoperative gastric volume and pH compared with children permitted unlimited fluids up to 2 hours preoperatively. Children permitted fluids have a more comfortable preoperative experience in terms of thirst and hunger.

Current guidelines suggest that for otherwise healthy infants (younger than 2 yr), children (2-16 yr), and adults, fasting from the intake of clear liquids at least 2 hours before elective procedures requiring general anesthesia, regional anesthesia, or sedation/analgesia (i.e., monitored anesthesia care) should be maintained. Examples of clear liquids include, but are not limited to, water, fruit juices without pulp, carbonated beverages, clear tea, and black coffee. The volume of liquid ingested is less important than the type of liquid ingested. It is appropriate to fast from intake of breast milk at least 4 hours and infant formula at least 6 hours before elective procedures. Fast from intake of a light meal or nonhuman milk should be 6 hours or more. Fried or fatty foods or meat may prolong gastric emptying time. Additional fasting time (e.g., 8 hours or more) may be needed in these cases. Both the amount and type of food ingested must be considered when determining an appropriate fasting period[66,67] (see Table 37-2).

Knowledge of the caloric requirements of the neonate can be used to estimate the maintenance fluid requirements. The classic "4-2-1" rule takes the caloric expenditure into consideration because it is calculated by body weight. A neonate weighing less than 10 kg will require 100 mL/kg/day or 4 mL/kg/hr.

Fluid deficits are a result of preoperative fasting or excessive gastrointestinal (GI) losses. Neonates receiving adequate preoperative maintenance will have no deficit and will require no deficit replacement calculated into the fluid management plan. If there has not been adequate maintenance, the fluid deficit can be calculated by multiplying the hourly maintenance rate by the number of hours without feeding. Total deficit restoration may require several hours or even days in the smallest babies. The goal is to restore and preserve the cardiovascular stability and renal perfusion.

In the presence of total parenteral nutrition (TPN), the amount of glucose/kg/min, as well as other components such as sodium, potassium, and calcium currently being administered, should be noted. If at all possible, the TPN should be maintained without interruption. If it must be discontinued, glucose must be monitored vigilantly and dextrose added to the fluid management plan.

Third-space losses need to be replaced with a solution that does not contain glucose (e.g., normal saline, lactated Ringer's, or Plasma-Lyte). In those patients with abdominal lesions such as gastroschisis or necrotizing enterocolitis (NEC), the third-space losses can be very large. These babies may need as much as 25 to 100 mL/kg/hr to replace fluid loss.

Urine osmolality and specific gravity and serum osmolality are important indices in managing intraoperative fluids in neonates. They provide information as to the need for fluid, solute, and electrolyte replacement. Normal urine osmolality in the neonate ranges from 49 to 800 mOsm/L, with an average of 270 mOsm/L. Osmolality should be maintained between 200 and 400 mOsm/L and specific gravity between 1.006 and 1.012. Serum osmolality ranges between 270 and 280 mOsm/kg.[68] Hyperosmolar states can result in intraventricular hemorrhage or kidney damage.

Fluid Management of the Premature Infant

Proper fluid management of the premature infant requires an understanding of several variables: the extensive variability in body fluid composition, renal maturation, neuroendocrine control of intravascular fluid status, and insensible fluid loss with age.[69] Renal tubular function develops after week 24 of gestation, and nephrons mature by week 36.[62] The premature infant has a lower GFR and immature tubular function. The immature kidneys are unable to excrete sodium and excess fluid. The inability to concentrate urine secondary to the inability to reabsorb sodium leads to the excretion of large quantities of dilute urine. Therefore, underestimation of fluid needs leads to more serious consequences than overestimation of fluid needs.[64,70]

Glucose homeostasis is volatile in the premature neonate. Hypoglycemia can be attributed to inadequate glycogen stores and deficient gluconeogenesis. Symptoms of hypoglycemia are jitteriness, cyanosis, apnea, lethargy, hypotonia, and seizures. If not treated rapidly, hypoglycemia in the preterm neonate can lead to neurologic damage. Preterm and SGA neonates can have a glucose requirement of 8 to 10 mg/kg/min to prevent hypoglycemia. Glucose as a D_5 or D_{10} solution followed by a 10% to 15% dextrose solution can be titrated to maintain a serum glucose level greater than 40 mg/dL.[17] It is as important to avoid hyperglycemia, which can result in intraventricular hemorrhage, osmotic diuresis, dehydration, and release of insulin, leading to hypoglycemia.

Electrolyte abnormalities are often seen in preterm neonates. Hypernatremia may result if water loss is greater than sodium

depletion combined with abnormal renal tubular function. Hypokalemia can result from respiratory alkalosis or aggressive diuresis. Hyperkalemia can be caused by infusion of large amounts of potassium-containing fluids.

Blood Replacement

Over the first 6 months of life, many physiologic changes are occurring that can complicate the decision to replace blood in the neonatal surgical patient. Fetal hemoglobin (HgbF), which has a higher affinity for oxygen than adult hemoglobin, can range from 70% to 80% of the neonate's total hemoglobin at birth. It can be as high as 97% in the preterm infant.[71] The clinical implication of this is that the younger the baby, the higher the fraction of HgbF and thus the lower the oxygen-carrying capacity and oxygen delivery to the tissues.

Replacement of blood loss is critical in the surgical neonate, especially the preterm infant. Their blood volume is very small (85 to 100 mL/kg), and a loss of 10 mL could be approximately 10% of total blood volume. The clinical indication for blood administration should not be some predetermined percentage of total blood volume. Maintaining oxygen-carrying capacity and oxygen delivery to peripheral tissues and improving coagulation are the primary concerns. The transfusion trigger in this age group will need to be at higher hemoglobin levels than the older infant or child. Rapid blood loss in neonates can result in cardiovascular complications quicker than in the adult; therefore, transfusion may be required sooner. In the sick neonate scheduled for surgery and particularly in the preterm baby scheduled for surgery, the hematocrit should be approximately 30% to 40%. The decision to transfuse should be based on the underlying and current cardiorespiratory status, ongoing blood loss, anticipated further blood loss, and baseline hemoglobin. Another concern is the presence of congenital heart disease or lung disease, resulting in a decreased ability to oxygenate blood.

The accurate measurement of blood loss in neonates and infants is crucial to any replacement regimen. The margin of safety is reduced in the neonate, and because the oxygen consumption is twice that of the adult, a smaller percentage of blood loss will result in cardiovascular instability. A major cause of cardiac arrest in pediatric surgical patients results from hypovolemia from blood loss and hyperkalemia from transfusion of stored blood.[72] It is mandatory to monitor loss by the weighing of sponges, the use of small calibrated suction containers, and vigilant visual estimation of ongoing blood loss. Every 1 of sponge weight is equal to 1 mL of blood loss.

As noted earlier, volume expansion (VE) in neonates or infants during anesthesia may lead to fluid overload and can be difficult to assess. New techniques to evaluate transfusion effects include the use of transesophageal Doppler (TED), a noninvasive cardiac output monitoring technique, which can provide a comprehensive estimation of the volume status. TED-derived indexed stroke volume measurement is useful to predict and follow VE responsiveness in neonates and infants without myocardial dysfunction.[73]

Estimating Allowable Blood Loss

The estimated blood volume (EBV) and allowable blood loss (ABL) must be calculated prior to induction of anesthesia for any procedure in which blood loss is expected. Estimated blood volume is calculated based on age and body weight (see Table 47-2).

A predetermined acceptable low hematocrit is identified based on the clinical situation and the baby's health. Maximum allowable blood loss (MABL) can be calculated with the formula below in which Hct_0 is the original hematocrit, H_l is the lowest acceptable hematocrit, and H_a is the average hematocrit, $(Hc + {}_0 + Hc_1)/2$.

$$MABL = wt\ (kg) \times EBV \times (Hct_0 - Hct_1)/Hct_a$$

Example: A surgical neonate who weighs 4 kg is going to have an abdominal procedure. Beginning hematocrit is 42%. The lowest acceptable hematocrit is 30%. The MABL for this patient is 106 mL.

$$MABL = 4 \times 320 \times (42 - 30)/(42 + 30)/2 = 106$$

When the blood loss equals or exceeds the calculated allowable loss, transfusion should be considered. The volume of packed red blood cells (RBCs) to be infused may be determined by the following formula:

$$\text{Packed RBCs (mL)} = \frac{(\text{Blood loss} - \text{ABL}) \times \text{Desired hematocrit (30\%)}}{\text{Hematocrit of PRBCs (75\%)}}$$

Using the previous example of a 4-kg infant, with a total blood loss of 100 mL, the volume of packed RBCs (PRBCs) would be 175 − 106 × 30/75 = 27.6 mL.

The administration of PRBCs can lead to a significant increase in the plasma potassium and cardiac arrest. Hyperkalemia associated with massive transfusion has been reported to be the most common cause of arrest in noncardiac procedures.[74] Rapid administration via handheld syringes and small-gauge catheters (23-gauge or smaller) of PRBCs stored less than 2 weeks also have been reported to result in hyperkalemia.[75] Hypocalcemia and cardiovascular instability can result from the rapid administration of blood due to the amount of citrate contained in the stored blood. Whole blood should not be used, and irradiated blood should be given only in immunocompromised patients. Irradiation accelerates the leakage of potassium from red blood cells into serum. To reduce the risk of hyperkalemia, washed or fresh (i.e., less than 7 days old) PRBCs should be used.[71]

ANESTHETIC EQUIPMENT

Anatomic differences in the face and upper airway of neonates affect the design of the masks, laryngoscopes, and tracheal tubes. Physiologically, the need to minimize the resistance and dead space has design implications for breathing systems, connectors, and tubes. Disposable, humidified pediatric circle systems are more commonly used in neonates for some important reasons. These systems have low compliance, they are lightweight, and with the addition of plastic valves have eliminated the high resistance associated with older systems. They also offer a more reliable method of monitoring end-tidal carbon dioxide. Ventilation is usually controlled in these patients, reducing the deleterious effects of the work of breathing in the spontaneously ventilating baby.

The anesthesia machine should be equipped to deliver air when nitrous oxide is not desirable, for example, in the neonate undergoing some type of abdominal procedure or when it is necessary to reduce the inspired oxygen concentration to avoid retinopathy of prematurity (ROP). Most patients are mechanically ventilated. The newest anesthesia machines have ventilators designed to deliver very small tidal volumes at appropriately high rates and pressures. It is also possible to adapt and use the ventilators used in the neonatal intensive care units (NICUs). However, this is not the most desirable method of mechanical ventilation in the operating room. In some pediatric centers, with the most critically ill neonates, certain operative procedures are actually performed in the NICU to avoid disturbing the delicately balanced ventilation patterns and to preserve cardiorespiratory stability.

The anatomy of the upper airway makes a straight blade preferable. The blade is placed along the right side of the mouth,

TABLE 47-12 Recommended Endotracheal Tube Sizes

Neonatal Age	Endotracheal Tube Size
Preterm neonate	2.0-3.0
Full-term neonate	3.0-3.5
3 months to 1 year of age	4.0

sweeping the tongue to the left. The epiglottis is picked up with the tip of the blade and the tracheal inlet exposed. The tube is inserted with the convex side to the left. When the tip approaches the glottic opening, rotate the tube 90 degrees counterclockwise. The advantage of one over another is the characteristic that allows the large tongue of the neonate to be manipulated out of the visual field. There are also modifications of straight blades that allow insufflation of oxygen into the pharynx during intubation.

Oral endotracheal tube (OET) size for neonates cannot be calculated by formula because of the rapid growth during the immediate postnatal period. It can be determined from a table based on kilogram weight (Table 47-12). It is common for the full-term neonate to accommodate a 3.0 mm OET and a premature infant (less than 2 kg) to need a 2.5-mm OET. A clinical shortcut is to look at the size of the tip of the fifth ("pinkie") finger. It is wise to select a tube that will result in an air leak at 20 to 30 cm H_2O pressure to avoid postextubation airway edema.

The length of the trachea (vocal cords to carina) in neonates and infants up to 1 year varies from 5 to 9 cm. Insertion distance of an oral endotracheal tube should be less than 10 cm, falling within the 8 to 10 cm range.

Traditionally, it was taught that in pediatric patients up to 8 years of age, the use of an uncuffed endotracheal tube was the accepted method for endotracheal airway management. The standard of practice in neonatal anesthesia has been the use of uncuffed endotracheal tubes for reasons of airway resistance and tracheal damage from inflated cuffs. The proper use of specially made cuffed endotracheal tubes under certain clinical situations is considered acceptable. Indications include the use of a cuffed OET in certain thoracic or abdominal procedures or when high-pressure or complex ventilatory modes are planned. The advantages include a decrease in air pollution, the use of lower fresh gas flow rates (more economical), the possible avoidance of repeated laryngoscopy and intubation to assess and seal leaks, more accurate capnography readings, and better control of ventilation.[76-78]

Monitoring of the neonate during anesthesia is important in detecting those small changes that can be very significant because of their smaller physiologic margin of safety. The anesthetist should not devalue the use of clinical observation skills—hearing, seeing, touching, and the rest.

The precordial or esophageal stethoscope, as the case allows, is a simple means of assessing heart rate, rhythm, and sound, and secondarily extrapolating vascular volume. Continuous ECG monitoring is used for monitoring of not only heart rate but also for detection of arrhythmias, particularly in the baby that has electrolyte imbalances. Pulse oximetry is the standard of care for all patients in a critical care or surgical environment. The other standard monitoring parameters are blood pressure; inspired oxygen concentration; end-tidal carbon dioxide and inhalation agent concentration; and peak airway and end-expiratory pressure monitoring. Neuromuscular monitoring is technically difficult in the neonate, particularly preterm and very low-birth-weight babies, owing to their small muscle mass. The use of needle electrodes must be justified because of the risk of infection and bleeding.[17] The monitoring of urine output is difficult due to technical problems of size of the catheters and accessibility of the patient.

PREOPERATIVE ASSESSMENT

The perioperative management of any neonate is determined by the nature of the surgical procedure, the gestational age at birth, postgestational age at surgery, and associated medical conditions.

Gestational Age and Postgestational Age at Surgery

The gestational age, postgestational age, and birth weight are critical to the determination of the physiologic development of the neonate. The history of the delivery and the immediate postdelivery course can influence the choice of anesthetic technique and assist in anticipating possible postoperative complications.

One method of classification notes that preterm neonates are classified as *borderline preterm* (36 to 37 weeks' gestation); *moderately preterm* (31 to 36 weeks' gestation); and *severely preterm* (24 to 30 weeks' gestation).[79] Neonates can be classified according to their weight, as well as their gestational age. Full term is considered to be 37 to 42 weeks' gestation. Large for gestational age (LGA) is defined as weight above the 90th percentile at gestational age. Small for gestational age (SGA) refers to weight below the 10th percentile at gestational age. Low birth weight (LBW) is a weight below 2500 g, very low birth weight (VLBW) is a weight below 1500 g, and extremely low birth weight (ELBW) is below 1000 g. Full-term neonates that are SGA often present with conditions requiring surgical intervention. SGA neonates have different pathophysiologic problems from preterm infants (less than 37 weeks' gestation) of the same weight.[80] Gestational age and neonatal problems are closely related. Maternal health problems also can have significant implications for all neonates. Table 47-13 lists several common maternal problems and the possible associated neonatal sequelae.

Prematurity

Because of advances in neonatal medicine, many preterm babies born at exceptionally early gestational age and extremely low birth weights are surviving to be challenged with a plethora of unique diseases and they pose many anesthetic challenges. The premature infant is not an infrequent visitor to the operating room for either elective or emergent surgical intervention. Prematurity presents its own set of complications, which include anemia, intraventricular hemorrhage, periodic apnea accompanied by bradycardia, and chronic respiratory dysfunction. It is beyond the scope of this chapter to address all issues regarding preterm neonates and anesthetic implications.

Premature neonates are challenging to evaluate, and considerable controversy exists regarding the appropriateness of elective surgical intervention and proper postoperative care. Postgestational age (gestational age + postnatal age) should be determined at the time of the anesthetic evaluation. Premature infants of less than 60 weeks' postgestational age have the greatest risk of experiencing postanesthetic complications. The manifestations of prematurity are thought to occur as a result of inadequate development of respiratory drive and immature cardiovascular responses to hypoxia and hypercapnia. Therefore, premature infants have a significant risk of postoperative apnea and bradycardia during the first 24 hours after general anesthesia.[81-83] Box 47-3 lists contributing factors that may influence the occurrence of apnea in premature infants.

Apnea in the Premature Infant

Apnea of prematurity (AOP) is a significant clinical problem manifested by an unstable respiratory rhythm reflecting the immaturity

TABLE 47-13 Maternal History with Commonly Associated Neonatal Problems

Maternal History	Anticipated Neonatal Sequelae
Rh-ABO incompatibility	Hemolytic anemia Hyperbilirubinemia Kernicterus
Toxemia	Small for gestational age and its associated problems Muscle relaxant interaction after magnesium therapy
Hypertension	Small for gestational age and its associated problems
Drug addiction	Withdrawal and small for gestational age
Infection	Sepsis, thrombocytopenia, viral infection
Hemorrhage	Anemia, shock
Diabetes	Hypoglycemia, birth trauma, large or small for gestational age and associated problems
Polyhydramnios	TE fistula, anencephaly, multiple anomalies
Oligohydramnios	Renal hypoplasia, pulmonary hypoplasia
Cephalopelvic disproportion	Birth trauma, hyperbilirubinemia, fractures
Alcoholism	Hypoglycemia, congenital malformation, fetal alcohol syndrome, small for gestational age and associated problems

Adapted from Ghazal EA, et al. Preoperative evaluation premedication and induction of anesthesia. In Cote CJ, et al, eds. *A Practice of Anesthesia for Infants and Children*. 5th ed. Philadelphia: Saunders; 2013:31-63.
TE, Transesophageal.

of respiratory control systems. Ventilatory responses to hypoxia and hypercarbia are impaired and inhibitory reflexes are exaggerated in the neonate. Treatment strategies attempt to stabilize the respiratory rhythm. Caffeine and continuous positive airway pressure (CPAP) remain the primary treatment modalities; the methylxanthines such as caffeine are presumed to work through blockade of adenosine receptors. AOP typically resolves with maturation suggesting increased myelination of the brainstem.[84,85]

Apneas occur in 7% of babies born between 34 and 35 weeks, 14% born between 32 and 33 weeks, 54% between 30 and 31 weeks, and in 80% of neonates born earlier than 30 weeks' gestation. Although most apneas resolve by the time the infant reaches 37 weeks' postconceptional age (PCA), 80% of very low-birth-weight infants, in one study, still had significant apneas at 37 weeks. There are a variety of conditions that predispose an infant to apnea, including CNS lesions, infections and sepsis, ambient temperature fluctuations, cardiac abnormalities, metabolic derangements, anemia, upper airway structural abnormalities, necrotizing enterocolitis, drug administration (including opiates and general anesthetics), and possibly gastroesophageal reflux. Various monitoring techniques are used to detect apneic episodes although pulse oximetry and abdominal-pressure transduction are the most common. As noted above, standard therapy is with caffeine 5 to 10 mg/kg.[84-86]

Apnea Prevention and Treatment. Anesthetic techniques with the lowest risk for postoperative apnea appear to be a spinal anesthetic without sedation for lower extremity procedures. Spinals have a high failure rate in neonates (up to 20%). Supplementation with light general anesthesia may be necessary; however, that raises the risk of apnea postoperatively. General anesthesia with desflurane or sevoflurane is preferred due to the rapid emergence. Opiates and intravenous sedatives should be avoided. Caudal anesthesia is also popular. It is performed after instituting a light general anesthetic. Local anesthetic agents are used alone without opiates or other additives.

BOX 47-3

Factors Contributing to the Incidence of Apnea in the Premature Infant

Physiologic Contributors
- Inadequate development of respiratory centers
- Incomplete myelination of central nervous system
- Incomplete cardiovascular development leading to altered responses to stress

Metabolic Contributors
- Hypothermia
- Hypoglycemia
- Hypocalcemia
- Acidosis
- Respiratory instability

Anesthetic Contributors
- Residual anesthetics, opiates, relaxants, sedatives
- Prolonged intubation and ventilation

Intubation provides the safest airway control. Extubation should occur when the infant is wide awake with vigorous purposeful movement. All infants under 62 weeks' postmenstrual age (PMA) should be monitored postoperatively with an oxygen saturation monitor and an abdominal pressure transducer. Infants over 62 weeks' PMA with a significant history of apnea or respiratory disease also should be monitored. Infants over 62 weeks' PMA can be discharged following minor surgery after an appropriate period of recovery (4 hours minimum) if they are stable and otherwise healthy. Higher-risk infants require an overnight stay and monitoring.[84-87]

Preanesthetic Assessment and Neonatal Anesthetic Implications

The anesthesia provider is responsible for coordinating preoperative evaluation and acting as a gatekeeper to ensure that undue risks are minimized. Valuable information is obtained from those caring for the baby in the NICU. It is often best to alter the infant's plan of therapy as little as possible (i.e., management of ventilation, acid base status, glucose, etc). Consultation with the neonatologist is essential.

A birth history is important. A thorough review of the pregnancy course, complications such as gestational hypertension, preeclampsia, gestational diabetes, vaginal bleeding, infections, and any other pertinent information is helpful. Any cigarette, alcohol, or drug (prescription, herbal, illicit) use should be ascertained.

All of the information gathered during the assessment will lead to the anesthetic plan based on the implications of all the transitioning body systems. Table 47-14 gives the characteristics of the body system and the anesthetic implications.

System Review and Examination

The two body systems that are of primary interest in a preanesthetic system review are the respiratory and cardiovascular systems. However, there are other important metabolic and structural problems that can have a significant impact on the anesthesia plan. When performing a physical assessment, one should look carefully for congenital anomalies. A rule of thumb is that if there is one anomaly present, there are probably more because many occur in

TABLE 47-14 Preanesthetic Assessment and Neonatal Anesthetic Implication

System	Characteristics	Anesthetic Implications
Central Nervous System	Incomplete myelination	Judicious use of muscle relaxants
	Lack of cerebral autoregulation	Cerebral perfusion pressure control
	Cortical activity	Pain relief/adequate level of anesthesia
	Retinopathy of prematurity (ROP)	Oxygen saturation (94%-98%)
	Birth history	A review of the pregnancy, including complications such as pregnancy-induced hypertension, preeclampsia, gestational diabetes, vaginal bleeding, infections, and falls; also any cigarette, alcohol, or drug (prescription, herbal, illicit) use
Respiratory		
Birth History		Weeks of gestation, neonatal intensive care unit admission, history of intubation or oxygen requirement, maternal complications including infection with herpes simplex virus (HSV) or HIV, and prenatal smoke exposure
Mechanical	↓ Lung compliance ↓ Elastic recoil ↓ Rigidity of chest wall ↓ $\dot{V}/\dot{Q}$ due to lung fluid ↑ Fatigue of respiratory muscles ↓ Coordination, nose/mouth breathing	Assist or control ventilation during general anesthesia Do not obstruct nasal passages
Anatomic	Large tongue	
	Position of larynx, epiglottis, vocal folds, subglottic region	
Biochemical	Response to hypercapnia not potentiated by hypoxia	Avoid hypoxia Maintain normothermia
Reflex	Hering-Breuer reflex Periodic breathing Apnea	Apnea/no desaturation/stimulation Stimulation/airway support
Cardiovascular	↓ Myocardial contractility/↓ myocardial compliance	Maintain adequate volume Maintain heart rate
	CO rate dependent	Use vagolytic agents
	Vagotonic	
	Limited sympathetic innervation	
	Reactive pulmonary vasculature	Avoid hypoxemia resulting in ↓ PBF and possible shunting
	PDA/FO shunting	
Renal	↓ GFR	Maintain vascular volume/CO
	↓ Tubular function	Avoid overhydration
	Low glucose threshold	Avoid excess glucose (0.5-1.0 g/kg)
Hepatic	Depressed hepatic enzymes	Judicious use of drugs metabolized by liver
	↓ Metabolism and clearance of drugs Altered (decreased) protein binding Hypoglycemia due to ↓ glycogen stores Low prothrombin levels	 Vitamin K (1 mg) before surgery
Hematologic	Fetal hemoglobin (does not readily release O_2 to tissues) Oxyhemoglobin curve shifted left	Avoid hypoxia

CO, Cardiac output; *GFR*, glomerular filtration rate; *PBF*, pulmonary blood flow; *PDA/FO*, patent ductus arteriosus/foramen ovale.

clusters, labeled a syndrome. These problems can occur most often in small- and large-for-gestational-age neonates (Box 47-4).

Head and Neck Abnormalities

Any abnormality of the head and/or neck should raise concerns regarding airway management. The shape and size of the head, with or without the presence of pathology, can make airway management difficult. The small mouth and large tongue can obstruct the airway during mask ventilation. Neonates have very small nares, and when obstructed by an anesthesia facemask, they do not convert to mouth breathing, particularly if the mouth is being held closed. A nasogastric tube can obstruct half of the neonate's airway and should be placed orally. A small and/or receding chin, as seen in Pierre Robin and Treacher Collins syndromes, may make direct laryngoscopy and visualization of the glottis impossible, requiring other types of airway management. Cleft lip, with or without cleft palate, may complicate intubation. Anomalies such as cystic hygroma or hemangioma of the neck can produce upper airway obstruction. In the case of a preterm neonate, it should also be determined whether the patient has retinopathy of prematurity (ROP), cataracts, or glaucoma.

BOX **47-4**

Common Metabolic and Structural Problems in SGA and LGA Infants

Small for Gestational Age (SGA)
- Congenital anomalies
- Chromosomal abnormalities
- Chronic intrauterine infection
- Heat loss
- Asphyxia
- Metabolic abnormalities (hypoglycemia, hypocalcemia)
- Polycythemia/hyperbilirubinemia

Large for Gestational Age (LGA)
- Birth injury (brachial, phrenic nerve, fractured clavicle)
- Asphyxia
- Meconium aspiration
- Metabolic abnormalities (hypoglycemia, hypocalcemia)
- Polycythemia/hyperbilirubinemia

From Gregory GA, Brett C. Neonatology for anesthesiologists. In: Davis PJ, Cladis FP, Motoyama EK, eds. *Smith's Anesthesia for Infants and Children*. 8th ed. Philadelphia: Mosby; 2011:515.

Atropine administration could result in significant increases in intraocular pressure and further damage to the eye.

Respiratory System Abnormalities

The incidence of respiratory distress syndrome (RDS) and bronchopulmonary dysplasia (BPD) is inversely related to gestational age at birth. The onset of RDS can be as early as 6 hours after birth. The symptoms include tachypnea, retractions, grunting, and oxygen desaturation. BPD is a disease of the newborn that manifests as a need for supplemental oxygen, lower airway obstruction and air trapping, carbon dioxide retention, atelectasis, bronchiolitis, and bronchopneumonia. Oxygen toxicity, barotrauma of positive-pressure ventilation on immature lungs, and endotracheal intubation have been reported as causative factors. Management of the patient's oxygenation can be challenging. Careful monitoring of the acid-base status, the use of increased peak inspiratory pressure, and positive end-expiratory pressure may be needed to maintain oxygenation during surgery.

Cardiovascular System Abnormalities

In evaluation of the neonate's cardiovascular system, several variables should be examined: heart rate, blood pressure patterns, skin color, intensity of peripheral pulses, and capillary filling time. Presence of a murmur or abnormal heart sound, low urine output, metabolic acidosis, dysrhythmias, or cardiomegaly, alone or in combination, raises the concern of some type of congenital heart lesion, and these patients should be evaluated with a chest x-ray, ECG, echocardiogram, and other indicated cardiac tests. The results of these diagnostic tests will allow for effective planning of the anesthetic, decreasing the possibility of complications (Table 47-15).

It is beyond the scope of this chapter to discuss all anesthetic implications of congenital heart disease in the neonate; however, there are some important assessment points[88]:
- Direction and flow through any shunt
- Baseline oxygenation
- Dependence of the systemic or pulmonary circulation on flow through the ductus arteriosus
- The presence and size of any obstruction to blood flow
- Heart failure (high output, low output, or hypoxic)
- Drug therapy
- Antibiotic prophylaxis against bacterial endocarditis

Central Nervous System Abnormalities

An assessment of the CNS should include the status of the infant's intracranial pressure and intracranial compliance. Intraventricular hemorrhage (IVH) is almost exclusively seen in preterm babies. There is spontaneous bleeding into and around the lateral ventricles of the brain. The more preterm the neonate is and the smaller the weight, the more likely it is that intraventricular hemorrhage will be found. The hemorrhage is usually the result of RDS, hypoxic-ischemic injury, and/or episodes of acute blood pressure fluctuation that rapidly increase or decrease cerebral blood flow. The classic example is laryngoscopy in the presence of inadequate anesthesia.[89] The symptoms of IVH include hypotonia, apnea, seizures, loss of sucking reflex, and a bulging anterior fontanelle. Particular evaluation of the neonate with myelomeningocele (spina bifida) is discussed subsequently.

Preoperative Laboratory Values

Neonates who are premature (younger than 60 weeks' postgestational age), those with concurrent cardiopulmonary disease, and babies in whom major blood loss is anticipated during the surgical procedure should have a complete blood count, electrolytes, blood gases, and serum osmolality measured. The test values will assist in the fluid, electrolyte, and blood replacement during the surgical procedure. Other testing will be dictated by the history and physical.

Preoperative Treatment of Significance for Anesthesia

Many of the preexisting conditions in the neonate will require medical treatment. Table 47-16 illustrates some of the preoperative drugs and their anesthetic implications.

Parental preparation is important. In the case of institutions that do not have a NICU, the patient will have been transferred in from another institution, and the parents may still be in the institution where the baby was delivered. It is imperative that the parents be prepared and the informed consent for anesthesia be obtained. Often this must be done via telephone, or consent is obtained from the father only, who may have accompanied the neonate to the NICU. The anxiety of the parents of a newborn with a serious illness requiring surgical intervention is very high. The anesthetist will foster trust and confidence through a courteous and understandable explanation of the anesthetic experience.

Regional Anesthesia in the Neonate

Regional anesthesia in the neonate can be a useful option when the risks of complications from general anesthesia and endotracheal intubation are very high. These techniques have allowed surgical procedures to be done on critically ill neonates under minimal general anesthesia, with considerable reduction in the need for CNS depressant drugs. The use of regional techniques must be associated with sufficient knowledge about the various techniques, as well as adherence to adequate dosage guidelines and other safety precautions. Regional anesthesia may offer advantages in these patients, although opinions differ on which techniques are appropriate.[90,91] The preterm baby with respiratory distress syndrome and the former preterm baby who is at higher risk for postanesthetic apnea are example candidates for regional anesthesia. An additional benefit to the use of regional anesthesia in this age group is postoperative pain control. The two most common techniques used in the neonate are the spinal and caudal epidural blocks.

TABLE 47-15 Pathophysiology and Clinical Picture of Congenital Heart Defects

Lesion Type	Pathophysiology	Clinical Signs and Symptoms
Shunt Lesion Without Outflow Tract Obstruction		
Atrial septal defects Ventricular septal defects Atrioventricular canal defects Patent ductus arteriosus Aortopulmonary window	Intracardiac L-R shunt Increased pulmonary blood flow	CHF (systemic and pulmonary vascular congestion) No cyanosis (unless high pulmonary blood flow leads to increased left atrial pressure, pulmonary edema, and intrapulmonary $\dot{V}/\dot{Q}$ mismatch and shunt)
Shunt Lesions with Right Ventricular Outflow Tract Obstruction		
Tetralogy of Fallot Ebstein's anomaly Pulmonary stenosis with atrial or ventricular septal defects Eisenmenger's syndrome	Intracardiac R-L shunt Decreased pulmonary blood flow	Cyanosis
Transposition Physiology (Intercirculatory Mixing)		
Dextro-transposition of the great arteries	Intracardiac L-R and R-L shunts are equal	Cyanosis
Single-Ventricle Physiology		
One-Ventricle Lesions		
Hypoplastic left heart syndrome Tricuspid atresia Double-inlet left ventricle	Mixing of systemic and pulmonary venous blood Parallel distribution of pulmonary and systemic blood flow determined by relative circuit resistances	CHF (systemic and pulmonary vascular congestion) Cyanosis
Two-Ventricle Lesions		
Truncus arteriosus Tetralogy of Fallot with pulmonary atresia Severe neonatal aortic stenosis		
Left Ventricular Obstructive Lesions		
Mitral Stenosis		
Valvular Cor triatriatum		
Aortic Stenosis		
Valvular Subvalvular (subaortic membrane) Supravalvular (Williams-Beuren syndrome)	Left ventricular pressure overload from aortic lesions Increased left atrial pressure from left ventricular systolic and diastolic dysfunction; OR obstruction to left atrial emptying	CHF (if high left atrial pressure leads to pulmonary vascular congestion) No cyanosis (unless high left atrial pressure leads to pulmonary edema and intrapulmonary $\dot{V}/\dot{Q}$ mismatch and shunt)
Coarctation		
Shone's syndrome (mitral stenosis, aortic stenosis, coarctation)		
Mixing of Systemic and Pulmonary Venous Blood with Series Circulation		
Partial anomalous pulmonary venous return (PAPVR) Total anomalous pulmonary venous return (TAPVR)	Mixing of systemic and pulmonary venous blood Increased pulmonary blood flow	*CHF* Systemic and pulmonary vascular congestion; pulmonary vascular congestion is severe if pulmonary venous obstruction No cyanosis *PAPVR* Cyanosis *TAPVR* Exacerbated if pulmonary venous obstruction leads to pulmonary edema and intrapulmonary $\dot{V}/\dot{Q}$ mismatch and shunt

From Davis PJ, Cladis FP, Motoyama EK. *Smith's Anesthesia for Infants and Children*. 8th ed. Philadelphia: Mosby; 2011.
CHF, Congestive heart failure;.

TABLE 47-16 Preoperative Treatment of Significance for Anesthesia

Drug	Implication
Diuretics for heart failure bronchopulmonary dysplasia (BPD)	Hypokalemia
Digoxin for heart failure	ECG abnormalities
Steroids for BPD	Hyperglycemia
Immunocompromised	
Anticonvulsants	Cardiac arrhythmia Potent inducer of hepatic enzymes
Indomethacin	Increases risk of bleeding Displaces bilirubin from protein-binding sites Transient hyponatremia
Renal Impairment	
Theophylline or caffeine	Significant toxic side effects; convulsions, tachycardia, tremor
Prostaglandins E_1 or E_2	Ventilatory depression and apnea Hypotension, cerebral irritability, seizures, tachycardia, pyrexia, cardiac irritability, transient oliguria, increased gastric acid
Prostacyclin	Hypotension Inhibition of platelet aggregation Rebound PPHN with withdrawal

PPHN, Persistent pulmonary hypertension of the newborn.

Anatomic differences in the neonate must be considered, particularly the location of the terminal end of the spinal cord, the dural sac, and the volume of cerebrospinal fluid (CSF). The spinal cord extends as far as L3 in the newborn and does not reach the adult position of L1 until 1 year of age. The dural sac extends to S3 to S4 in these babies and does not reach the adult position of S1 until approximately 1 year of age (see Figure 47-5). The volume of CSF is twice that of the adult (4 mL/kg vs 2 mL/kg). This dilutes the local anesthetics injected and could explain the higher dose requirements and shorter duration of analgesia.

Patients in this age group have been reported to have fairly stable cardiovascular responses to regional anesthesia. Bradycardia and hypotension are not often seen. It is thought that this could be due to the immature sympathetic nervous system or the proportionately small blood volume in the lower limbs, decreasing the amount of venous pooling.[92,93] The ventilatory response to the regional anesthetic is related to the level of the block. With a level as high as T2 to T4, there could be intercostal muscle weakness that requires the dependence on diaphragmatic movement for tidal breathing, but tidal volume and respiratory rate are not usually affected.[94]

There are pharmacologic considerations when regional anesthesia is used in neonates. The extracellular space is larger. This means the initial dose of local anesthetic will be diluted into a larger volume of distribution, resulting in a lower initial plasma peak concentration. Local anesthetics, particularly the amides, are broken down more slowly in neonates due to immature hepatic degradation. The major elimination pathway for ester local anesthetics is hydrolysis via plasma cholinesterases, and these levels are lower in the neonate as well. The demonstrations of the previous differences are shorter duration of blocks when compared with adults and larger initial doses of local anesthetic per kilogram to achieve the same extent of blockade.

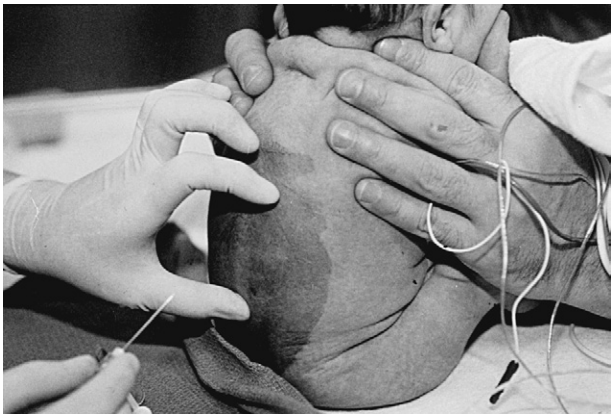

FIGURE 47-7 Spinal block performed in sitting position. Note that the head is in neutral position to prevent airway obstruction. (From Suresh S, et al. Regional anesthesia. In Cote CJ, et al, eds. *A Practice of Anesthesia for Infants and Children*. 5th ed. Philadelphia: Saunders; 2013.)

Most neonates will have a regional technique performed after the induction of general anesthesia because of the age of the patient and the possibility of agitation and continuous movement affecting the placement and success of the block.[95] The use of ultrasound-guided blocks has decreased the risk of complications associated with the placement of spinal and epidural needles and catheters, as well as enabled monitoring the spread of local anesthetics.[96] It is difficult to assess a dermatome level, because these patients are nonverbal.

Spinal Anesthesia

The use of spinal anesthesia in neonates and infants was common in the early part of the twentieth century, but its use declined with the advent of safer general anesthesia in this young age group. There has been a renewed interest in various regional techniques in select patients such as those at risk for apnea of prematurity. It is useful in neonates and infants when presenting for surgical procedures of the lower abdomen. Caudal blocks are common in neonatal anesthesia because of their simplicity and ability to provide excellent analgesia, which helps avoid large amounts of opioid analgesia with potential side effects that can impair recovery. Spinal anesthesia via catheters in the younger infant, neonate, and even preterm neonate remains controversial. The potential for such invasive maneuvers themselves to augment risk can be argued to outweigh the benefits.[97]

Spinal anesthesia can be performed in the sitting or lateral position; however, the neck should be extended to prevent airway obstruction (Figure 47-7). The lumbar puncture is performed at the L3 to L4 or L4 to L5 interspace because the spinal cord ends at L3 in the neonate. A 1½-inch, 22-gauge needle is inserted, and even with this small needle, resistance can be felt when the needle enters the ligamentum flavum, and the characteristic "pop" occurs when the needle enters the subarachnoid space. The distance is approximately 1 cm.[98] Large amounts of local anesthetics are necessary to produce an adequate block (0.14 mL/kg of bupivacaine 0.5%). When the local anesthetic is injected, the neonate should be immediately placed in the supine position, and the legs should be secured with tape to prevent them from being raised for any reason.

Caudal Anesthesia

Caudal anesthesia is the most commonly used regional block in pediatric anesthesia. It can be used for any procedure involving

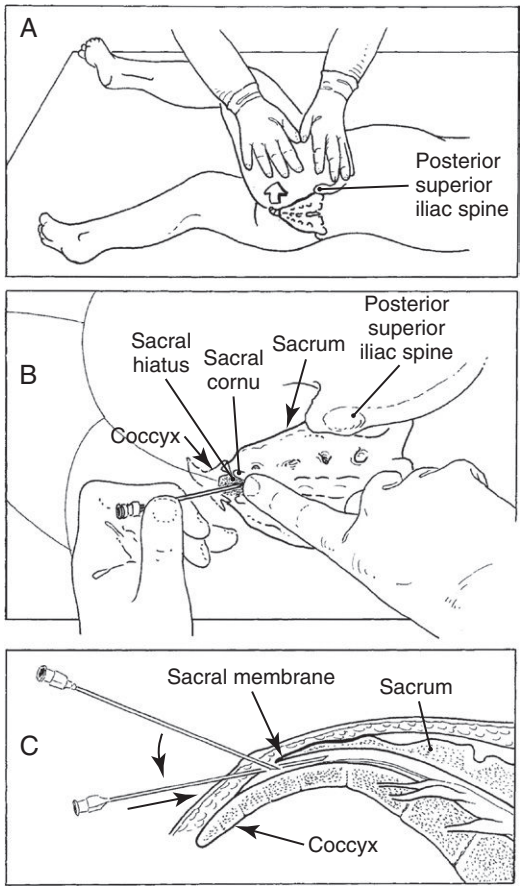

FIGURE **47-8** Performing a caudal block. (From Suresh S, et al. Regional anesthesia. In Cote CJ, et al, eds. *A Practice of Anesthesia for Infants and Children*. 5th ed. Philadelphia: Saunders; 2013.)

innervation from the sacral, lumbar, or lower-thoracic dermatomes.[93] In the youngest patients, the caudal block can be used as an adjunct to general anesthesia or solely for postoperative analgesia. In the neonate, it is most often placed after induction of general anesthesia prior to the beginning of the surgical procedure.

With ultrasound, it is now possible to visualize the injection of local anesthetics in the caudal space as well as monitor the cranial spread. The use of ultrasound is highly recommended in neonates who receive concomitant general anesthesia, but is much more difficult to use in the awake and mobile baby.[91] The patient is placed in the lateral position with the upper knee flexed (Figure 47-8). The landmarks are identified: the tip of the coccyx to fix the midline and the sacral cornua on either side of the sacral hiatus. These landmarks form the points of an equilateral triangle with the tip resting over the sacral hiatus. A 22-gauge needle is placed bevel-up at a 45-degree angle to the skin. When the sacrococcygeal membrane is punctured, a distinctive loss of resistance is felt, and the angle of the needle is reduced and advanced cephalad. Saline should be used with the loss of resistance technique because the use of air has been reported to cause both intravascular air embolism as well as permanent spinal cord injury. With aspiration, if there is not CSF or blood, the local anesthetic can be administered. Any local anesthetic can be used. The volume of the local anesthetic determines the height of the block. Volumes of 1.2 to 1.5 mL/kg provide analgesia and anesthesia to the T-4 to T-6 dermatome. No matter which local anesthetic is used, the concentration is adjusted to deliver no more than 2.5 mg/kg. The addition of epinephrine (1:200,000) or clonidine (1 to 2 mcg/kg) will prolong the block significantly.

ANESTHETIC CONSIDERATIONS FOR SELECTED CASES

Gastrointestinal

Anesthesia and surgery in neonates and infants present unique challenges. The acuity of intraabdominal procedures can range from a simple hernia repair in a healthy neonate to a complex abdominal/thoracic procedure in a critically ill preterm infant.

Pyloric Stenosis

Pyloric stenosis is an obstructive lesion characterized by an "olive-shaped" enlargement of the pylorus muscle. It is a common gastrointestinal anomaly, particularly in males. It is usually diagnosed between 2 and 12 weeks of life, and clinical symptoms include nonbilious postprandial emesis that becomes more projectile with time, a palpable pylorus, and visible peristaltic waves. The procedure to correct the problem is a pyloromyotomy.

Historically, pyloric stenosis was considered an emergency situation. However, as with medical progress on many fronts, the procedure is now considered semi-elective. The use of laparoscopy has become standard and has greatly facilitated the surgical course.[99] It is not wise to anesthetize a neonate emergently for this procedure if the baby is dehydrated or has electrolyte abnormalities. Fluid, electrolyte, and acid-base balance should be corrected prior to anesthesia.

Prior to induction, the neonate's stomach must be emptied via orogastric tube. Some anesthetists will irrigate the stomach via the orogastric tube with warm normal saline until the aspirate is clear and minimal. Others will tilt the baby in various directions to evacuate the remaining contents.

After preoxygenation, the induction should be a modified rapid sequence with properly applied cricoid pressure and gentle positive-pressure ventilation via mask. An awake oral intubation is also common. Oral endotracheal intubation is mandated to protect the airway from any gastric contents that may be residual. Maintenance can be with inhalation anesthetics or in combination with intravenous drugs. These babies should be extubated awake.

Postoperatively, these patients, particularly a preterm or SGA neonate, could exhibit drowsiness, lethargy, or apnea. This could be attributed to electrolyte abnormalities, postgestational age, or residual anesthetics.

Inguinal Hernia

Inguinal hernia is particularly prevalent in the preterm infant. The surgical problem presents the possibility of incarceration of the small bowel in the hernia defect, resulting in ischemia and tissue death. Also of concern is the potential injury to the ipsilateral testicle. These babies routinely have hernia repair prior to discharge from the NICU. The surgical approach can be the standard abdominal incision, or in some centers, laparoscopy is the preferred technology. In most situations, the contralateral side is explored to rule out the presence of another defect because of the high incidence of bilateral involvement. When this procedure is performed by a urologist, the contralateral side is most often not explored.

Because of the many possible patient issues, the anesthetic technique must be tailored for each patient. The most frequent indication for the awake caudal technique in neonates is inguinal hernia repair.[91] Inhalation or intravenous induction is acceptable, as well as airway management with a mask, laryngeal mask airway (LMA), or endotracheal tube. The use of the laparoscopic

approach will necessitate the use of the endotracheal tube. Maintenance can be accomplished with inhalation anesthetics or in combination with intravenous drugs. Small neonates who are at risk for postoperative apnea may benefit from spinal anesthesia.[100]

Congenital Diaphragmatic Hernia

A congenital diaphragmatic hernia (CDH) is a defect of the diaphragm that allows extrusion of the abdominal contents into the thoracic cavity. This disorder has an incidence of 1 in 2500 live births.[101,102] The herniated abdominal contents act as a space-occupying lesion and prevent normal lung growth and development. The diagnosis of congenital diaphragmatic hernia should be made prenatally in virtually all cases where routine maternal ultrasonography is available. The prognosis can be predicted based on whether it is isolated and assessment of lung size and/or the position of the liver. Prenatal intervention may be offered in fetuses that have a predicted poor outcome. The aim of this procedure is to reverse the key determinant of survival—pulmonary hypoplasia. Percutaneous fetal endoscopic tracheal occlusion by a balloon is a minimally invasive procedure that has been shown to be safe and yields a 50% survival rate in severe cases. The outcome can be predicted by the gestational age at birth, the lung size before and after balloon placement, and whether the balloon has been removed prenatally.[103] The lung affected to the greatest extent is on the ipsilateral side, but the other lung can be affected as well. The lungs have reduced-sized bronchi, less bronchial branching, decreased alveolar surface area, and abnormal pulmonary vasculature. There is a thickening of the arteriolar smooth muscle extending to the capillary level of the alveoli. This results in increased pulmonary artery pressure and causes right-to-left shunting.[104]

Neonates with CDH present immediately after birth with dyspnea, tachypnea, cyanosis, absence of breath sounds on the affected side, and severe retractions. Their physical appearance is a scaphoid abdomen and a barrel chest. Between 44% and 66% of neonates with CDH have other anomalies, particularly heart lesions.

The emergent nature of the repair has been reexamined in the past decade, and more emphasis is now placed on stabilizing pulmonary hypertension and other medical issues. A recent review of these cases noted that the median age at operation was 4 days and the median weight was 3800 g. Laparotomy, thoracoscopic repair, and a laparoscopic approach may be used.[105]

Studies published by Azarow et al.[106] and Jona[107] in the late 1990s demonstrated that the ventilation parameters were a major factor in survival of these babies. Permissive hypercarbia with high-frequency, oscillatory ventilation was most successful in improving outcomes. A thorough assessment of the baby, including laboratory values, radiographic findings, and physical symptoms, is mandatory. Listening to breath sounds will assist in evaluating the degree of ventilation on each side of the chest after intubation. Because of the respiratory manifestations of the problem, most of the patients will be already intubated and have intravenous access and arterial lines in place when they arrive in the operating room. If they are not intubated, an endotracheal tube should be placed after a rapid-sequence induction. If a difficult airway is suspected, an awake intubation should be done.

It is important in these patients to administer an anticholinergic (atropine 0.02 mg/kg) intravenously just prior to induction to prevent the bradycardia during induction. If an awake intubation is planned, some type of analgesia should be used to decrease the stress response of airway instrumentation. Ventilation should be delivered gently to avoid inflating the stomach with air, further compromising the pressure in the chest.

The patient's hemodynamic stability should determine the anesthetic drugs used. The use of inhalation agents and narcotics are guided by the cardiovascular stability. Nitrous oxide should be avoided because it will increase the volume of gastrointestinal tissue and further impair ventilation.

Monitoring must include blood pressure, ECG, pulse oximetry, capnography, temperature, and heart rate. To monitor for right-to-left shunting, oximeter probes should be placed preductal (right upper extremity) and postductal (lower extremity). The use of arterial blood pressure monitoring will not only allow beat-to-beat assessment of blood pressure but also provide an outlet for easier blood sampling. All conditions that can increase pulmonary vascular resistance—hypoxia, hypothermia, or acidosis—must be avoided. Carbon dioxide should be kept at normal or slightly elevated levels and oxygen saturation maintained above 80 mmHg. Any derangement of electrolytes must be corrected quickly and any significant blood loss replaced.

In the event that cardiorespiratory instability prevents the neonate from being transported to the operating room, the anesthetist might be required to administer anesthesia in the NICU while the baby is still on extracorporeal membrane oxygenation (ECMO). Under these circumstances, the recommended anesthetic choice is an opioid and nondepolarizing muscle-relaxant technique instead of an inhalation agent. Postoperative ventilation is required, with the goal of keeping the arterial oxygenation greater than 150 mmHg and slowing weaning to lower oxygen concentrations over a 48- to 72-hour period.[104]

Omphalocele and Gastroschisis

Omphalocele and gastroschisis anomalies are both defects in the abdominal wall that occur during gestation when the visceral organs fail to move from the yolk sac back into the abdominal cavity. It is more common to encounter omphalocele in term newborns and gastroschisis in preterm newborns. There are several differences in the two defects that are noted in Table 47-17. The defects occur at the insertion of the umbilicus. They are often associated with other anomalies. Some of those anomalies might be cardiac, genitourinary (bladder exstrophy), metabolic (e.g., Beckwith-Wiedemann syndrome with macroglossia, hypoglycemia, organomegaly, gigantism), malrotation, Meckel's diverticulum, and intestinal atresia. When the omphalocele is in the epigastric region, cardiac and thoracic problems are more prevalent. If the omphalocele is located in the hypogastric area, cloacal anomalies and exstrophy of the bladder are seen more

TABLE 47-17 Differences Between Gastroschisis and Omphalocele

	Gastroschisis	Omphalocele
Covering membrane	No	Yes
Location of defect	Right of umbilicus	Midline including umbilicus
Umbilical cord insertion	Body wall at normal location	Omphalocele membrane
Herniated abdominal organs	Bowel	Bowel and sometimes liver
Associated anomalies	Uncommon	Very common
Prognostic factors	Condition of bowel	Associated anomalies

From Ledbetter DJ. Congenital abdominal wall defects and reconstruction in pediatric surgery: gastroschisis and omphalocele. *Surg Clin North Am.* 2012;92(3):714.

often.[101] These abdominal wall defects have very different surgical management techniques and outcomes. Gastroschisis outcomes have improved dramatically over the past 4 decades but still comprise the largest group of patients needing bowel transplant. Omphalocele outcomes remain poor overall despite many advances in care. Large omphaloceles are one of the most difficult things to manage in pediatric surgery, and there is no standardized closure technique.[108] Both gastrointestinal anomalies, although very different in presentation, are similar as far as the anesthetic management needed.

A newborn with an omphalocele or gastroschisis is usually brought to the operating room very soon after birth to minimize the possibility of infection, the loss of fluid and heat, and the possible death of bowel tissue. A thorough preoperative evaluation must be done to identify the presence of any of the previously mentioned associated anomalies. Historically, the surgical approach was to immediately attempt primary closure of the defect. This entailed placing a large amount of abdominal contents into a cavity that was not usually large enough, and the result was a significant increase in intraabdominal pressure, which impeded ventilation and caused profound hypotension secondary to aortocaval compression. Over the past decade, surgeons have opted for a staged closure, using a Silastic silo as a temporary housing for the bowel. This silo is sutured to the defect, and over the next 3 to 7 days, the silo is reduced to allow for accommodation of the gastric contents and abdominal-wall stretching. The neonate is usually then brought to surgery for complete closure of the defect.[108-110]

The choice of anesthetic agent and technique is determined by several guiding principles: severe dehydration and massive fluid loss from exposed viscera and internal third-spacing of fluid due to bowel obstruction, hypothermia, the potential for sepsis, associated anomalies, and postoperative ventilation requirements. It is not uncommon for the anesthetist's choice to be an opioid and nondepolarizing muscle relaxant technique; however, even with the use of muscle relaxants, the abdominal wall may not allow primary closure. Ventilatory compromise and decreased organ perfusion are major problems as intraabdominal pressure increases. It is imperative to have adequate intravenous access to infuse large amounts of fluid quickly and invasive monitoring to guide the replacement. A pulse oximeter probe on a lower extremity will indicate whether there is compromise in the perfusion to the lower extremities due to obstruction of venous return.

Postoperative ventilation is mandatory on all of these babies, requiring the continued use of paralytics and sedation with an opioid until their clinical status stabilizes.

Tracheoesophageal Fistula and Esophageal Atresia

Esophageal atresia (EA), with or without tracheoesophageal fistula (TEF) can be suspected prenatally by the presence of polyhydramnios and finding an absent stomach bubble on ultrasound. It is normally diagnosed immediately after birth when an orogastric tube cannot pass into the stomach, when there is coughing and choking after the first feeding, or after recurrent pneumonia associated with feedings.[101] In the past this condition was often lethal. Today there is an expectation of almost 100% survival.[111]

There is a significant association of other serious congenital anomalies in these babies. Some sources report as high as 30% to 50% of newborns with AE and TEF have other anomalies, particularly VACTERL (vertebral anomalies, *a*nal atresia, *c*ardiac, *t*racheo*e*sophageal fistula, *r*enal and *l*imb malformations) syndrome. Preoperative echocardiography is mandatory to exclude both associated cardiac defects and a right-sided aortic arch that occurs in 2.5% of cases. An identified congenital heart defect may need to be managed preoperatively after consultation with a pediatric cardiologist, although surgical correction is almost always performed after the TEF/EA surgery. In the case of a right-sided aortic arch, surgical access to the esophagus and the TEF via the typical right thoracotomy is more hazardous, so a left thoracotomy may be performed.[111]

Esophageal atresia with a distal fistula is the most common presentation of TEF in approximately 80% to 90% of patients.[101] The esophagus ends in a blind pouch, and the distal esophagus forms a fistula with the trachea, usually above the carina. There are other configurations of this anomaly, varied by the location of the fistula and the presence or absence of EA (Figure 47-9). The morbidity and mortality of TEF are directly related to the resulting pulmonary complications from aspiration.[112] The focus of the preoperative preparation should be to minimize the pulmonary complications by discontinuing oral feedings, placement of a tube to suction nasopharyngeal secretions that accumulate in the blind esophageal pouch, maintain the infant in a semirecumbent position to minimize aspiration of secretions, and placement of a gastrostomy tube to prevent excess gastric distention from impairing ventilation. The surgical procedure is performed via a thoracotomy incision, usually on the right side. The sequence of the repair is the ligation of the fistula and then anastomosis of the two ends of the esophagus if possible.

Standard monitors should be used. The cardiorespiratory condition of the neonate should dictate the use of more invasive monitoring techniques such as an arterial line, umbilical or radial. Preductal and postductal oximeter probes should be used.[17] In view of the unknown features and potential problems with airway management of patients with these anomalies, some clinicians advocate

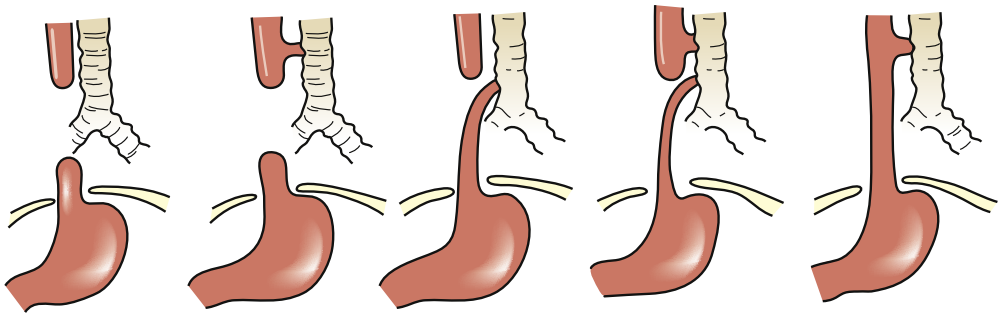

FIGURE **47-9** Anatomic variants and incidence of esophageal atresia with tracheoesophageal fistula. (From Townsend CM, et al. *Sabiston Textbook of Surgery: The Biologic Basis of Modern Surgical Practice*. 19th ed. Philadelphia: Saunders; 2012:1838.)

performing bronchoscopy intraoperatively before intubation and thoracotomy. Bronchoscopy has been used effectively to assess the presence, type, number, size, and location of fistula, as well as to determine or exclude additional fistulas that may otherwise be missed and leave the patient with an ongoing source of aspiration.

The technique of induction should be based on the clinician's evaluation of the airway. Some clinicians feel that an inhalation induction with spontaneous respiration avoids overventilation and reduces the stress of airway manipulation. This technique minimizes the gastric distention from anesthetic gases passing through the fistula and allows proper placement of the endotracheal tube without positive-pressure ventilation. If this technique is used, care must be taken to avoid hypoxemia that will result from the respiratory depression produced by high concentrations of inhalation agents. With any of the described techniques, once the endotracheal tube is placed, proper position must be verified. A common method of verifying the correct position is to actually intubate the right mainstem bronchus and then withdraw the endotracheal tube until breath sounds are heard on the left side of the chest. The tip of the tube is likely between the fistula and the carina (Figure 47-10). Another method, if there is a gastrostomy in place, is to submerge the gastrostomy tube in water and if there are bubbles on ventilation, the fistula is being ventilated and the tube must be repositioned. The bevel of the endotracheal tube should be turned anteriorly to allow the posterior surface of the endotracheal tube to occlude the fistula. In one configuration of TEF, the fistula is located very close to the carina. In this case, the endotracheal tube may need to be placed in the bronchus of the nonoperative lung until the fistula can be ligated. After ligation, the tube can be withdrawn to above the carina.

During the procedure, it is essential to monitor ventilation very carefully. Airway obstruction can occur if the trachea is compressed or if secretions or blood block the openings of the endotracheal tube. This must be corrected immediately.

The neonate without significant pulmonary complications who is awake and moving vigorously is most often extubated in the operating room. Blood and secretions may be present in the endotracheal tube, and it should be suctioned gently prior to removal. If there is any concern about airway obstruction or impaired ventilation, mechanical ventilation should be continued. It is thought that should bag-and-mask ventilation or reintubation be required, undue stress could be placed on the suture lines of the repair with laryngoscopy and neck extension, resulting in damage to the esophagus, necessitating further surgical procedures. Another problem that can occur with early extubation in smaller neonates is an inability to maintain the work of breathing due to preoperative lung disease. If postoperative mechanical ventilation is needed, the endotracheal tube should be positioned 1 cm away from the fistula repair to allow for healing of the suture line. A suction catheter should be clearly marked with a distance for insertion that approximates the distance just above the anastomotic repair.[113] Postoperative pain can be managed with opioids and/or a caudal epidural, placed intraoperatively.

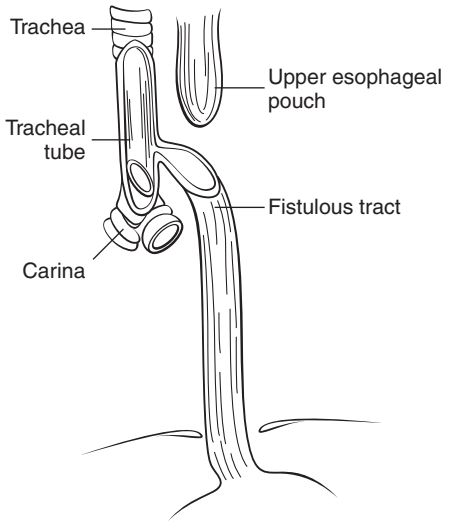

FIGURE **47-10** Correct placement of endotracheal tube—between fistula and carina.

Complications may occur later that could influence anesthetic management. Neonates who have had EA/TEF repair early in life can develop a diverticulum at the site of the old tracheal fistula. This could present problems in the future if inadvertent intubation of the diverticulum occurs. Esophageal stricture could develop at the site of esophageal anastomosis requiring repeated dilation or possible resection.[114]

Malrotation and Midgut Volvulus

Intestinal malrotation in the newborn is usually diagnosed after signs of intestinal obstruction, such as bilious emesis, and corrected with the Ladd procedure.[115] As the intestine is moving from its extraabdominal location during the first trimester of gestation, it can become twisted. The result can be a compromised superior mesenteric artery and intestinal ischemia. This ischemia can cause bowel strangulation, bloody stools, peritonitis, and hypovolemic shock. When this occurs, it is termed *volvulus*.[104]

Many of these neonates are diagnosed in the first week of life when the neonate presents with bilious vomiting, a tender and distended abdomen, and increasing hemodynamic instability. The surgical procedure relieves the obstruction by reducing the volvulus, dividing the fixation bands between the cecum and the duodenum or jejunum, and widening the base of the mesentery.

The major concerns in anesthetic management are airway management, fluid and electrolyte replacement, treatment of sepsis, and postoperative pain management. Any baby with intestinal obstruction will likely have abdominal distention (which could impede diaphragmatic movement) and is at higher risk for aspiration of gastric or intestinal contents. This necessitates the use of a rapid-sequence induction with the proper application of cricoid pressure. If there is concern for difficult airway, awake intubation should be considered. There is likely volume depletion due to peritonitis, ileus, bowel manipulation, and sepsis. It is absolutely necessary to have adequate intravenous access, and it is desirable to have a central line and an arterial line.

The choice of anesthetic agents should be dependent on the neonate's condition. It is not advisable to use nitrous oxide, but other inhalation agents could be acceptable. As with other emergent abdominal procedures, postoperative mechanical ventilation could be required, making the intraoperative choice of an opioid and nondepolarizing muscle relaxant a good choice (Box 47-5).

BOX **47-5**

Advantages of Neuromuscular Blockers in Neonatal Anesthesia

- Controlling efficient ventilation throughout surgery
- Facilitation of surgical procedure
- Reduction of inhalation anesthetic requirements
- Control of the airway via endotracheal tube
- Ability to provide adequate analgesia
- Complete reversibility

Although anesthetic agent choice is not critical, the maintenance of an adequate circulating volume and red blood cells is vital to ensure perfusion of vital organs.

Necrotizing Enterocolitis

NEC is an intestinal inflammation that is a life-threatening emergency situation. It occurs primarily in preterm babies with a gestational age of less than 32 weeks and a weight of less than 1500 g. The etiology of the problem is reported to be secondary to bowel ischemia and immaturity, probable bacterial invasion, and premature oral feeding.[101,104] The origin of infection may be the umbilical cord stump, infection due to circumcision, and similar lesions.[116] Box 47-6 lists the common symptoms of NEC. Diagnosis is confirmed by imaging studies that commonly show fixed dilated intestinal loops, pneumatosis intestinalis, portal vein air, ascites, and pneumoperitoneum. Accompanying laboratory values may show hyperkalemia, hyponatremia, metabolic acidosis, hyperglycemia, or hypoglycemia, and in the most serious cases, signs of disseminated intravascular coagulation.

When an attempt at medical management is unsuccessful, surgical intervention consists of an exploratory laparotomy or laparoscopy with resection of dead bowel, usually a colostomy, and peritoneal lavage.

These neonates are very sick and usually come to the operating room already intubated and on ventilator support. The anesthetic drugs chosen should depend on the patient's condition, but a common choice is a narcotic and relaxant technique. These are thought to be the safest choice in the presence of cardiovascular instability because the inhalation agents may further depress the myocardium and lower the blood pressure to unacceptable levels. Nitrous oxide is avoided, and if there is concern over high oxygen concentrations, saturations can be maintained at a lower level. If cardiac output is low and renal perfusion is below normal, inotropes may be indicated. The amount of third-space loss in these patients is very large and may require multiple blood volumes of crystalloid and colloid combinations to replace intravascular volume. Red blood cells, fresh frozen plasma, and platelets also may be required to increase oxygen-carrying capacity or to treat factor deficiency.[101,104]

The postoperative care should focus on continuation of the fluid resuscitation and cardiorespiratory support and mechanical ventilation until the baby stabilizes.

Imperforate Anus

During the first few days after birth, when there is no passage of meconium, the diagnosis of imperforate anus is considered. The degree of this anomaly can range from a mild stenosis to complete anal atresia that is associated with other anomalies. The VACTERL syndrome contains all the previously mentioned anomalies.[117] In male newborns, the operative procedure may be urgent to allow the passage of meconium via a colostomy. In female newborns, owing to the usual presence of a rectovaginal fistula, the procedure can be delayed for a few weeks. The anesthetic considerations for this neonate are based on the existence of associated anomalies and fluid and electrolyte balance.

BOX 47-6

Common Symptoms of Necrotizing Enterocolitis

- Increased gastric residuals with feeding
- Abdominal distention
- Bilious vomiting
- Lethargy
- Occult or gross rectal bleeding
- Fever
- Hypothermia
- Abdominal mass
- Oliguria
- Jaundice
- Apnea and bradycardia
- Fever

Other Intestinal Obstructive Lesions

Duodenal obstruction, jejunoileal atresia, and meconium ileus can all result in a complete intestinal obstruction. Although each of these pathologies are different in etiology and presentation, the anesthetic management is very much like that for the previously mentioned midgut volvulus.

Neurosurgical

Neonatal Hydrocephalus

Hydrocephalus is usually the result of some existing pathologic process. It is usually due to an obstruction in the CSF or an inability to absorb CSF. The standard treatment is the placement of a shunting catheter from the ventricle of the brain to another location to allow absorption of the fluid. Most often the shunt is placed from the ventricle to the peritoneal cavity. Occasionally the catheter is placed in the right atrium or pleural cavity. In the newborn and neonate, if the hydrocephalus develops slowly, the cranial vault will expand to accommodate the increase in brain bulk. When there is no more ability to expand, intracranial pressure (ICP) begins to increase, and the baby could be in serious trouble. The signs and symptoms of increasing intracranial pressure are a tense anterior fontanelle, irritability, somnolence, and/or vomiting.

Anesthetic management is directed at controlling the ICP and relieving the obstruction. The urgency of the procedure is determined by the preanesthetic assessment of the ICP. The major risk associated with delay is the possible herniation of the brain due to increasing pressure in the cranial vault. Comorbidities such as prematurity and all associated problems must be addressed.

Induction in the presence of increased ICP is usually a rapid-sequence induction and tracheal intubation. A variety of anesthetic agents are acceptable for maintenance, with the goal being to extubate the patient at the end of the procedure. If the neonate is preterm, it is advisable to adjust the oxygen concentration to maintain a lower oxygen saturation. This decreases the risk of ROP. The neurologic status of the neonate could affect the decision to extubate immediately, and mechanical ventilation could be required.

Myelomeningocele

Myelomeningocele is the most common CNS defect that occurs during the first month of gestation. Another common name for this defect is *spina bifida*. It is failure of the neural tube to close, resulting in herniation of the spinal cord and meninges through a defect in the spinal column and back. If the herniation only contains meninges, it is a meningocele. If the herniation contains meninges and neural elements, it is a myelomeningocele. These lesions mostly occur in the lumbosacral region but can occur at any level of the neuroaxis. The repair of the defect is considered urgent and is usually undertaken with the first 24 hours of life to avoid the increasing risk of bacterial contamination of the spinal cord and further deterioration of neural and motor function (Figure 47-11). Most newborns with myelomeningoceles do not have other associated anomalies or congenital heart disease. These neonates, however, often have an Arnold-Chiari malformation.

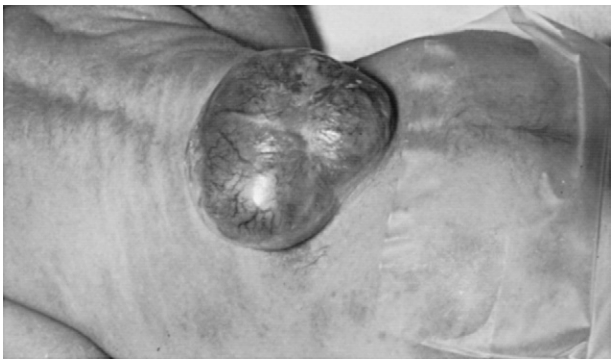

FIGURE **47-11** A lumbar myelomeningocele is covered by a thin layer of skin. (From Kliegman RM, et al. *Nelson Textbook of Pediatrics*. 19th ed. Philadelphia: Saunders; 2011:2001.)

The Arnold-Chiari malformation is a result of the hindbrain being displaced downward into the foramen magnum, resulting in hydrocephalus. This will necessitate the placement of a ventriculoperitoneal shunt, usually during the myelomeningocele repair. There are usually significant neurologic deficits below the level of the lesion, and evaluation of the degree of deficit is important to anesthetic decision making. Preoperative assessment should include a thorough review of all other organ systems to rule out additional congenital anomalies. Minimal laboratory tests should include a blood count and a type of screen for blood.

Routine neonatal monitoring is necessary, and the use of invasive monitoring techniques should be based on the particular newborns status. Positioning and airway management is one of the biggest challenges for the anesthetist. Most of these babies can be induced and intubated in the supine position with the lumbosacral defect supported in a "donut" ring or with strategically placed towels to avoid direct pressure on the dural sac. If the defect is very large or if there is accompanying severe hydrocephalus, it may be necessary to place the neonate in the lateral position for induction and intubation. If there is a suspicion of a difficult airway, the endotracheal tube may be placed with the patient awake, after administration of atropine and preoxygenation. Adequate intravenous access is essential because of the possibility of significant blood loss during the procedure. If the defect is large, the surgeon may be required to undermine a large amount of tissue for closure, resulting in a large blood loss.

Anesthesia can be induced with an inhalation or intravenous technique. After the endotracheal tube is placed, the procedure is performed in the prone position with appropriate protection of all body parts. In some institutions, the use of muscle relaxants is discouraged to allow for stimulation and identification of neural tissue. Anesthesia can be maintained with a variety of drugs, keeping in mind the goal of extubation at the end of the procedure and the possibility of postoperative apnea.

These patients are prone to hypothermia, and conservation of body heat should include warming the operating room to at least 80° F before the procedure and until the baby is draped. Radiant heat lamps should be used during the preparation and positioning of the patient. A forced-air warmer also should be placed underneath the neonate to maintain body temperature. Anesthetic gases should be humidified to prevent heat loss and minimize pulmonary complications. There has been reported an increased sensitivity to latex in these babies. As a precaution, they should be treated as latex allergic, avoiding all products that contain latex.[118,119]

SUMMARY

Despite the advances in neonatal medicine, surgery, and particularly anesthesia, the anesthetic management of critically ill neonates continues to be a challenge. A thorough knowledge of developmental physiology and knowledge of neonatal disease states and their treatment is imperative to providing safe anesthesia. Many conditions that were once thought to be a death sentence for neonates are now surgically treated with increasingly good outcomes. Neonatal anesthesia requires the anesthetist to have astute clinical observation skills, to be intensely vigilant, and to be capable of sound judgments.

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Pediatric Anesthesia

◆ *Sass Elisha and Carla Percy*

CHAPTER 48

Pediatric subspecialty practice requires a mastery of the foundations of pediatric growth and development, the anatomic and physiologic differences during various stages of maturation, and the influence of immature organ systems on anesthetic pharmacokinetics and pharmacodynamics. Anesthetic management for the pediatric patient requires integration and application of this specialized knowledge and refinement of the acquired technical skills of adult anesthetic management.

The content of this chapter provides an extensive discussion of the essentials for pediatric practice. The foundation of anesthetic management is developed through an understanding of pediatric anesthetic morbidity and mortality; the pharmacologic and physiologic differences among adults, infants, and children; and a clinical strategy for anesthetic management.

PEDIATRIC ANATOMY AND PHYSIOLOGY

A thorough understanding of the anatomic and physiologic differences between pediatric and adult patients is of paramount importance in providing safe anesthesia care. Because of the immaturity of children's organ systems—which is most significant until 2 years of age—the psychological and physical stress of surgery, the effects of anesthetic medications, and related pathology all play an integral role in patient outcomes. A thorough discussion of anatomy and physiology for the pediatric patient is presented in Chapter 47.

Pediatric patients are commonly subdivided by age. Categorical groupings include: neonate up to 4 weeks old; infant 4 weeks to 1 year; toddler 1-3 years; preschool 4-6 years; school age 6-13 years; and adolescent 13-18 years.

PEDIATRIC PHARMACOLOGIC CONSIDERATIONS

A complete discussion regarding the recent concern over possible cognitive changes associated with anesthetic drugs in developing children is included in Chapter 47.

Immature organ systems are responsible for the pharmacologic differences that exist between the infant and child. Physiologic characteristics that modify the pharmacokinetic and pharmacodynamic activity include differences in total body water (TBW) composition, immaturity of metabolic degradation pathways, reduced protein binding, immaturity of the blood-brain barrier, greater proportion of blood flow to the vessel-rich organs (i.e., brain, heart, liver, and lungs), reductions in glomerular filtration, a smaller functional residual capacity, increased minute ventilation, and immature receptor responses.

Water freely diffuses across cell membranes and is essential for the transport of cellular nutrients and substrates that support metabolic reactions. Total body water (TBW), expressed in liters, is determined as a percentage of total body weight (1 L of water weighs 1 kg) and steadily decreases with increasing age and varies according to sex and body habitus. Total body water is distributed into the intracellular (ICF) and extracellular (ECF) fluid compartments. With maturation, there is an accompanying decrease in the relative fluid compartment volumes of TBW and ECF during the first year of life, followed by additional decreases in ECF later in childhood. Table 47-8 illustrates the changes in TBW, ICF, and ECF during maturation.

Volume of Distribution

Drug distribution is best described by the volume of distribution, which is determined by dividing the dose of the administered drug by the resulting plasma concentration. Accordingly, body water composition influences the volume of drug distribution. Infants have a larger extracellular fluid compartment and greater TBW content. Due to a dilutional effect, lower plasma drug concentrations occur immediately after administration of water-soluble drugs. Accordingly, a larger drug loading dose is required to achieve the desired plasma concentration. The fat, muscle, and fluid volume compartments are compared in Table 48-1. Higher plasma concentrations occur for lipid-soluble drugs when administered according to weight due to decreased fat and muscle concentrations as compared with an adult.[1]

Protein Binding

Alterations in protein binding theoretically affect the availability of the free-drug fraction of highly protein-bound drugs. Reductions in plasma proteins such as albumin and α-1-acid glycoprotein (AAG) increase the free-drug fraction, which may increase the availability of active drug. Total plasma protein is decreased in the infant, reaching equivalent adult concentrations by 5 to 6 months of age. Albumin, the predominant plasma protein, is responsible for the binding of primarily acidic pharmacologic compounds and AAG, and other proteins are responsible for the binding of basic drugs. Both albumin and AAG concentrations are diminished at birth but reach the adult equivalency by 5 to 6 months, and the fully functional binding capacity of albumin approaches adults at about 1 year old. Albumin concentrations

TABLE 48-1 Body Composition During Growth

	Preterm Newborn (1.5 kg)	Full-Term Newborn (3.5 kg)	Adult (70 kg)
Muscle mass % BW	15	20	50
Fat % BW	3	12	18
Total body water	90%	80%	60%
Extracellular fluid	50%	40%	20%
Intracellular fluid	40%	40%	40%

BW, Body weight.

may fluctuate, decreasing in chronic disease states with parallel increases in inducible AAG concentration. Protein binding of many anesthetic drugs is decreased relative to adults, but there is little clinical consequence. The major factor affecting drug action is the reduced clearance. A highly protein-bound drug with a high extraction ratio and a narrow therapeutic index, such as lidocaine, requires reduced doses.[2] Drug metabolism takes place in the liver, gastrointestinal tract, gastric mucosa, and lungs. In most instances, metabolism reduces drug activity; however, the metabolite may be activated as with a prodrug. The ultimate goal of drug metabolism is the production of a water-soluble compound that can be more easily excreted.

Drug metabolism occurs in two phases. Phase I metabolism consists of three enzymatic reactions (oxidation, reduction, and hydrolysis) catalyzed by the cytochrome P-450 enzyme system. Enzyme systems within the red blood cell, plasma, and other extrahepatic tissues are capable of hydrolyzing a variety of pharmacologic agents, including local anesthetics, the depolarizing relaxant succinylcholine, and the nondepolarizing relaxants atracurium and cisatracurium. Esmolol is hydrolyzed by esterases in red blood cells. Phase I reactions produce a water-soluble metabolic product with the introduction of polar hydroxyl, amino, sulfhydryl, or carboxyl groups for excretion within the bile or urine. Phase II reactions, which are immature at birth, consist of conjugation or synthesis. Conjugation couples the drug with an endogenous substrate (i.e., glucuronidation, methylation, acetylation, and sulfation) to facilitate excretion. The newborn lacks the capacity to efficiently conjugate bilirubin due to decreased glucuronyl transferase activity.

Although the necessary enzyme systems are present at birth, enzyme activity is reduced, thereby increasing drug elimination half-lives. Drugs that produce a prolonged plasma half-life in the pediatric patient include bupivacaine (25 hours),[3] mepivacaine (8.5 hours),[4] diazepam (up to 100 hours),[5] indomethacin (15 to 20 hours),[6] meperidine (22 hours), and phenytoin (21 hours).[7]

Drug Administration

Absorption

The majority of drugs used in anesthesia are given by the inhalation or intravenous routes. Routine medications are also given by oral and rectal drug administration. Drugs are usually formulated as liquids for oral administration in children. Midazolam may be administered orally for premedication, and the rectal route may be selected for the administration of acetaminophen, opioids, and benzodiazepines.[8] Both routes rely on passive diffusion for drug absorption, although the rectal route can be erratic and variable. The resulting plasma drug concentration is dependent on the molecular weight, degree of drug ionization, and lipid solubility.

The degree of ionization of orally administered drugs is dependent on gastric and intestinal pH levels. Acidic drugs are nonionized and are favorably absorbed in an acidic environment such as the stomach. Basic drugs have more favorable absorption in the alkaline medium of the intestine. Most oral medications are absorbed in the intestine. The rate of absorption of most orally administered drugs is slower in neonates and young children because of a delayed gastric emptying time, which prolongs the time to reach the intestines. Gastric emptying time reaches adult values by 6 months of age.[9-11]

Rectal drug absorption is directly affected by drug formulation and rectal blood flow. The superior (upper third of the rectum), middle, and inferior rectal veins carry blood away from the rectal mucosa. The superior rectal vein empties into the portal system, whereas the middle and inferior rectal veins empty into the systemic circulation by way of the inferior vena cava. For example, the administration of acetaminophen into the upper third of the rectum results in a lower plasma concentration because of first-pass metabolism with drug transport to the liver. Opioids and midazolam undergo first-pass metabolism, and their administration into the upper third of the rectum should be avoided.

Acetaminophen is a popular antipyretic commonly administered to children during the perioperative period. Acetaminophen is capable of inducing dose-dependent hepatocyte injury in high doses. Acetaminophen is metabolized by the hepatic microsomal enzyme system, and approximately 80% of the parent drug is conjugated with glucuronic acid and sulfate (phase II metabolism). Animal data suggest that a small amount of the parent drug is metabolized by the cytochrome P-450 enzyme system (phase I metabolism), producing an intermediate metabolite that undergoes conjugation with glutathione and is excreted in the urine. High doses of acetaminophen may deplete glutathione, increasing the accumulation of this intermediate metabolite, which is thought to be responsible for acetaminophen-induced liver necrosis. Glutathione depletion may develop with continued administration of high doses of acetaminophen.[12] Doses used in anesthesia rarely approach toxic levels.

Intravenous acetaminophen (Ofirmev) is marketed for mild to moderate pain and to reduce fever in adults and children. Given in conjunction with an opioid for moderate to severe pain, it has been shown to have an opioid-sparing effect. The recommended dose of Ofirmev for patients 13 years old or older weighing 50 kg or more is 1000 mg every 6 hours or 650 mg every 4 hours IV; the maximum daily dose of acetaminophen by any route is 4000 mg. For patients 2 years old or older weighing less than 50 kg, the recommended dose is 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours IV.[13]

Types of Agents

Inhalation Agents

The rapid increase in alveolar concentration of inspired anesthetic is quantified by the ratio of the alveolar to inspired concentration (F_A/F_I). Factors that affect the F_A/F_I ratio include the delivered inspired anesthetic concentration, the inhalation agent blood-gas partition coefficient, alveolar ventilation (V_A), cardiac output (Q), and the distribution of Q to the vessel-rich organs (i.e., heart, brain, kidneys, and liver). Although tidal volume is similar between children and adults (5 to 7 mL/kg), children have greater minute ventilation and a higher ratio of tidal volume to functional residual capacity (5:1) compared with the adult (1.5:1). The greater minute ventilation and higher Q in infants and children are responsible for rapid inhalation anesthetic uptake and rapidly increasing alveolar anesthetic concentration. In addition, their decreased distribution of adipose tissue and decreased muscle mass affect the rate of equilibration among the alveoli, blood, and brain. The percentage of blood flow to the vessel-rich organs is greater than in the adult, and the blood-gas partition coefficients are lower in infants and children.[14,15]

The minimum alveolar concentration (MAC) of inhalation anesthetics is an indicator of dose and anesthetic requirements that change with age. Neonates have a somewhat lower MAC, which peaks at around 30 days of age (Figure 48-1). MAC is higher in infants from age 1 to 6 months of age; thereafter, MAC values are known to decrease with increasing age.[16,17] These increased requirements are a reflection of increased basal metabolic rate.

Myocardial depression may be exaggerated when inhalation anesthetics are administered to pediatric patients.[18,19] A more rapid rise in F_A/F_I ratio, the greater percentage of blood flow to the vessel-rich organs, and higher administered anesthetic

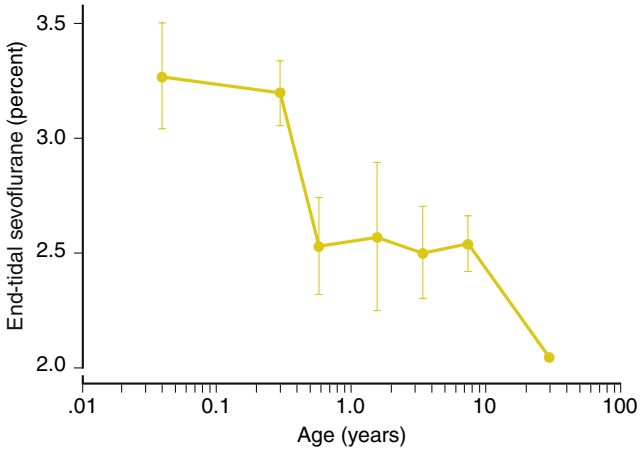

FIGURE **48-1** Effects of age on maximum alveolar concentration. (Data from Lerman J, et al. The pharmacology of sevoflurane in infants and children. *Anesthesiology*. 1994;80:814-824.)

concentrations are central to the cause of myocardial depression. To summarize, inhalation induction is more rapid in pediatric patients and is accompanied by a higher incidence of myocardial depression than in adults.

Sevoflurane. The MAC of sevoflurane in oxygen is 3% for the infant up to 6 months of age, decreasing to 2.5% to 2.8% up to 1 year of age.[20,21] Sevoflurane produces a rapid induction and emergence due to its low blood-gas partition coefficient.[22] Sevoflurane is easily breathed and is readily accepted for mask induction. Sevoflurane is the inhalation agent of choice for pediatric anesthesia. Sevoflurane depresses minute ventilation and, at deeper levels, respiratory rate. At high inspired concentrations, apnea will occur. [23,24]

Sevoflurane metabolism may produce concentration-dependent elevations in serum fluoride levels that decline when sevoflurane is discontinued.[25] Concerns regarding fluoride-induced renal damage have not been a clinical issue. Sevoflurane does not sensitize the myocardium to the effects of endogenous and exogenous catecholamines. As with any inhalation agent, the degree of myocardial depression is dependent on the concentration—higher concentrations cause a greater degree of inhibition of myocardial contractility. The MAC of sevoflurane in oxygen is 2% to 3%.

Isoflurane. The MAC of isoflurane in oxygen is 1.6% in infants and children. Inhalation induction with isoflurane produces more adverse respiratory events (i.e., breath-holding, coughing, and laryngospasm with copious secretions) than sevoflurane. Administration of isoflurane to adults produces dose-dependent decreases in peripheral vascular resistance, whereas increases in heart rate maintain blood pressure. This touted advantage (i.e., increase in heart rate to maintain blood pressure) does not occur in infants. Anesthetic induction in infants with isoflurane produces significant dose-dependent decreases in heart rate, blood pressure, and mean arterial pressure.[26]

Desflurane. The MAC of desflurane in oxygen is 9% for infants and 6% to 10% for children. Desflurane has the lowest blood-gas partition coefficient of all the inhalation anesthetics (0.42), which facilitates a rapid induction, rapid alterations in anesthetic depth, and emergence. Like isoflurane, desflurane is pungent and is associated with more adverse respiratory events during inhalation induction including breath-holding, laryngospasm, coughing, and increased secretions with accompanying hypoxia. After inhalation induction with sevoflurane, desflurane is appropriate for the maintenance of general anesthesia with facemask, endotracheal tube, or laryngeal mask airway. As in the adult population, dramatic increases in desflurane concentrations may induce sympathetic stimulation evidenced by tachycardia and hypertension.[27,28]

Emergence Delirium. A variety of terms are used interchangeably when referring to postoperative agitation. These include *emergence delirium*, *emergence agitation*, and *postanesthetic agitation*. These terms describe altered behavior in the immediate postoperative period manifested as nonpurposeful restlessness, crying, moaning, incoherence, and disorientation.[29,30] These episodes can be very upsetting to the parents and caregivers. Emergence delirium is fortunately self-limiting but may manifest for as long as 45 minutes. The incidence ranges from 10% to 80%. It occurs during the early stage of emergence during initial wakening. No single factor has been identified as the cause of emergence agitation, which is a composite of biologic, pharmacologic, psychological, and social components.[31] Recent hypotheses have implicated the rapid emergence associated with the newer low-solubility anesthetic agents such as sevoflurane and desflurane. This may create a dissociative state in which children awaken with altered cognitive perception, although others dispute the speed of emergence as a factor. There is conflicting research as to the incidence with the slower emergence of isoflurane.[32,33] Proposed causes also include rapid awakening in unfamiliar settings, pain, stress during induction, hypoxia, airway obstruction, noisy environment, anesthesia duration, child's personality, premedication, and type of anesthesia. A recent meta-analysis found that propofol, ketamine, fentanyl, dexmedetomidine, and preoperative analgesia had a prophylactic effect in preventing agitation and treating acute episodes. Midazolam and $5HT_3$ inhibitors do not have a protective effect.[34]

Intravenous Anesthetics

As discussed previously, infants and children have a higher proportion of cardiac output delivered to vascular-rich tissues (i.e., heart, brain, kidneys, and liver). Intravenously administered drugs are readily taken up by these tissues and are subsequently redistributed to muscle and fat, tissues that are less well perfused. Intravenously administered drugs may have a prolonged duration of action in infants and children because of decreased percentages of muscle and fat. The central nervous system (CNS) effects of opioids also may be prolonged because of the immaturity of the blood-brain barrier.[35,36] Although this evidence suggests that intravenously administered anesthetic doses should be reduced, one must also recall the effect of increased body water. Increased doses of propofol and ketamine are required, presumably because of a greater volume of distribution.[37]

Propofol. Propofol has a rapid onset and a short duration of action and is the most popular agent for induction and maintenance of general anesthesia. It also may be combined with an opioid and nitrous oxide to provide total intravenous anesthesia. Propofol may be delivered as a continuous infusion for short diagnostic and radiologic procedures and is used as a primary sedative in chronically ventilated intensive care patients. Its antiemetic properties may reduce the incidence of postoperative nausea and vomiting in children undergoing strabismus correction.[38] Infants require larger induction doses (2.5 to 3 mg/kg) than children (2 to 2.5 mg/kg).[39,40] These induction doses produce decreased systolic blood pressure.[41,42] The pain that accompanies intravenous administration may be reduced with the addition of small amounts of lidocaine. Additional strategies used to decrease the pain during injection include a slower injection of propofol into a rapid-running intravenous line or injection into larger intravenous catheters placed in the antecubital space.[43]

In 1992, Parke et al. reported the deaths of five children who received long-term, high-dose propofol infusions.[44] The large doses were administered by continuous infusion in critical care units with long-term sedation over several days and were not associated with short-term anesthesia use. Additional case reports followed, further characterizing this serious reaction, subsequently referred to as *propofol infusion syndrome*. Propofol infusion syndrome is characterized by severe lactic acidosis, followed by rhabdomyolysis and lipidemia. It frequently results in cardiovascular collapse and death. The likely mechanism involves propofol inhibiting mitochondrial function and uncoupling oxidative phosphorylation (see Chapter 9). Children with mitochondrial defects may have an increased risk with propofol administration.[45,46] Algorithms have been proposed to prevent this adverse drug effect.[47]

Neuromuscular Blocking Agents

Neuromuscular blocking drugs are highly ionized and have a low lipophilicity, restricting their distribution to the ECF compartment. The ECF compartment is larger in the neonate and infant than in the child and adult, causing a dilutional effect and thereby increasing the volume of distribution. Increases in ECF volume and the ongoing maturation of neonatal skeletal muscle and acetylcholine receptors affect the pharmacokinetics and pharmacodynamics of neuromuscular relaxants. Table 47-9 references the effective doses of neuromuscular blocking drugs in various age groups.

The neuromuscular junction is incompletely developed at birth, maturing after 2 months of age.[48] Skeletal muscle, acetylcholine receptors, and the accompanying biochemical processes essential in neuromuscular transmission mature during infancy into childhood.

The presynaptic release of acetylcholine is slowed compared with the adult, which explains the decreased margin of safety for neuromuscular transmission in the neonate. The acetylcholine receptors of the newborn are anatomically different from the adult receptors, which may explain the sensitivity of the neonate to the nondepolarizing class of neuromuscular relaxants.[49] This neuromuscular immaturity may be demonstrated with the appearance of fade after tetanic stimulation in the absence of neuromuscular blocking drugs.[48,50]

Succinylcholine. In the early 1990s a series of unexpected cardiac arrests were reported after the routine administration of succinylcholine in apparently healthy children, with less than 40% of patients successfully resuscitated. After much research it was found that the patients had undiagnosed Duchenne muscular dystrophy. Succinylcholine administration produces massive hyperkalemia and subsequent cardiac arrest in these children.[51] The U.S. Food and Drug Administration (FDA) relabeled succinylcholine, restricting its use to emergency airway management in children.[52,53] It is now used only as a rescue drug in children younger than 8 years old. Most clinicians avoid using it for patients through the early teen years and in patients with muscle disorders. It is contraindicated in patients with malignant hyperthermia.[54,55]

Nondepolarizing Neuromuscular Blocking Agents. Infants and children are more sensitive than adults to the effects of nondepolarizing neuromuscular blocking drugs (see Table 47-9). A lower plasma concentration of the selected neuromuscular relaxant is required to achieve the desired clinical level of neuromuscular blockade. This does not imply that the selected dosage should be decreased because infants have a greater volume of distribution. The larger volume of distribution and slower drug clearance result in longer elimination half-life, decreasing the need for repeated drug dosing (longer dosing intervals). Neuromuscular function monitoring must be used to guide repeated administration of these drugs in all pediatric patients. The degree of neuromuscular blockade should be assessed using physical signs (e.g., strength of movement, spontaneous respirations with adequate tidal volume) and neuromuscular monitoring (i.e., train-of-four and sustained tetanus). Checking neuromuscular function should be accomplished by assessing the adductor pollicis muscle on the forearm because function in this region is more reflective of diaphragmatic activity as compared with the orbicularis oculi (temporal region). The selection of a nondepolarizing neuromuscular relaxant should take into consideration the desired degree and duration of skeletal muscle paralysis, the immaturity of organ systems, and the associated side effects of the selected relaxant.[56,57]

Antagonism of Neuromuscular Blockade. Residual neuromuscular blockade places the infant and child at risk of hypoventilation and the inability to independently and continuously maintain a patent airway. Because of increased basal oxygen consumption, impaired respiratory function will lead to arterial oxygen desaturation and CO_2 retention. The detection of residual neuromuscular blockade requires the integration of clinical criteria and the assessment of neuromuscular blockade via a peripheral nerve stimulator. Conventional doses of the anticholinesterase inhibitors (50 to 60 mcg/kg of neostigmine; 500 to 1000 mcg/kg of edrophonium) combined with appropriate doses of atropine or glycopyrrolate are acceptable for antagonism of nondepolarizing neuromuscular blockade.

Voluntary clinical tests are obviously not applicable to the infant and young child. Useful clinical signs of successful antagonism of neuromuscular blockade include the ability to flex the arms, lift the legs, and flex the thighs upon the abdomen, providing evidence of the return of abdominal muscle tone, in addition to the return of a normal responses to nerve stimulation.[58] Neonates are capable of generating a negative inspiratory force (NIF) of −70 cm H_2O with the first few breaths after birth.[59] A negative inspiratory force of at least −32 cm H_2O has been found to correspond with leg lift, which is indicative of the adequacy of ventilatory reserve required before tracheal extubation.[60,61]

PREOPERATIVE PREPARATION

Preoperative preparation is typically done shortly before scheduled surgery, in the preoperative anesthesia clinic or in the patient's room in the hospital. Patients who are acutely ill or medically unprepared need to be screened appropriately in the preoperative area.

Preoperative Assessment

Parents or caretakers offer invaluable insight into the history of their child. It is important to have good communication and establish the trust of the patient's family member. Parental preparation is important to allay fear and answer questions. A thorough preoperative assessment will foster trust and confidence through a courteous and understandable explanation of the anesthetic experience. Parental anxiety may be driven by personal past anesthetic experiences, such as painful intravenous catheter placement, coerced mask induction, and postoperative pain, nausea, and vomiting. Parents offer invaluable information regarding their child's past anesthetic experiences. When the child appears for a repeat surgical procedure, the parents may have important information relative to what works and may be helpful in detailing a successful approach.

Review of Systems

Reviewing the medical record can answer many questions before approaching the patient/parents for information. Understanding congenital history can help preparation and development of a plan of care. Previous anesthetic records can be useful tools. Table 48-2 lists the anesthetic implications of the review of systems and history.

TABLE 48-2 Medical History and Review of Symptoms: Anesthetic Implications

System	History	Possible Anesthetic Implications
Central nervous and neuromuscular	Seizures	Medications: Drug interactions, possible inadequate serum levels, valproate-induced hepatitis
	Head trauma	Elevated intracranial pressure
	Hydrocephalus	Possible elevated intracranial pressure
	CNS tumor	Possible elevated intracranial pressure, chemotherapeutic drugs and interactions
		Possible risk of malignant hypothermia
Cardiovascular	Heart murmur	Septal defect, avoid air bubbles in IV line
	Cyanosis	Right-to-left cardiac shunt
	History of squatting	Possible tetralogy of Fallot
	Diaphoresis with feedings	Congestive heart failure
	Hypertension	Possible coarctation of the aorta; renal disease; pheochromocytoma
	Transplant recipient	Fixed heart rate; insensitivity to anticholinergic drugs
Respiratory	Prematurity	Increased risk of postoperative apnea; possible lower respiratory tract illness
	Bronchopulmonary dysplasia	Lower airway obstruction; reactive airways; possible subglottic stenosis; possible postoperative hypoxia and apnea; pulmonary hypertension
	Lower respiratory infection, cough	Reactive airways; bronchospasm; medication history; drug interactions
	Croup	Possible subglottic stenosis or anomaly
	Snoring, sleep apnea	Perioperative airway obstruction; hypoxia
	Asthma	β-Agonist or theophylline drugs; pulmonary hypertension or cor pulmonale; steroid use; adrenal insufficiency; postoperative hypoxia
	Cystic fibrosis	Drug interactions; pulmonary toilet; pulmonary dysfunction; reactive airways
	Recent cold	Possible lower respiratory tract infection; reactive airways
Gastrointestinal and hepatic	Vomiting, diarrhea	Electrolyte abnormality; dehydration; full stomach
	Growth failure	Possible anemia
	Gastroesophageal reflux	Risk of aspiration; reactive airways; hypoxia
	Jaundice	Altered drug metabolism; risk of hypoglycemia
	Liver transplant recipient	Altered drug metabolism; immunosuppression
	Frequency, nocturia	Unrecognized diabetes, urinary tract infection
	Renal failure or dialysis	Electrolyte abnormality; hypervolemia or hypovolemia; anemia; medication history
	Renal transplant recipient	Immunosuppression
Endocrine and metabolic	Hypoglycemia	Hypoglycemia
	Diabetes	Insulin requirement; intraoperative hypoglycemia
	Steroid therapy	Adrenal insufficiency
	Pregnancy	Teratogenic effects of N_2O and other drugs; risk of spontaneous abortion
Hematologic	Anemia	Transfusion requirement
	Bruising, excessive bleeding	Coagulopathy
	Sickle cell disease	Anemia; transfusion; hydration; oxygenation; orthopedic tourniquet use
	AIDS	Susceptibility to infection; infectious risk to medical personnel
Allergies	Medication history	Drug reactions; drug interactions
Dental	Loose teeth	Dental trauma; aspiration of tooth

Modified from Coté CJ, et al, eds. *A Practice of Anesthesia for Infants and Children*. 5th ed. Philadelphia: Saunders; 2013.
AIDS, Acquired immunodeficiency syndrome; *CNS*, central nervous system; *IV*, intravenous; N_2O, nitrous oxide.

- *Birth and development*. Was the child born prematurely or term? Did the child experience any neonatal complications or spend any time in the neonatal intensive care unit? Does the child have any history of apnea or bradycardia? Is there any history of sudden infant death syndrome in the child's family? Are there any developmental or learning setbacks?
- *Heart disease*. Does the patient play at school without severe shortness of breath or syncope? Does the child have a heart murmur?
- *Pulmonary problems*. Does the child have asthma, bronchitis, or pneumonia? Does the child currently receive, or has received in the past, supplemental oxygen therapy? Has the child had a recent cold, cough, or respiratory infection? Many times the child will have a persistent runny nose due to an inner ear infection. It is important to ask the parent about the color, consistency, and duration of drainage.
- *Bleeding disorders*. Does the child have sickle cell anemia? Does the child bleed or bruise easily?
- *Liver disease*. Has the child had jaundice or liver problems?
- *Urology problems*. Has the child had problems with the kidneys, ureters, or bladder? Any urinary tract infections?
- *Gastrointestinal problems*. Has the child had gastric acid reflux or a hiatal hernia? Has the child experienced problems with diarrhea or vomiting?
- *Neurologic problems*. Has the child experienced any neurologic symptoms such as seizures?
- *Obstetric history*. Could the patient possibly be pregnant? (controversial topic)
- *Airway*. Does the patient have a history of a difficult intubation? Does the child have trouble opening the mouth? Are there any chipped, missing, or loose teeth?
- *Other concerns*. Does the child have diabetes or hypoglycemia problems? Does the child have any problems with the thyroid or adrenal glands?
- *Medications*. Is the child currently on any medications or has he or she taken any within the last 3 months? Has the child taken steroids within the last year? If so, for what condition?
- *Allergies*. Is the patient allergic to any medication or food? Any problems with latex or other environmental items?

Fasting Status

The risk of pulmonary aspiration in the pediatric patient is extremely low (1 in 10,000).[62] Accordingly, traditional fasting guidelines have become broader. Although the goal of preoperative fasting is to ensure an empty stomach at the time of anesthetic induction, prolonged fasting may produce irritability as a result of thirst and hunger. Prolonged fasting also may alter fluid balance, producing preinduction hypovolemia and hypoglycemia. Hypoglycemia is especially problematic in premature infants. Preoperative access to clear fluids (e.g., apple juice, water) 2 hours before anesthetic induction has been shown to have a minimal impact on gastric volume. Current recommendations by the American Society of Anesthesiologists (ASA) are 2 hours of fasting for clear liquids, 4 hours for breast milk, 6 hours for infant formula and non-human milk and a light meal, and 8 hours for a regular meal including fatty foods (see Table 43-2). The guidelines are commonly referred to as the 2-4-6-8 rule.[63] These parameters are suggested for healthy patients undergoing elective surgery. No gum is to be chewed after midnight; also, prescribed medications can be taken with a sip of water or prescribed liquid mixture. If a patient should present with a history of hiatal hernia while preparing for elective surgery and has not been *nil per os* (NPO; nothing by mouth) for the recommended period of time, providers must collaborate to make the best decision in regard to keeping the patient safe. For a patient such as this, the best decision will likely be to postpone surgery until the proper fasting time has been achieved.

In patients that have not had the proper amount of fasting time or have an injury or anatomic differences that increase their risk for aspiration, it will be important to premedicate with a nonparticulate antacid such as sodium citrate (0.5mL/kg), metoclopramide (0.1mg/kg), and/or an H-2 blocking agent such as ranitidine (2.5 mg/kg).

Upper Respiratory Infection

Upper respiratory infections (URIs) are common in the pediatric age group, are seasonal in occurrence, and may be accompanied by cough, pharyngitis, tonsillitis, and croup. The child with an active or resolving URI has increased airway reactivity, a propensity for the development of atelectasis and mucous plugging of the airways, and the potential to experience postoperative arterial hypoxemia.[64] In addition, bronchial reactivity may persist for 6 to 8 weeks after a viral lower respiratory tract infection. The presence of chronic respiratory disease (asthma or bronchopulmonary dysplasia) requires a thorough assessment and medication review to ensure that the disease is well controlled and the child is not currently experiencing an exacerbation. A history of steroid use necessitates consideration of steroid supplementation throughout the perioperative period.

Healthy children who are scheduled for the placement of tympanostomy tubes frequently have rhinitis. In deciding whether to proceed with anesthesia, additional patient history must be obtained to differentiate between a chronic allergic or an acute infectious presentation and to determine whether there is lower-airway involvement. The assessment of the color and the duration of nasal drainage will assist in deciding whether rhinorrhea is chronic or acute. Purulent nasal discharge associated with pharyngitis, cough, or fever may be indicative of a bacterial or viral URI. Additional information may be obtained by questioning the parents regarding their assessment of the child's current health. Helpful questions include: Does your child appear sick? Is your child eating, sleeping, and playing normally? Is there anyone in the family (including siblings) who is currently ill? Children with chronic allergic rhinorrhea who exhibit a clear nasal drainage without accompanying signs of illness (e.g., no cough, pharyngitis, wheezing, or associated fever) are probably in satisfactory condition for elective general anesthesia with no imposed increased risk.

Lower respiratory tract dysfunction typically accompanies viral or bacterial URI. This combination may be associated with a greater frequency of laryngospasm (fivefold greater incidence) and bronchospasm (tenfold greater incidence) during anesthetic management, particularly when endotracheal intubation is performed.[65] Although mild URI may be inconsequential during the intraoperative period, significant problems may develop in the immediate postoperative period. Studies have noted an increase in the incidence of postintubation croup, hypoxemia, and bronchospasm in patients with URIs compared with asymptomatic children.[65-67]

Multiple factors must be considered when one is deciding whether to cancel an elective procedure. Children with signs and symptoms of acute airway dysfunction should have further medical evaluation by a pediatrician. A white blood cell count of 12,000 to 15,000/mm^3 suggests the presence of infection, and the surgery should be canceled. Clearly, elective surgery should be postponed for children who have a cough and pharyngitis accompanied by

fever and wheezing. Acute verses chronic symptoms need to be deciphered. Children with a fever 38.4° C and higher, malaise, wheezing, dyspnea, rhonchi, nasal congestion, and a productive cough are showing signs of an acute infection necessitating the postponement of surgery.[68,69] Evidence-based recommendations are given in Box 48-1.

Laboratory Testing

Laboratory testing should be ordered preoperatively based upon the patient's medical history and physical examination. Indications for preoperative laboratory testing are listed in Box 48-2. The American Academy of Pediatrics (AAP) states routine laboratory tests do not need to be performed in healthy patients undergoing outpatient surgery.[70] However, in patients presenting with an abnormality, preoperative testing is imperative to guide the surgical and anesthetic plans.

Preoperative laboratory tests should be ordered based on abnormal findings from the medical history and physical examination. Preoperative hemoglobin determination has characteristically been obtained to provide an assessment of anesthetic fitness. An "adequate" hemoglobin concentration is essential for oxygen delivery and has been arbitrarily defined as a hemoglobin of 10 g/dL or a hematocrit of 30%. No scientific studies support or refute this "acceptable" quantity. The determination of an acceptable value requires an understanding of the child's current medical history, the proposed surgical procedure, and an understanding of global oxygen transport and use. The value of a routine hemoglobin determination has been questioned for some time and has been found rarely to affect the anesthetic management of children.[71] The frequency of asymptomatic anemia in a prospective study of 2649 pediatric outpatients was found to be less than 1%, with 7 of 14 anemic patients younger than 1 year of age. However, the frequency of anemia may be as high as 12% in immigrant and indigent children.[72] Children who benefit from preoperative hemoglobin determinations include premature infants less than 60 weeks' postconceptional age, children with concurrent cardiopulmonary disease, children with known hematologic dysfunction (e.g., sickle cell disease), and children in whom major blood loss is anticipated during the surgical procedure.

Premedication

The selection and administration of premedication for the pediatric patient requires an understanding of the desired goals, the planned surgical procedure (inpatient or outpatient procedure), the familiarity and previous experiences with the particular drug, and the availability of nursing staff to monitor the child after the drug's administration (Box 48-3). The ideal premedicant should be dependable, with a rapid and reliable onset and offset, and should be devoid of undesirable effects. The use of "cookbook" doses of premedicants is hazardous and may produce general anesthesia in some children while producing ineffective sedation in others.[73] Table 48-3 lists commonly prescribed pediatric premedicants. Premedication must be individualized to account for differences in maturation and development and the child's previous surgical experiences. The reliance on pharmacologic premedication in preparing the child for the surgical experience should not be routine; rather, it should be reserved for children who are extremely apprehensive. Anxiolytics and sedatives may prolong the time to discharge, thereby increasing patient care costs.[74] Older children may benefit from anxiolytic premedication to decrease preoperative anxiety and modify behavioral changes after discharge. Analgesics are important for children experiencing pain and to provide some postoperative relief.[75] Midazolam is the most common premedicant in the pediatric patient. This short-acting, highly lipophilic benzodiazepine produces amnesia and anxiolysis and in sufficient dosages may also produce sleep (hypnosis). Many pediatric centers develop their own proprietary "cocktail" of a mixture of agents for use in children.

Parental Presence During Anesthetic Induction

Children may have difficulty with parental separation and may require premedication to ease their anxiety. In addition to

BOX 48-1

Recommendations for Patients with Upper Respiratory Tract Infections

When feasible, efforts should be made to make parents aware of the problems with respiratory tract infections and anesthesia, and parents should be encouraged to call before the day of surgery to discuss the symptoms and possible need for delay. There may be a role for pediatricians and other primary care practitioners to play in the process of perioperative evaluation and education.

First, an emergency case mandates judicious airway management and logically must proceed regardless of the presence or absence of respiratory symptoms. In patients undergoing elective nonurgent surgery, initial consideration should be with respect to the severity of respiratory tract symptoms. Often, careful questioning of parents can differentiate acute from chronic symptoms. Patients with severe symptoms such as fever greater than 38.4° C, malaise, productive cough, wheezing, or rhonchi should be considered for delay of elective surgery. A reasonable period of delay would be 4 to 6 weeks.

If mild symptoms are present, such as nonproductive cough, sneezing, or mild nasal congestion, surgery could proceed for those having regional or general anesthesia without endotracheal tube (ETT) placement. The intraoperative plan should include early use pulse oximetry, decision of facemask or laryngeal mask airway use, and careful suctioning of the nasal and oropharynx under deep anesthesia before emergence. Additional management considerations for patients with upper respiratory tract infection (URI) or lower respiratory tract (LRI) undergoing anesthesia include hydration status, use of airway humidification, and the potential benefit of pharmacologic agents such as anticholinergics and beta-agonists to help with airway secretions and airway hyperreactivity.

However, for those patients who require ETT placement for anesthesia, especially children less than 1 year of age, it is important to identify risk factors such as passive smoke exposure and underlying conditions (e.g., asthma, chronic lung disease) because these children may benefit from a slight delay of 2 to 4 weeks. Finally, those patients with resolving respiratory tract infections with severe symptoms or mild symptoms should have the same relative waiting periods fulfilled to minimize risks of proceeding with surgery (i.e., 2 to 4 weeks after resolution of minor URI and 4 to 6 weeks after resolution of severe URI or LRI).

Modified from McKee CT, et al. Should a child with a respiratory tract infection undergo elective surgery? In Fleisher LA, ed. *Evidence-Based Practice of Anesthesiology*. 2nd ed. Philadelphia: Saunders; 2009:475-481.

BOX **48-2**

Indications for Preoperative Laboratory Testing

Complete Blood Count
- Hematologic disorder
- Vascular procedure
- Chemotherapy
- Unknown sickle cell syndrome status

Hemoglobin and Hematocrit
- Less than 6 months of age (less than 1 year of age if born premature)
- Hematologic malignancy
- Recent radiation or chemotherapy
- Renal disease
- Anticoagulant therapy
- Surgical procedures with potential for large blood loss
- Coexisting systemic disorders (e.g., cystic fibrosis, prematurity, severe malnutrition, renal failure, hepatic disease, congenital heart disease)

White Blood Cell Count
- Leukemia or lymphomas
- Recent or concurrent radiation or chemotherapy
- Suspected infectious process
- Aplastic anemia
- Hypersplenism
- Autoimmune collagen vascular disease

Blood Glucose
- Diabetes mellitus
- Current corticosteroid use
- History of hypoglycemia
- Adrenal disease
- Cystic fibrosis

Serum Chemistry
- Renal disease
- Adrenal or thyroid disease
- Previous or concurrent hemotherapy
- Pituitary or hypothalamic dysfunction
- Body fluid loss or shifts (e.g., dehydration, bowel preparation)
- Central nervous system disease

Potassium
- Digoxin or diuretic therapy

Creatinine and Blood Urea Nitrogen
- Hypertensive cardiovascular disease
- Renal disease
- Adrenal disease
- Diabetes mellitus
- Digoxin or diuretic therapy
- Body fluid loss or shifts (e.g., dehydration, bowel preparation)
- Administration of intravenous radiocontrast material

Liver Function Tests
- Hepatic disease
- Exposure to hepatotoxic agents

Coagulation Studies
Prothrombin Time
- Activated partial thromboplastin time (aPTT)
- Leukemia
- Hepatic disease
- Known coagulation disorder (e.g., hemophilia, Christmas disease)
- Concurrent anticoagulant therapy
- Severe malnutrition or malabsorption

Platelet Count or Bleeding Time
- Known coagulation disorder (e.g., hemophilia, Christmas disease)
- Purpura (increase in bruising)

Pregnancy Test
- Serum human chorionic gonadotropin (HCG) in menstruating, sexually active patient

Electrocardiogram
- Family history of prolonged QT interval
- Congenital heart disease
- History of sleep apnea or chronic airway obstruction (adenotonsillar hypertrophy)
- Possible previously undiagnosed heart murmur

Chest Radiograph
- Suspected intrathoracic pathology (e.g., tumors, vascular ring)
- Congenital heart disease
- History of prematurity with residual bronchopulmonary dysplasia
- Obstructive sleep apnea with cardiomegaly

Cervical Spine Radiograph
- Down syndrome (rule out subluxation of atlanto-occipital junction)

BOX **48-3**

Goals for Premedication

- Anxiolysis (especially in children undergoing repeat procedures)
- Amnesia (insertion of intravenous access)
- Analgesia (children in pain)
- Antisialagogue (airway manipulation, but rarely needed)
- Increase gastric pH
- Reduction of gastric volume
- Reduce anesthetic requirements
- Blunting of central nervous system reflex responses
- Subacute bacterial endocarditis
- Allergic reactions (latex)
- Postoperative nausea and vomiting
- Infectious processes

TABLE 48-3 Commonly Prescribed Pediatric Premedicants

Drug Name	Pediatric Dose
Opioids	
Morphine sulfate	0.1-0.3 mg/kg IM 0.05-0.1 mg/kg IV
Fentanyl	0.5-1.0 mcg/kg IV 10 mcg/kg oral transmucosal
Benzodiazepines	
Midazolam	0.07-0.1 mg/kg IM 0.2 mg/kg nasally 0.025-0.05 mg/kg IV 0.25-1.0 mg/kg PO 0.5-1 mg/kg rectally
Ketamine	5-10 mg/kg PO 2-10 mg/kg IM 1-2 mg/kg IV
Clonidine	2.5-5.0 mcg/kg PO 1-2 mcg/kg IV
Dexmedetomidine	0.5-1.0 mcg/kg intranasally 2-5 mcg/kg PO 0.4-0.6 mcg/kg IV infusion in 100 mL saline
Anticholinergics	
Atropine	0.02 mg/kg PO, IV, IM
Glycopyrrolate	0.01 mg IV

IM, Intramuscular; *IV*, intravenous; *PO*, orally.

preoperative medication, many anesthetic departments allow a parent present for anesthetic induction. The frequency of allowing parents to accompany a child during anesthesia induction varies widely among institutions and even individual clinicians. Parents may stay with their children during diagnostic procedures such as bone-marrow biopsy, immunization, dental rehabilitation, and the induction of anesthesia. Anesthesia departments may have age limitations, not allowing parental presence for children less than 12 to 18 months of age. Clearly the parent should not be invited to participate in the induction of a child with a full stomach or perhaps a child with a compromised airway. Studies examining the effectiveness of parental presence are mixed. Parental presence has been demonstrated to reduce the child's anxiety, precluding the need for premedication.[76] However, an evidence-based review noted no advantage, and oral midazolam was found to be more effective for the control of the child's preoperative anxiety than parental presence.[77] Mothers who are motivated to be present in the operating room during the induction of anesthesia may be very anxious, and their children are likely to have high anxiety levels during anesthetic induction. Before entering the operating room with parent and child, a thorough explanation of the expected behavior of the child during anesthetic induction (e.g., excitement, spontaneous involuntary movements, snoring, floppy appearance with unconsciousness) should be provided to the parent or guardian. It is important that there be a clear line of communication between the anesthetist and the parent. In addition, the parent should agree to leave the operating room accompanied by an escort when the child has lost consciousness or when requested to do so. Hospitals and anesthesia departments occasionally request the parent to sign a waiver of liability prior to accompanying the child to the operating room.

BOX 48-4

Manipulation of the T-Piece (Open Circuit)

Manipulation to Increase Pao_2
- Increase inspired oxygen delivery at blender
- Increase fresh gas flow (decreases entrainment of room air from reservoir tubing)
- Increase length of reservoir tubing (increases oxygen storage capacity)

Manipulation to Decrease $Paco_2$
- Increase fresh gas flow (wash out expired air from reservoir tubing)
- Decrease length of reservoir tubing (decreases volume of expired air; also decreases Fio_2)

From Litman RS. *Pediatric Anesthesia: The Requisites*. Philadelphia: Mosby; 2004:102.

ANESTHETIC MANAGEMENT

Airway Management

Pediatric Breathing Circuits

In the United States standard pediatric breathing circuits are generally used in children. Occasionally, an open circuit is used for complex neonatal procedures or during transport. Characteristics of an ideal pediatric breathing circuit include lightweight, minimize dead space, have a low resistance and a low compressible volume, be adaptable for both spontaneous and controlled ventilation, be capable of providing humidification and warming of inspired gases, and permit the collection and scavenging of exhaled anesthetic gases. An easy method to conceptualize pediatric breathing circuits is to characterize the circuit according to the presence of the number of valves within the circuit.[78] A circuit without valves is an open circuit. The Ayre's T-piece is an excellent example of an open circuit (Box 48-4). It is commonly used throughout hospitals to provide supplemental oxygen during patient transport. The T-piece was first used for the delivery of anesthesia to infants undergoing cleft palate and cleft lip repair. The T-piece, which is in a T configuration, is formed by an inspiratory limb for the delivery of oxygen and anesthetic gas, a limb directed to the patient for connection to a facemask or endotracheal tube (ETT), and an opposite expiratory limb that is open to the atmosphere for the removal of exhaled gas. This expiratory limb also may serve as a reservoir for oxygen that may be rebreathed. Because there are no valves, inspired air is drawn from both the inspired limb and expiratory limb. The rebreathing of expired CO_2 can be prevented with the administration of fresh gas flows at least two times the patient minute ventilation. The T-piece can be configured to increase oxygen delivery or decrease $Paco_2$.

The modification of the Ayre's T-piece with the addition of a single valve allows the delivery of positive-pressure ventilation. A variety of modifications of the Ayre's T-piece have been classified by Mapleson. The Mapelson A circuit is best employed for the spontaneously ventilating patient. The Mapleson D system contains an expiratory valve at the distal end of the expiratory limb and is used for controlled ventilation. The Mapleson E system was modified by Jackson-Reese with the addition of a reservoir bag with an adjustable valve at the tail of the bag. Spontaneous ventilation is permitted with the opening of the adjustable valve, whereas closing the valve fills the reservoir bag, and repeated manual compression allows the delivery of continuous positive airway pressure, or positive-pressure ventilation. With an expiratory pause

of sufficient duration and sufficient fresh gas flows, exhaled CO_2 is washed from the reservoir tube, preventing the inhalation of exhaled CO_2 with subsequent inspiration. Fresh gas flows of two to three times the child's minute ventilation are required to prevent rebreathing of exhaled gases. Because of the required high fresh-gas flow rates, this circuit is not economical for children who weigh more than 20 kg.

The circle breathing system has become popular for anesthetic gas delivery in the past decade, because most pediatric centers have abandoned the use of the Bain or Mapleson F circuit for the circle system. Technologic advancements in anesthesia-machine design have decreased the resistance imparted by the absorbent canisters and the one-way inspiratory and expiratory valves. Overall system compliance is greater than that of the open circuits. The breathing tubing for the pediatric circle systems is a smaller diameter than the adult tubing and has a lower compression volume, allowing accurate delivery of desired tidal volumes. The circle breathing system is characterized by the presence of CO_2-absorbent canisters and a total of three valves (a one-way inspiratory valve, a one-way expiratory valve, and a pop off or adjustable pressure-limiting [APL] valve) that directs exhaled gas to the scavenging system. Advantages of the circle system include the conservation of potent inhalation agents, the ability to retain both heat and humidity, and the ease of collecting and scavenging waste gases.

The reservoir bag contains the anesthesia machine–delivered anesthetic mixture inspired by the patient and serves as a visual and tactile monitor of ventilation. Reservoir bags are shaped to allow compression with one hand and are constructed of rubber and latex, although latex-free bags are readily available. Reservoir bags range in size from 0.5 to 6 L. The selected reservoir bag must be appropriate for the patient's size, that is, capable of containing a volume in excess of the child's inspiratory capacity. The use of an inappropriately small reservoir bag may restrict respiratory efforts, and the use of a large reservoir bag inhibits the ability to use the reservoir bag as a monitor of ventilation.[79-81]

Anesthetic Induction

Inhalation (Mask) Induction

Anesthetic induction may be accomplished in a variety of ways and is dependent on the child's current state of health, the age and level of anxiety, the proposed surgical procedure, and the parents' agreement with regard to the proposed anesthetic plan. Inhalation or commonly called *mask induction* is the most popular and is easily accomplished in infants less than 8 months of age, as well as children who do not have initial intravenous access. Mask induction can be offered to children through the age of 16 years who have needle phobia. Standard monitors are applied when appropriate. A pulse oximeter and precordial stethoscope are used initially, and an assistant such as the circulating nurse places the remaining monitors during the induction period, following the loss of consciousness.

Anesthetic induction commonly begins with a 70:30 mixture of nitrous oxide and oxygen via mask or a cupped hand placed on the child's chin, with the anesthetic mixture directed toward the mouth and nose. Some clinicians do not use nitrous oxide and begin with sevoflurane oxygen mixtures instead. A pacifier may quiet the infant during the induction, or the infant may suck on the end of the anesthetist's gloved finger. Sevoflurane is added to the nitrous oxide–oxygen mixture beginning with a 2% concentration, with a rapid increase to 8%. The mask may then be introduced as the inspired concentration is increased. Unconsciousness is produced with inspired sevoflurane concentrations of 6% to 8%. Following the loss of consciousness, nitrous oxide is discontinued, and sevoflurane is administered in 100% oxygen.

At this time the anesthetist should begin to assist respiration and promptly decrease the inspired anesthetic concentration of sevoflurane to 2% to 2.5%. During assisted ventilation, intravenous access should be established. The age of the child, proposed surgical procedure, and ease of airway management during induction are the determining factors for whether to proceed with intravenous access.

Establishing intravenous access in all children before laryngoscopy and endotracheal intubation is advised. For elective surgical procedures, neonates may be managed with a 24-gauge catheter, infants with a 22-gauge catheter, and children with a 20- or 22-gauge catheter. Surgical procedures with expected large third-space fluid loss or blood loss require an additional intravenous catheter. Preferred sites for intravenous access include the nondominant upper extremity (dorsum of the hand, antecubital fossa) and the lower extremity (dorsum of the foot, or the saphenous vein). The deep saphenous vein is most easily accessed with a 20- or 22-gauge catheter. This vein can be identified by placing the thumb over the medial malleolus and moving it toward the anterior portion of the tibia. By extending the foot and piercing the skin parallel to the tibia and passing subcutaneously, the saphenous vein may be entered. To prevent the child from dislodging the catheter, tincture of benzoin is applied to the intravenous site and adjacent skin, and the catheter is secured with a sterile bioclusive dressing. The extremity is secured with a padded board, and the intravenous site is covered with a gauze dressing.

Following the establishment of intravenous access, preparations are made for endotracheal intubation. Intubation may be accomplished using the inhaled anesthetic agent without muscle relaxation or subsequent to the administration of a nondepolarizing neuromuscular relaxant. The administration of a neuromuscular relaxant decreases the potential for the cardiovascular depression that accompanies the administration of high concentrations of inhalation agents that may be required to facilitate laryngoscopy and intubation. The inspired concentration required for acceptable intubating conditions with sevoflurane in children ages 1 to 8 years is 3.54 ± 0.25%. The addition of 66% nitrous oxide decreases the required concentration by 40%.[82] A survey of members of the Society of Pediatric Anesthesia found that inhalation agent administration without neuromuscular blockade was used to facilitate endotracheal intubation 38% of the time in infants (0 to12 months) and 43.6% of the time in children (1 to 7 years old).[83,84] Whichever method is selected, the inhalation agent should be discontinued immediately before laryngoscopy. This practice minimizes the contamination of the operating room with free-flowing inhalation agent from the patient breathing circuit, and the delivery of high inspired anesthetic concentrations is avoided immediately after intubation during the confirmation of ETT placement. Following confirmation that the ETT is secured, the position of the tube at the alveolar ridge or lip is noted on the anesthetic record.

Single Breath Induction

This method can be used for children older than 3 years. The anesthesia circuit is filled with nitrous oxide, oxygen, and sevoflurane. The child is asked to take a deep breath and exhale fully. The mask is then applied to the face, and the child is asked to take in another deep breath. This method is not used to the extent it has been in the past; however, some providers still prefer this method due to the somewhat faster onset of induction.

Intravenous Induction

Intravenous (IV) induction is generally reserved for the child with an existing intravenous line. An IV induction may be clinically indicated when the child has a full stomach or a history of

gastroesophageal reflux. IV induction is quicker and more dependable, facilitating the rapid securing of the airway with endotracheal intubation. Venipuncture can be a frightening experience for the needle-phobic child. Oral premedication with midazolam before the child received the IV in the preoperative area can be given to decrease the child's anxiety and gain cooperation. The eutectic mixture of local anesthetic (EMLA cream) is applied well in advance (30 to 60 minutes) to aid in IV insertion and help decrease anxiety and increase cooperation. IV induction is performed similar to the method used for an adult. Standard monitors are placed after the child is moved to the operating room table, and preoxygenation given, followed by IV induction and securing of airway.

Intramuscular Induction

On rare occasions, an intramuscularly (IM) administered drug may be required in children who are uncooperative, mentally challenged, or who have reduced consciousness or in children who refuse alternative routes (i.e., oral, nasal, or rectal) for premedication. Ketamine is an excellent induction agent in these situations. It can be administered IM, and respirations and protective airway reflexes and vital signs are maintained during loss of consciousness. After intramuscular administration, the child may appear to be in a catatonic state. Parents who witness the administration of ketamine should be warned that their child might exhibit spontaneous involuntary movements and nystagmus. The psychogenic effects may be decreased with the concomitant administration of a benzodiazepine. Intramuscular ketamine in a dose of 4 to 6 mg/kg facilitates inhalation induction in children who are reluctant to be subjected to inhalation induction or venipuncture. Once unconsciousness is accomplished, an IV can be placed and standard anesthetic techniques begun.

Pediatric Airway Equipment

The child's age, weight, and proposed surgical procedure guide the selection of essential pediatric anesthesia equipment. The anesthesia workroom should be appropriately stocked with a variety of sizes of masks, airways, laryngeal mask airways (LMAs), laryngoscope blades, endotracheal tubes, endotracheal tube stylets, blood pressure cuffs, pulse oximeter probes, calibrated pediatric fluid sets, syringe pumps for the delivery of both fluids and drugs, an assortment of intravenous catheters, tape, and armboards.

Airway Equipment

The pediatric facemask is designed to fit the smaller facial features of the child and eliminate mechanical dead space. Contemporary masks are manufactured from transparent plastics and have a soft inflatable cuff that sits on the face. The transparent feature allows continuous observation of skin color and the appearance of gastric contents if vomiting occurs. Appropriately sized oral airways must be readily available. The relatively large infant tongue predisposes to airway obstruction after the induction of general anesthesia. Oral airways that are too large may produce airway obstruction and inhibit venous and lymphatic drainage, producing macroglossia and creating further airway compromise. The oral airway should be inserted with the aid of a tongue blade, displacing the tongue toward the floor of the mouth to allow smooth insertion of the airway. The insertion and rotation of an oral airway should be avoided in children, because the rotation may dislodge loose deciduous teeth. Nasal airways are infrequently used in children less than 1 to 2 years of age. The internal diameter of the nasal airway may unnecessarily increase the work of breathing. Adenoid hypertrophy may make nasal airway placement difficult and produce severe epistaxis.

Endotracheal Tubes. Traditional teaching since the 1960s has been that the use of a cuffed endotracheal tube (ETT) in infants and children less than 8 to 10 years of age should be avoided. Although this adage is widely accepted, recent literature suggests that this belief is not universally applied, is empirical rather than scientifically based, and is a perpetuated "myth" of pediatric anesthesia. The age-old argument against the use of a cuffed ETT in infants and children is quite logical; the narrowest portion of the infant and child airway has traditionally been understood to be at the level of the cricoid cartilage. The lumen of the noncompressible cricoid was thought to be round in shape. Traditional concepts outlining the differences in the adult and pediatric airways are noted in Table 47-3.

Sizing the Endotracheal Tube. Early detailed accounts of the laryngeal framework suggested that the larynx is shaped as a cone, with the apex at the level of the cricoid cartilage.[85,86] The compression of the tracheal mucosa at the level of the cartilaginous cricoid ring by an oversized ETT will produce mucosal edema. This traditional understanding has recently been challenged. Magnetic resonance imaging of sedated children ages newborn to 14 years has demonstrated that the lumen of the cricoid cartilage is not round but elliptical in shape, with the narrowest dimension in the transverse plane at the level of the vocal cords.[87] Another recent study questions this traditional teaching. Video bronchoscopic images and magnetic resonance spectrographs were obtained in 135 children, aged 6 months to 13 years. Measurement of laryngeal dimensions, including cross-sectional area, anteroposterior, and transverse diameters at the level of the glottis and the cricoid were performed. They found that the glottis rather than cricoid was the narrowest portion of the pediatric airway. They also noted that like adults, the pediatric airway is more cylindrical than funnel shaped.[88] Accordingly, the pressure exerted upon the laryngeal and tracheal mucosa with the use of an uncuffed ETT is in the posterior lateral position. This has been verified, as evidenced by the associated pathologic lesions found posteriorly in the subglottis. In addition, trauma that appears within the trachea occurs anteriorly from the impingement of the distal end of the ETT upon the anterior tracheal wall. The goal of ETT selection is the placement of an appropriately sized tube that allows controlled ventilation but minimizes laryngeal or tracheal injury. Because of patient variability, many formulas exist for the determination of the correct ETT size and for the depth of insertion. Despite countless practitioner recommendations, there is no agreed-upon standard formula. In addition, may practitioners fail to appreciate the differences in the internal diameter of small ETTs. Endotracheal tubes for neonates are sized by the internal diameter, yet the external diameters may differ by as much as 0.9 mm among manufacturers in tubes with identical internal diameters.[89]

The approximate size of an ETT for children 2 years of age and older may be determined with the following formula: 16 + age ÷ 4. Another formula used, especially for patients younger than 2 years old, to calculate ETT size is as follows: age ÷ 4 + 4. To accommodate the variability in patient airway size, ETTs a half size larger and a half size smaller should be immediately available.

The depth of ETT insertion from the dental alveoli may be estimated using the "1, 2, 3, 4/7, 8, 9, 10" rule—for example, the ETT is inserted to a depth of 7 cm in a neonate weighing 1 kg and to a depth of 8 cm in a 2-kg neonate. Another approximate method is to insert the ETT to a depth in centimeters three times the internal diameter of the ETT in millimeters. For example, a 3-mm ETT should be inserted to a depth of 9 cm. Uncuffed ETTs are marked distally with a double black line that provides a visual indication of the depth of the ETT. During intubation, the ETT is passed until the double black line has reached the level of the vocal cords. Optimal ETT size is one that easily passes through the glottis and subglottic regions. Clinicians are more inclined to

TABLE 48-4 Airway Device Details

			INFANT		CHILD									
	Preterm Neonate	Full-Term Neonate	6 mo	1 yr	2 yr	3 yr	4 yr	5 yr	6 yr	8 yr	10 yr	12 yr	14 yr	Adult
Average weight (kg)		3.5	7	10	12	14	16	18	20	25	30	40	50	70
Approx. BSA (m^2)		0.25	0.38	0.49	0.55	0.64	0.74	0.76	0.82	0.95	1.18	1.34	1.5	1.73
ETT size (age + 16)/4	2.5-3	3-3.5	3.5-4	4	4.5	4.5	5	5	5.5	6	6.5	7	7	7.5-8
Teeth to midtrachea (cm)	7-8	9	11	12	13	14	14	15	15	16	17	18	20	20
Nare to midtrachea (cm)	8-9	10	12	14	15	16	17	18	19	20	21	22	23	24
Laryngeal mask airway		1	1.5	1.5	2	2	2	2	2.5	2.5	2.5	3	3	4

From Davis PJ, Cladis FP, Motoyama EK. *Smith's Anesthesia for Infants and Children*. 8th ed. Philadelphia, Mosby; 2011.
Calculations for estimating the internal diameter (ID) of an endotracheal tube:
(16 + age in years)/4
(Age in years/4) + 4
The diameter of the fifth finger
Calculations for estimating the length required for an orotracheal tube:
Height (in cm)/10 + 5
Weight (in kg)/5 + 12
Advance the endotracheal tube:
30 times the ID from the alveolar ridge
(Age in years/2) + 12
Insert the endotracheal tube to the first or second black line marked on the tube.
Advance the endotracheal tube into a bronchus, then withdraw it, 2 cm.
BSA, Body surface area; *ETT*, endotracheal tube.

use a cuffed ETT without inflating the cuff than an uncuffed ETT. One recent study suggests checking cuff pressure for long cases to decrease the incidence of edema and tracheal damage.[90] Confirmation of proper ETT placement is imperative. Positive end-tidal CO_2, chest rise, and bilateral breath sounds are checked. Lung auscultation helps confirm proper ETT position. As the ETT is secured, it is important to not dislodge or pull out the ETT, which would necessitate re-intubation. The provider can place a stethoscope over the patient's mouth to check for leaks for proper cuff pressure. Table 48-4 notes airway device details.[91] Alignment of the head and its effect on the airway are depicted in Figure 47-3.

Laryngeal Mask Airway. The original LMA device was intended as an alternative to the anesthesia facemask rather than endotracheal intubation. The LMA is used for short surgical procedures that do not require endotracheal intubation and resuscitation situations. The LMA is available in sizes specific for the neonate, infant, child, and adolescent (Table 48-5). Many alternative designs for special uses are being introduced. The inflation of the pharyngeal cuff can produce undue pressure on pharyngeal structures. Like the adult ETT cuff, the LMA cuff may be expanded during the course of the anesthetic procedure with the administration of nitrous oxide. The initial volume of air injected into the laryngeal cuff may be regulated by identifying the amount of air and airway pressure that produces an audible leak. This pressure is generally between 15 and 25 cm H_2O. The LMA cuff should be inspected before each use, the volume of air required for cuff inflation should not exceed the manufacturer's recommendation, and the LMA cuff should be periodically checked during the administration of nitrous oxide to prevent overinflation.[92]

TABLE 48-5 Laryngeal Airway Mask Sizes

Laryngeal Airway Mask Size	Suggested Inflation Volume
1	6 mL
1½	10 mL
2	15 mL
2½	21 mL
3	30 mL
4	45 mL
5	60 mL

The LMA has traditionally been removed in the adult when airway reflexes return. Removal of the LMA in the pediatric patient can be associated with biting, pulmonary edema, severe laryngospasm, and separation of the tube from the pharyngeal mask.[93,94] Several studies have examined the appropriate time of LMA removal in children. In one study, oxygen desaturation was more prevalent (31.3%) after awake removal, compared with removal in a deep anesthetic plane (4.5%), whereas airway obstruction occurred more frequently (20%) with deep removal.[95] Researchers have reported a 10% incidence of severe laryngospasm with awake removal, compared with 5% with deep removal.[96]

Special Airway Equipment. Specialized uncuffed and cuffed oral and nasal ETTs may be chosen for otolaryngologic, ophthalmologic, and dental procedures. The RAE (right angle endotracheal; Mallinkrodt; Argyle, New York) tube is premolded, with the acute angle of the tube designed to be positioned over the lower

lip. The nasal RAE tube is premolded with a 180-degree bend that directs the tube toward the top of the head. These tubes facilitate the routing of the breathing circuit away from the surgical field. RAE tubes are longer than straight ETTs and place the distal end of the tube in closer proximity to the carina, thereby minimizing the chance of inadvertent extubation with neck extension. The RAE tube is designed with two Murphy eyes located at the distal end of the tube to facilitate uninterrupted ventilation if the tube migrates in a caudad fashion. However, proper ETT placement must be determined with confirmation of bilateral breath sounds after intubation and repositioning of the head. The use of a precordial stethoscope placed over the left anterior area of the chest will aid the detection of right bronchial migration of the RAE tube.

The clinical application of laser technology for the treatment of airway pathology necessitates the use of a specialized ETT. Endotracheal tube ignition may occur in as many as 1.5% of patients during CO_2 laser laryngeal procedures.[97] Modern polyvinylchloride ETTs absorb infrared light and may be ignited with a direct hit from a CO_2 laser or as a result of burning material in close proximity to the tube. Laser-resistant or "laser-safe" ETTs are available from several manufacturers and are marketed for specific laser applications (e.g., CO_2; neodymium-doped: yttrium-aluminum-garnet [Nd:YAG]; and potassium titanyl phosphate [KTP]). An alternative is wrapping the external surface of a polyvinylchloride ETT with a metallic foil (see Chapter 42).

Maintenance of a Patent Airway

A variety of anatomic and neurologic interactions are essential for the maintenance of a patent pharyngeal airway. It is truly remarkable that airway patency is continuously maintained with changes in posture as well as extremes of head and neck position. The larynx is innervated by a variety of receptors that react to stretch, the flow of inspired and expired gas, and muscle movement. Airway patency is also dependent upon lung stretch reflexes, central and carotid body chemoreceptor reflexes, and CNS arousal mechanisms. Pharyngeal patency is established and maintained through a delicate balance of CNS-derived dilating and collapsing forces upon the pharyngeal airway.[98,99] The pharynx may be conceptualized as a collapsible tube within a box, bordered by the tongue and soft palate, and enveloped by the bony elements of the mandible anteriorly and the cervical vertebra posteriorly. Pharyngeal patency is a function of the overall size of this box, and the amount of soft tissue between the bony elements and the pharynx. An increase in the amount of soft tissue within the box (e.g., obesity, hypertrophy of adenoids and tonsils, large tongue), or a decrease in the size of the bony elements (e.g., small craniofacial structures or craniofacial deformity) will limit the content of the box, resulting in compression of the pharyngeal airway. In effect the pharyngeal airway functions as a Starling resistor.[100]

Airway Management of the Infant and Child

In the awake infant and child, the tongue, the upper airway muscles (i.e., genioglossus, geniohyoid, sternohyoid, and sternothyroid) interact to tent the pharynx, preventing collapse. Anesthetic agents inhibit the neural activity of these airway muscles, resulting in pharyngeal narrowing or collapse.[101,102] The young infant depends upon compensatory mechanisms to maintain pharyngeal patency but is disadvantaged because of an anatomic imbalance (i.e., small maxilla and mandible, large cranium, large tongue).[103] A steadily increasing anesthetic depth during inhalation induction will depress these compensatory mechanisms, leading to pharyngeal narrowing and collapse.

Incomplete airway obstruction may be clinically evident early in the inhalation induction as audible inspiratory or expiratory sounds are evident through the precordial stethoscope. As the obstruction increases, a tracheal tug becomes notable with attempted inspiration. The infant has a compliant chest wall, and because of forceful diaphragmatic contraction, the chest is noted to collapse with inspiratory efforts against partial pharynx collapse. With continued inspiratory attempts, a paradoxical movement of the chest and abdomen (i.e., the contraction of the chest with abdominal expansion) is also appreciated. This thoracoabdominal asynchrony is an important clinical sign of upper airway obstruction. With complete pharyngeal collapse, the audible signs of obstruction are no longer appreciated, and thoracoabdominal asynchrony continues.

Perhaps as a result of immaturity, the CNS regulation of the pharyngeal dilator muscles is ineffective in opening the pharyngeal airway in the infant.[104] The application of continuous positive airway pressure (CPAP) 5 to 10 cm H_2O is essential in the reestablishment of a patent pharyngeal airway until sufficiently anesthetized to allow the placement of an oral airway. The application of CPAP accompanied by airway opening maneuvers (more importantly a chin lift) will reverse the anatomic imbalance, increase tidal volume, and diminish thoracoabdominal asynchrony.[105] The chin lift is an important airway maneuver because it widens the anteroposterior (at the epiglottis) and transverse diameters (at the level of the soft palate) of the pharyngeal airway.[106]

Because of the general anesthetic depression of CNS compensatory mechanisms for the maintenance of a patent pharyngeal airway, tracheal extubation should be undertaken when the young infant is awake and has adequate respirations. Thoracoabdominal asynchrony appearing immediately after extubation is indicative of upper airway obstruction and is not accompanied by traditional sounds of upper airway obstruction (i.e., snoring) as in the adult. Following extubation, the lateral decubitus position may be advantageous in that it has been shown to decrease the compressive effects of soft tissue that surround the pharynx in individuals with obstructive sleep apnea.[107]

Pharyngeal patency improves during the first year of life as the anatomic imbalance is lessened with continued growth of the maxilla and mandible, and CNS regulation matures. This is evidenced by the fact that there is generally less airway obstruction with inhalation induction in older infants and children. However, when airway obstruction develops during inhalation induction, the obstruction is generally easily managed with the previously cited airway opening maneuvers. "Deep" extubation can be safely accomplished in children with the prior insertion of an oral airway, and after extubation, continued maintenance of pharyngeal patency may be facilitated with the application of airway-opening maneuvers previously discussed.

Airway Complications

Two common airway complications with a pediatric patient are laryngospasm and bronchospasm. The larynx is the gatekeeper of the airway, protecting the lungs from the aspiration of foreign material. This function is most evident during swallowing, when the glottic closure reflex is initiated by stimulation of the superior laryngeal nerve facilitating sphincteric closure of the airway. Laryngospasm is a magnified glottic closure reflex in response to noxious stimuli of the superior laryngeal nerve and may persist despite the immediate removal of the stimuli. Laryngospasm precipitates a host of serious complications, including complete airway obstruction, gastric aspiration, postobstruction pulmonary edema, cardiac arrest, and death.[108]

The frequency of laryngospasm is greatest in patients with an upper respiratory infection (95.8/1000).[108] Children exposed to

BOX **48-5**

Risk Factors for Laryngospasm

Preoperative Factors

- Exposure to secondhand tobacco smoke
- Concurrent or recent upper respiratory tract infection
- Gastroesophageal reflux (GERD)
- Mechanical irritants (oropharyngeal secretions)

Intraoperative Factors

- Excitement phase of inhalation induction
- Tracheal intubation/extubation during "light" anesthesia
- Upper airway surgical procedures (e.g., tonsillectomy, adenoidectomy, nasal/sinus procedures, palatal procedures, laryngoscopy/bronchoscopy)

BOX **48-6**

Preventive Measures for Laryngospasm

- Avoid noxious airway/surgical stimulation during "light" anesthesia
- Assure sufficient anesthesia prior to airway instrumentation
- Topical application of lidocaine to suppress laryngeal sensory nerve activity
- Intravenous lidocaine prior to extubation
- Suction oral pharynx prior to extubation
- Tracheal extubation when fully awake
- Administer 100% oxygen for 3 to 5 minutes prior to extubation

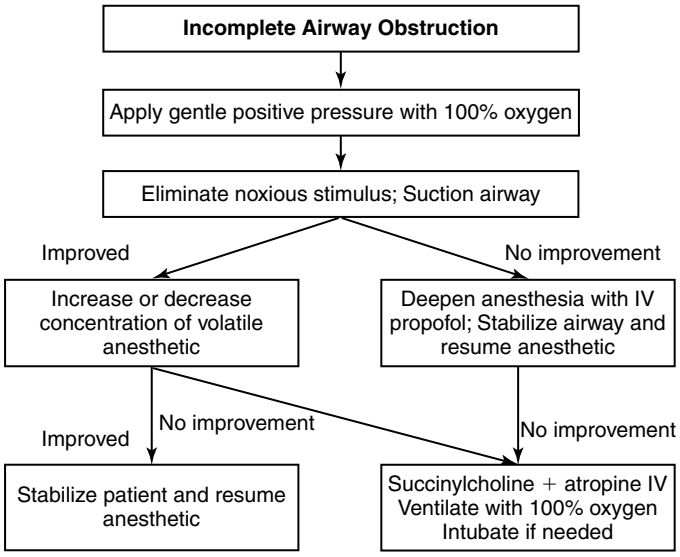

FIGURE **48-2** Incomplete airway obstruction algorithm. (From Wittkugel E. Pediatric laryngospasm. In: Atlee JL, ed. *Complications in Anesthesia*. 2nd ed. Philadelphia: Saunders; 2007:601.)

secondhand tobacco smoke have a 10-fold increase in the relative risk of laryngospasm (0.9% with no exposure, versus 9.4% with exposure).[109] Although laryngospasm may be self-limiting, the clinical importance of proper management is exemplified by the fact that five of every thousand children who experience laryngospasm have a subsequent cardiac arrest.[108]

The incidence of laryngospasm may be greater in the pediatric population because of specific practices in the anesthetic management of infants and children. Several factors are generally associated with the development of laryngospasm (Box 48-5). The risk of laryngospasm is increased when airway instrumentation is attempted before an adequate depth of anesthesia has been achieved, without the benefit of neuromuscular blocking drugs, and in infants and children with residual effects of previous upper respiratory tract infections.

The precise pathophysiologic mechanism responsible for laryngospasm remains elusive. To expand our understanding of laryngospasm and its clinical management, it is best to revisit the original description provided by Fink in 1951.[110] The basic execution of laryngeal closure follows superior laryngeal nerve stimulation. The mechanism resembles a shutter, where the laryngeal inlet is closed by the action of the supraglottic folds, the false vocal cords, and the true vocal cords. Fink has suggested that glottis closure is a dual mechanism. The first response is the closure of the vocal cords (a shutter effect) followed by a ball-valve effect with closure of the false cords and the subsequent rounding of the supraglottic tissue after the shortening of the thyrohyoid muscle. This produces an envelopment of the laryngeal inlet by the supraglottic tissue with continued inspiratory effort, producing complete airway obstruction.

The prevention of laryngospasm requires an understanding of the risk factors. Box 48-6 lists measures that may be undertaken for the prevention of laryngospasm. Prompt recognition and management is imperative to prevent hypoxemia and the subsequent development of bradycardia and cardiac arrest.

Incomplete airway obstruction (Figure 48-2) may be evident as "grunting" or audible inspiratory and expiratory sounds as heard through a precordial stethoscope, accompanied by tracheal tug and thoracoabdominal asynchrony. Management consists of three essential processes. First, the responsible noxious stimuli should be discontinued (e.g., surgical stimulation, attempted airway instrumentation during "light" anesthesia, removal of pharyngeal secretions with gentle suctioning). Next, anesthetic depth should be increased by the delivery of increased concentration of inhalation agent or intravenous administration of a small dose of propofol. Third, gentle positive-pressure ventilation using 100% oxygen should be attempted using a properly applied facemask with concurrent airway opening maneuvers (i.e., slight head extension, chin lift, and jaw thrust). On occasion, this may require two individuals, one to firmly apply the facemask and open the airway, and one individual to attempt positive-pressure ventilation.

The transition to complete airway obstruction (Figure 48-3) becomes evident with the absence of inspiratory and expiratory sounds, as well as the inability to deliver positive-pressure ventilation. The application of positive airway pressure for the treatment of complete airway obstruction may not be successful. Further deterioration of arterial oxygen saturation with accompanying bradycardia may occur despite the continued application of positive-pressure ventilation, and the envelopment of the laryngeal inlet supraglottic tissue may be worsened. The administration of succinylcholine will then be required to break the laryngospasm.

Bilateral firm and direct application of pressure toward the skull base produces an anterior displacement of the mandible. In addition to producing a jaw thrust, the intense stimulation with

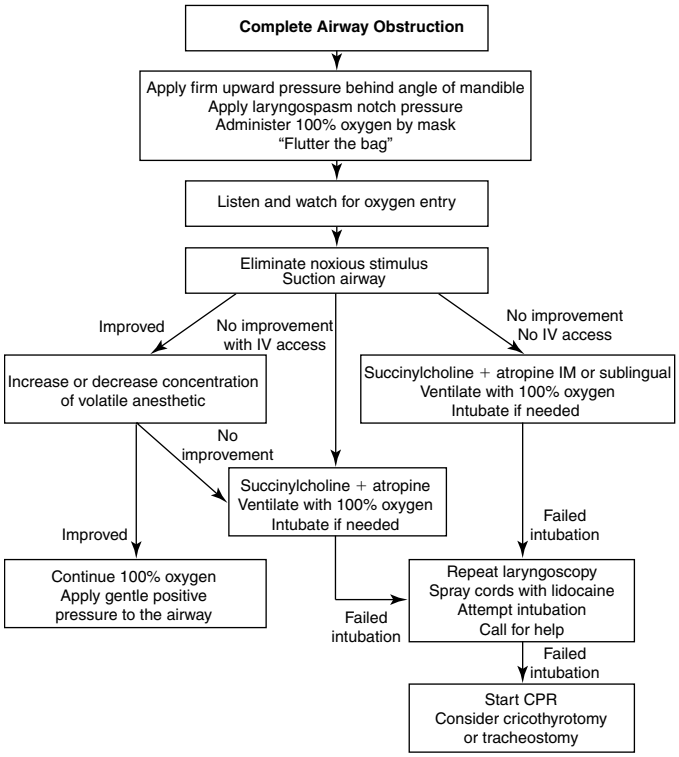

FIGURE **48-3** Complete airway obstruction algorithm. (From Wittkugel E. Pediatric laryngospasm. In: Atlee JL, ed. *Complications in Anesthesia*. 2nd ed. Philadelphia: Saunders; 2007:600.)

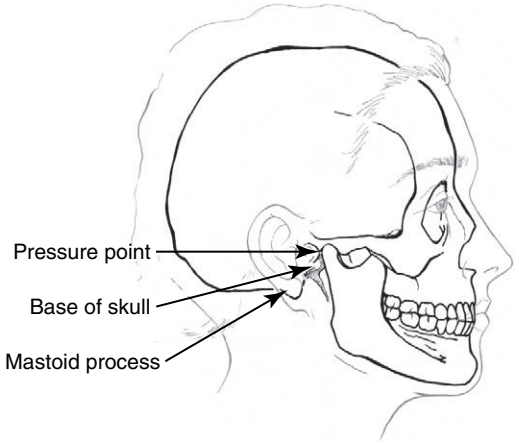

FIGURE **48-4** The laryngospasm notch.

postcondylar pressure in the lightly anesthetized patient often produces a ventilatory sigh.[111] This maneuver may be successful for the treatment of laryngospasm.[112] Figure 48-4 shows the laryngospasm notch.

If complete airway obstruction continues unabated, intravenous administration of atropine and succinylcholine should be administered without delay. In the absence of intravenous access, intramuscular succinylcholine (4 mg/kg) is administered in the deltoid muscle. Following intramuscular administration, the vocal cords will begin to relax within 60 seconds, permitting positive-pressure ventilation and relaxation to facilitate endotracheal intubation. With continued deterioration in arterial oxygen saturation, intubation may be required prior to the onset of skeletal muscle relaxation. In an extreme situation, the application of lidocaine to the vocal cords may produce sufficient relaxation, allowing endotracheal intubation. Severe hypoxia and hypercarbia are known to terminate laryngospasm.[114] Certainly these are not desired treatment options for laryngospasm.

Bronchospasm is increased airway resistance that eventually resolves spontaneously or with pharmacologic intervention. It is the disorder of smooth muscle. It is known that airway resistance increases after instrumentation of the airway. Rarely does this result in the complication of bronchospasm (0.4%); however, in children with known asthma or a current upper respiratory infection, the incidence is increased (4.1%) and can cause the anesthesia provider some concern.[115-117]

Bronchospasm may manifest as an audible wheeze. Under anesthesia, however, the provider may notice an upward slope of the end-tidal carbon dioxide monitoring with a rise in end-tidal carbon dioxide, prolonged expiration, decrease in oxygen saturation, increased peak inspiratory pressures, decrease in tidal volume, and difficulty ventilating. Before the diagnosis of bronchospasm is confirmed, the anesthesia provider must think of possible causes: anaphylaxis to drugs, IV fluids, latex; airway manipulation, irritation, secretions; esophageal intubation; pneumothorax; and inadequate anesthetic depth.[118]

The first intervention when an airway issue is suspected is placing the patient on 100% oxygen. Auscultation of the lungs may reveal wheezing. If the problem is severe, the surgeon should be informed to stop the surgery, and the anesthesia provider should have the operating room staff call for help. Anesthetic depth should be assessed and deepened and the patient should be ventilated by hand. A bronchodilator medication, such as albuterol, should be given via endotracheal tube.

After adequate time has passed, reassess the patient's lungs, oxygenation, color, placement of endotracheal tube, capnography, and overall status.[118] When treating a pediatric patient, their respiratory reserve is minimal. It may be necessary to intervene and treat the bronchospasm with epinephrine sooner than treating an adult for a similar diagnosis. Epinephrine 5 to 10 mcg/kg should be used as the initial subcutaneously injected bronchodilator in children.[119] In life-threatening emergencies, dilute a 1-mg vial of epinephrine in a 10-mL syringe, give 1 to 2 mL (100-200 mcg) IV push, in increments, for a maximum dose of 0.5 mg per dose of a 1:1000 solution and wait for the child's reaction.[120]

Another treatment for bronchospasm is corticosteroids. Intravenous steroids may help long-term treatment but do little in acute emergencies.

Difficult Airway. A difficult airway may be defined as difficulty in accomplishing mask ventilation and/or endotracheal intubation. The identification of the difficult pediatric airway begins with a thorough history followed by physical examination of the mouth, head, and neck. The physical examination should focus upon the assessment of facial skeletal features, specifically the size and shape of mandible and maxilla, size of the tongue in relation to the oral cavity, absence of dentition, presence of loose dentition, and the range of motion of the neck. Box 48-7 lists some features of pediatric airway physical examination. Box 48-8 lists pathologic conditions that impact pediatric airway management.

A history of snoring, difficulty breathing with feeding, current or recent upper respiratory tract infection, and past history of croup should be obtained. Previous anesthetic records are an invaluable resource in determining the history of difficult airway management. However, a prior uneventful anesthetic does not preclude

BOX 48-7

Physical Examination of the Pediatric Airway

- Note the size and shape of the head
- Facial features—size and shape of mandible and maxilla
- Oral examination—size of tongue, loose or missing dentition, prominence of upper incisors
- Range of motion of jaw and cervical spine

BOX 48-8

Pathologic Pediatric Airway Conditions

Nasopharynx
- Choanal atresia
- Foreign body/tumors
- Adenoid hypertrophy

Tongue
- Hemangioma
- Angioedema
- Down syndrome
- Beckwith-Wiedemann syndrome
- Mucopolysaccharidosis
- Cystic hygroma
- Lacerations

Skeletal Structure
- Pierre Robin syndrome
- Treacher Collins syndrome
- Goldenhar syndrome
- Fractures
- Juvenile rheumatoid arthritis
- Cervical spine injury
- Mandibular ankylosis
- Arnold-Chiari malformation

Pharynx and Larynx
- Laryngeal web
- Laryngeal stenosis
- Laryngomalacia
- Laryngeal papillomatosis
- Foreign body
- Postintubation croup
- Epiglottitis
- Peritonsillar abscess
- Retropharyngeal abscess

the possibility of difficulty of airway management with succeeding anesthetics.

If there is any indication from the history and physical of a potentially difficult airway, these guidelines should be followed:

1. Do not give neuromuscular blocking agents.
2. Prepare a variety of laryngoscope blades, endotracheal tubes, and oropharyngeal airways.
3. Plan for different induction options: awake fiberoptic; sedation, anesthetizing spray, and awake fiberoptic; inhalation induction.
4. After a deep plane of anesthesia is reached, use 100% oxygen.
5. Establish IV access (if not preoperatively), and consider atropine or glycopyrrolate to decrease oral secretions.
6. Always maintain spontaneous respirations.
7. Use external manipulation of the trachea when possible to make visualization of glottis easier.
8. Use and/or availability of adjunct airway equipment: GlideScope, fast-track LMA, blind nasal intubation, light wand, Eschmann stylet, cricothyrotomy.
9. Follow the standardized difficult airway algorithm (see Chapter 22).

Emergence and Extubation

Similar to adults, the end of surgery in the pediatric patient involves return of spontaneous breathing and weaning of anesthetic agents. It is important to have airway equipment readily available in case of the need to quickly reintubate. The child should show signs of alertness such as facial grimacing, spontaneous eye opening, and purposeful movement. It is best to extubate when the child is fully awake. Children are more prone to laryngospasm during extubation, especially when done during stage 2 of anesthesia. Judicious suctioning is also imperative to help prevent adverse airway events.

Deep extubation can be done after prudent suction of oropharynx and stomach in patients with a normal airway and an empty stomach. It should be carefully decided whether the patient is appropriate for a deep extubation. Also, the anesthesia provider must be aware of the level of care in the postoperative care unit where the patient will be recovering. Patients that were difficult to ventilate or intubate, those with a full stomach, and neonates and young infants should be fully awake prior to extubation.

All standard monitors should remain on the patient until extubation. When breathing remains satisfactory, transportation to the postanesthesia care unit (PACU) can ensue. Pediatric patients do well in the lateral position to keep them from obstructing their airway. Also, supplemental oxygen is recommended for all pediatric patients. The anesthesia provider can give a chin lift while feeling for exhalation with the hand and/or observing for condensation in the oxygen mask.

Fluid Management

The maintenance of fluid homeostasis is essential in the comprehensive intraoperative care of the pediatric patient. The restoration and maintenance of pediatric intravascular volume is crucial if cardiac output is to be optimized and tissue oxygen delivery ensured.

Intravascular fluid balance is influenced by a number of preoperative and perioperative circumstances. Preoperative intravenous fluid administration minimizes the degree of dehydration that accompanies the NPO period. Unless there exists a compelling reason to place an intravenous catheter preoperatively, intravenous therapy is generally avoided in the pediatric patient until general anesthesia has been induced via inhalation.

Perioperative fluid homeostasis is altered by a number of factors, including inhalation agent administration, the operating room environmental temperature, iatrogenic hyperventilation, and surgical stress. Potent inhalation agents produce peripheral vasodilation and varying degrees of myocardial depression, decreasing systemic blood pressure and end-organ perfusion. Dehydration after prolonged preoperative oral fluid abstinence aggravates these decreases in systemic blood pressure. The delivery of cold, dry anesthetic gases via an ETT bypasses normal anatomic humidification, increasing the loss of fluid from the respiratory tract. These insensible respiratory fluid losses can be minimized with the use of active or passive humidification systems during the intraoperative period. The operating room temperature also influences fluid balance. Basal caloric and water requirements are increased in a cold environment. Increases in core body temperature of 1° C may increase caloric expenditure by 12% to 14%.

General anesthesia modifies the neuroendocrine control of fluid balance. Surgical stress increases plasma glucose levels. Hyperglycemia results in an osmotic-induced renal loss of free water. Anesthetic agents modify neuroendocrine regulation of fluids and electrolytes. Opioids increase the release of antidiuretic hormone (ADH) from the posterior pituitary.[121] Antidiuretic hormone stimulates the release of aldosterone to conserve water through the renal reabsorption of sodium and water and the excretion of potassium. Decreased glomerular filtration, which parallels the decrease in renal perfusion, alters the kidneys'

TABLE 48-6 Hourly Fluid Requirements: The "4-2-1" Formula

Weight (kg)	Fluid
0-10	4 mL/kg/hr for each kg of body weight
10-20	40 mL + 2 mL/kg/hr for each kg greater than 10 kg
>20	60 mL + 1 mL/kg/hr for each kg greater than 20 kg

Sample Calculated Fluid Requirements	Maintenance Fluid per Hour
4 kg	16 mL
9 kg	36 mL
15 kg	50 mL
30 kg	70 mL

TABLE 48-7 Fluid Replacement for Third-Space Fluid Losses

Expected Surgical Trauma	Administration Rate (mL/kg/hr)	Recommended Intravenous Fluid
Minimal	3-4	Lactated Ringer's
	0.9% NS, Plasma-Lyte	
Moderate	5-6	Lactated Ringer's
	0.9% NS, Plasma-Lyte	
Severe	7-10	Lactated Ringer's
	0.9% NS, Plasma-Lyte	

NS, Normal saline.

ability to handle administered fluid loads. Decreased renal perfusion stimulates the release of renin, which cleaves angiotensin I to form angiotensin II, a powerful vasoconstrictor that acts to increase systemic blood pressure. Renin stimulates the release of aldosterone.

Surgical trauma modifies fluid balance, the degree of which is dependent on the invasiveness of the surgical procedure. Intravenous fluids are used to replace intraoperative blood loss and fluid loss resulting from fluid shifts that develop from evaporative and third-space fluid losses. Physiologic parameters, such as temperature, heart rate, blood pressure, capillary refill time, urine output, and ongoing blood loss, are continually assessed. The rate of intraoperative fluid administration is continuously modified to maintain circulatory homeostasis. Peripheral surgical procedures (extremity procedures) have minimal evaporative or third-space fluid losses. However, intracavitary procedures (intraabdominal or intrathoracic procedures) are associated with greater blood loss, third-space fluid loss, and substantial evaporative fluid losses that approach 10 mL/kg of body weight per hour.

Pediatric Fluid Compartments

The growth of the newborn is accompanied by a decrease in the relative fluid compartment volumes of TBW and ECF volumes during the first year of life, followed by additional decreases in ECF later in childhood. The TBW of the premature infant is as high as 80% of total body weight, whereas the TBW of the term infant is approximately 70% to 75% of total body weight. The adult value of TBW (55% to 60%) is reached between 6 months and 1 year of age. Knowledge of body fluid distribution is important when one is selecting specific fluids and volumes for administration. The differences in TBW, as well as in the ICF and ECF compartments in the premature infant, term infant, child, and adult, can be found in Table 47-8.[122]

Maintenance-Fluid Calculation

The most direct and widely accepted method for determining intravenous fluid requirements is based on body weight. Holliday and Segar proposed a formula for the calculation of hourly maintenance fluids based on caloric expenditure studies in children. The hourly maintenance fluid level is determined by the "4-2-1" formula and is calculated as follows (Table 48-6).[123] For the first 10 kg of body weight, 4 mL of crystalloid intravenous fluid (e.g., lactated Ringer's) is administered for each kilogram of body weight per hour. The hourly maintenance fluid requirement of a child who weighs 10 kg would be calculated as 10 kg × 4 mL/kg/hr = 40 mL/hr. Children weighing in excess of 10 kg but less than 20 kg would receive an additional 2 mL/kg/hr for body weight in excess of 10 kg. The child weighing 14 kg would receive 4 mL/kg/hr for the first 10 kg (40 mL) plus an additional 2 mL/kg/hr, for a total of 48 mL/hr. Children weighing in excess of 20 kg would receive an additional 1 mL/kg/hr in hourly fluid. This hourly maintenance fluid calculation serves as a basic guideline and does not take into account fluid deficits that develop during the NPO period and additional fluid losses (such as blood and third-space losses) that occur during the perioperative period.

Preoperative fluid deficits develop during the period of time in which the child has not received oral or intravenous maintenance fluids. The preoperative fluid deficit is calculated by determining the hourly maintenance fluid rate and multiplying this rate by the number of hours the child has been without intravenous or oral intake. The following calculations are used to determine the preoperative fluid deficit of an 8-kg child who has been NPO for 6 hours:

$$\text{Maintenance fluid} = 8\ \text{kg} \times 4\ \text{mL/kg/hr} = 32\ \text{mL/hr}$$

$$\text{Deficit} = \text{NPO hours} \times \text{maintenance fluid rate}$$
$$= 6\ \text{hr} \times 32\ \text{mL/hr} = 192\ \text{mL}$$

The calculated fluid deficit is replaced following the guidelines of Furman et al.[124]: half of the fluid deficit is replaced during the first hour, with the remainder divided in half and replaced in the subsequent 2 hours. Using the calculations just presented, the following plan for intravenous fluids is developed.

Weight = 8 kg	Hour 1	Hour 2	Hour 3
Maintenance fluid (mL/hr)	32	32	32
Deficit (mL/hr)	96	48	48
Hourly total (mL/hr)	128	80	80

In addition to the calculated maintenance and deficit fluids necessary to replace insensible fluid losses, additional intravenous fluid is required to replace third-space fluid losses that occur with surgical trauma. Lactated Ringer's solution, 0.9% normal saline, and Plasma-Lyte are acceptable for the replacement of insensible and third-space fluid losses at the rate of 1 to 2 mL/kg/hr. Expected third-space fluid losses can be categorized as minimal surgical trauma (an additional 3 to 4 mL/kg/hr), moderate surgical trauma (5 to 6 mL/kg/hr), and major surgical trauma (7 to 10 mL/kg/hr). Table 48-7 lists fluid replacement for third-space losses.

Glucose-Containing Solutions

Historically, glucose was administered during the perioperative period to prevent hypoglycemia, provide free water to replace the

insensible water lost during the NPO period, conserve protein, and avert ketosis by preventing gluconeogenesis.[125] Surgical stress (e.g., surgical incision) elicits a neuroendocrine response, increasing plasma glucose levels. Despite extended periods of fasting, studies have noted that healthy pediatric patients infrequently become hypoglycemic.[126,127] However, very critically ill infants and those weighing less than 10 kg may develop hypoglycemia with prolonged periods of fasting. Routine dextrose administration is no longer advised for otherwise healthy children receiving anesthesia.[128] Most clinicians administer a glucose-free intravenous solution (e.g., lactated Ringer's) for maintenance and replacement of third-space and intraoperative blood loss. If the child has had an extended NPO period, a glucose level may be determined intraoperatively and appropriate adjustments in therapy can be made. Although the CNS is totally dependent on a continuous supply of exogenous glucose for the maintenance of cellular energy requirements, the continuous administration of glucose or elevated plasma glucose levels may worsen neurologic outcome in the event of an ischemic or hypoxic event. This association between hyperglycemia and worsened neurologic outcome has been well established.[129,130]

Hypoglycemia is likely to develop in a variety of clinical circumstances. Examples include infants who are premature, infants of diabetic mothers, children with diabetes who have received a portion of daily insulin preoperatively, and children who receive glucose-based parenteral nutrition. A glucose-containing intravenous solution is administered to these patients as a controlled piggyback infusion, with frequent plasma glucose determinations performed to avoid hyperglycemia. Infants born of mothers with diabetes and infants of mothers who receive glucose-containing solutions during labor may require a continuation of these solutions for the prevention of rebound hypoglycemia. Premature infants who have had less time to store glycogen in the liver than term infants are more susceptible to hypoglycemia. For this reason, premature infants may receive an infusion of 10% dextrose in 0.2% normal saline.

Crystalloid Intravenous Fluids

Crystalloid intravenous fluids contain water, various concentrations of electrolytes, and varying amounts of glucose. These solutions move freely between the intravascular and interstitial fluid compartments. Crystalloid intravenous solutions are advantageous for perioperative administration, because they are the least expensive of the available intravenous solutions and are acceptable for the replacement of preoperative, intraoperative, and postoperative isotonic fluid deficits. Unlike colloid solutions, crystalloid solutions do not produce allergic reactions. Crystalloid intravenous solutions can be further subdivided by their tonicity in relation to plasma (i.e., hypotonic, isotonic, or hypertonic). Tonicity is a measurement of the comparative osmolarity of solutions, which is determined by the sodium chloride content. For example, a hypotonic solution (e.g., 0.45% normal saline) has a lower sodium concentration (less than 130 mEq/L) and an osmolarity less than 280 mOsm/L; an isotonic solution (e.g., lactated Ringer's) has a sodium concentration between 130 and 155 mEq/L and an osmolarity between 280 and 310 mOsm/L; a hypertonic solution (e.g., 3% normal saline) has a sodium concentration greater than 155 mEq/L and an osmolarity in excess of 310 mOsm/L. These sodium-containing solutions move freely about the extracellular space, whereas the sodium-free intravenous solutions such as 5% dextrose in water (D_5W) will be distributed throughout all fluid compartments. Table 48-8 lists the physical constituents and the osmolarities of popular crystalloid solutions. An isotonic solution does not need to be equivalent to plasma in exact physical constituents (e.g., sodium, chloride, potassium) to be considered an isotonic solution, because it is the number of particles dissolved in solution (principally sodium) that determines the osmolarity.

Estimation of Blood Volume

The goal of perioperative blood administration is the maintenance of acceptable oxygen-carrying capacity. Because pediatric patients have a relatively low intravascular volume compared with adults, vigilance and an accurate determination of intraoperative blood loss is fundamental to quality patient care. The intravascular volume may be estimated by multiplying the child's weight by the estimated blood volume. The estimated blood volumes are as follows: premature infant, 90 to 100 mL/kg; full-term newborn, 80 to 90 mL/kg; infants 3 months to 3 years, 75 to 80 mL/kg; and child older than 6 years, 65 to 70 mL/kg (see Table 48-2). For example, the estimated blood volume of a 6-month-old infant who weighs 7 kg is 525 mL (7 kg × 75 mL/kg = 525 mL).

The determination of intraoperative blood loss can be difficult. Subjective estimates of blood loss are grossly inaccurate. Blood

TABLE 48-8 Physical Characteristics of Popular Intravenous Crystalloid Solutions

	Sodium (Na) (mEq/L)	Chloride (Cl) (mEq/L)	Potassium (K) (mEq/L)	Calcium (Ca) (mg/mL)	Lactate (mg/mL)	Glucose (mg/dL)	mOsm/L
Hypotonic Solutions							
0.45% Normal saline	77	77					154
5% Dextrose in water						50	252
Isotonic Solutions							
0.9% Normal saline	154	154					308
Lactated Ringer's	130	109	4	3	28		273
Ringer's	130	109	4	3			309
Plasma-Lyte A	140	98	5				290
Hypertonic Solutions							
5% Sodium chloride	855	855					1700
7.5% Sodium chloride	1283	1283					2400

Adapted from Ellis D. Regulation of fluids and electrolytes. In: Davis PJ, Cladis FP, Motoyama EK. *Smith's Anesthesia for Infants and Children*. 8th ed. Philadelphia: Mosby; 2011:344-364.

collected from the surgical field in suction canisters can be easily measured, but up to one half of blood lost during surgery can be contained in items such as surgical drapes, sponges, and towels and is difficult to measure. Accurate accounting of surgical blood loss related to these items requires weighing them. Every 1 g of weight is equal to 1 mL of blood loss. Ongoing surgical blood loss requires frequent reassessment of the child's blood pressure, heart rate, and urine output. It is best to chart a running total and obtain hemoglobin and hematocrit levels as needed.

Mild dehydration is associated with a less than 5% decrease in body weight. Signs and symptoms are blood pressure, heart rate, and capillary refill within normal limits. Dry mouth and malaise can possibly be seen preoperatively; however, they are not evident if the patient is under general anesthesia. Urinary output of less than 1 mL/kg/hr should be maintained. Moderate dehydration is associated with a 5% to 10% decrease in the patient's body weight. Signs and symptoms include normotension and possible tachycardia with prolonged capillary refill. Patient may exhibit lethargy, thick and/or dry mucous membranes, decreased urine output, and depression of anterior fontanelle. Severe decreases in intravascular volume are associated with a greater than 10% decrease in body weight. Signs and symptoms are tachycardia, hypotension, narrowed pulse pressure, low urine output, decreased central venous pressure, pallor, and slow capillary refill. The patient will have a decreased level of consciousness, mottled and cool skin, and be anuric. A sudden decrease in blood pressure in neonates and infants with rate-dependent cardiac output is indicative of significant intravascular volume depletion.

Fluid management for dehydrated patients includes a 10 to 20 mL/kg fluid bolus over 10 to 30 minutes. After evaluation of fluid bolus, subsequent boluses also may be given. The goal is euvolemia for all surgical procedures.

Permissible Blood Loss

What amount of blood loss may be permitted, while the patient still maintains adequate tissue oxygenation? No published studies are available to guide the anesthetist in determining the optimal and safe lower limits for hemoglobin concentration. Historically a hemoglobin of 10 g/L or a hematocrit of 30% triggered blood transfusion. This "transfusion trigger" has been redefined in light of the risks of blood-borne pathogen transmission. Permissible blood loss must be defined individually for each patient based on current medical condition, surgical procedure, and cardiovascular and respiratory function. Children with normal cardiovascular function may tolerate a lower hematocrit and may compensate with an increased cardiac output if a higher inspired oxygen concentration is provided to improve oxygen delivery. An exception is the premature infant. The incidence of apnea is higher in neonates and the premature infant with hematocrit levels below 30%. The anesthetist, surgeon, and neonatologist should agree upon a target hematocrit level, and this discussion should be documented in the medical record.

Allowable blood loss may be calculated with the following formula:

$$ABL = EBV \times (H_O - H_L) / (H_A)$$

Where ABL is allowable blood loss, EBV is estimated blood volume, H_O is original hematocrit, H_L is the lowest acceptable hematocrit, and H_A is the average hematocrit. In place of H_A, (H_O + H_L) ÷ 2 can be used. For a 6-month-old infant who weighs 7 kg, with a starting hematocrit of 35% and the selection of the lowest acceptable hematocrit of 25%, we calculate the following:

$$ABL = 525 \times (35 - 25) / (25 + 35) / 2 = 174 \text{ mL}$$

Blood loss may be replaced with suitable crystalloid solutions (e.g., 0.9% normal saline, lactated Ringer's) by administering 3 mL for each mL of blood loss. Recall that the intravascular volume is one third of the ECF volume. Accordingly, one must administer 3 mL of an intravenous crystalloid solution to replace each mL of blood loss. A blood loss of 100 mL therefore requires replacement with 300 mL of crystalloid solution. Blood loss that is less than the calculated permissible blood loss may be replaced with colloid (1 mL for every 1 mL of blood loss).

When the blood loss equals or exceeds the calculated allowable loss, transfusion should be considered. Before transfusion is performed, a current hemoglobin and hematocrit should be obtained. The surgeon should be included in the decision process. These discussions and the resultant hemoglobin and hematocrit are recorded in the anesthetic record. The volume of packed RBCs (PRBCs) to be infused may be determined by the following formula:

$$\text{Packed RBCs (mL)} = \frac{(\text{Blood loss} - \text{ABL}) \times \text{desired hematocrit (30\%)}}{\text{Hematocrit of PRBCs (75\%)}}$$

Using the previous example of a 7-kg infant, with a total blood loss of 300 mL, the volume of PRBCs would be 300 − 174 × 30/75 = 50 mL.

Once the blood loss exceeds one blood volume, a coagulopathy can ensue. This occurs because of dilution of platelets and a reduction in circulating clotting factors. Platelets, fresh frozen plasma, and cryoprecipitate transfusions become necessary.

Blood Transfusion

Before blood component therapy is initiated, the proper equipment (e.g., filters, infusion devices, blood warming devices) should be obtained and tested. Blood is usually warmed before infusion. The American Association of Blood Banks has published standards for the use of blood-warming devices. Blood warmers must have a visible thermometer and an audible warning indicating excessive heating (greater than 42° C). Warming devices for adult transfusions (e.g., in-line water baths, countercurrent heating with water through large-bore tubing) are cumbersome to use for the small volumes to be transfused in the pediatric patient. The selected blood component containers may be placed under the forced-air warming blanket, or the measured aliquot of blood drawn into a syringe may be warmed with the hand. Syringes should not be placed into water baths, because bacterial contamination may occur.

Blood administration need not be complicated. It is difficult to accurately determine the amount of blood administered when it is infused via adult-intended warming devices. Accurate accounting of transfused blood products is facilitated by drawing the measured quantity by syringe with subsequent delivery of the measured quantity. A suitable device is an infusion set with an 80-mm blood component filter. This three-way infusion set is spiked into the blood component container, and the second limb of the set is placed into a stopcock, preferably located at the intravenous site. A syringe is attached to the remaining limb of the infusion set, allowing measured aliquots of blood to be drawn from the blood component container and then injected into the intravenous site.

The use of adult blood units is wasteful when the small infant requires transfusion. The blood bank can dispense small aliquots of blood into a calibrated syringe or provide 50- to 100-mL bags of the selected blood product transferred from an assigned donor unit. Blood used for neonatal transfusion is preferably less than 1 week old, to preserve 2,3 diphosphoglycerate levels, and

irradiated to prevent graft-versus-host disease. When packed RBCs are transfused, the blood should not be diluted prior to transfusion; this may contribute to hypervolemia. One rule of thumb states that in the absence of ongoing blood loss, 4 mL/kg of packed red cells will be required to raise the hemoglobin level by 1 g/dL.[131]

POSTOPERATIVE CARE

Similar to an adult patient, standard monitoring is continued when the pediatric patient arrives in the PACU. Although all the parameters are important, special attention to oxygenation is crucial. Postoperative hypoxia may be the result of several factors, but postextubation croup and laryngospasm are more likely in children than adults.[132]

After the "hand off" to the PACU nurse, the awakening patient begins the final phase of the perioperative process. All children wake up differently from anesthesia, it is not easy to predict. Some children awaken with emergence delirium (see previous discussion). This dissociative state of consciousness may leave the child restless and inconsolable. In most young children, it is important to let the parents help attend to the child's cries. Having a family member try to calm the patient may help the situation.

As mentioned earlier, oxygenation is an important area of concern in the PACU. Airway obstruction, obstructive sleep apnea, postextubation croup, and apnea of prematurity can all occur and need to be recognized with prompt intervention. Airway obstruction can be due to the positioning of the patient's head or oropharyngeal structures. Simply repositioning the head can sometimes relieve this problem. It would seem removal of the hypertrophic tonsil and adenoids would alleviate obstructive sleep apnea immediately postoperatively; however, surgical edema may cause these patients to continue to obstruct in the immediate postoperative period. Positioning and adequate oral suctioning can help prevent obstruction and possible laryngospasm.

The incidence of postextubation croup has been reported to be 1.6% to 6%. Prevention of tracheal irritation is the best way to prevent this problem. Using the right ETT size with pressures near 20 cm H_2O, prevention of friction of the tube in the trachea by securing properly, and prevention of unplanned extubation are ways to help decrease the risk of developing postextubation croup.[133]

Patients who were born before 36 weeks' gestation and whose postconceptual age is less than 60 weeks have a greater risk of central apnea. For this reason, these patients should be kept overnight for observation after any surgical procedures. The risk of apnea if the patient has received regional anesthesia versus receiving general anesthesia is less; however, these patients should be admitted and monitored postoperatively as well.[134]

Discharge from the PACU is typically done by a scoring system that includes blood pressure, heart rate, respirations, temperature, pain, nausea/vomiting, physical activity, and level of consciousness. The goal is for the patient to return to preprocedure parameters before discharge. One common method that is used is the modified-Aldrete scoring (see Chapter 51). When evaluating a patient in the ambulatory surgery center to be "fast tracked" a score of 12 or higher is needed.[135] When fast tracking is anticipated, the anesthetic can be planned to allow for short PACU times and quick discharge to home.

REGIONAL ANESTHESIA

During the past 10 years, the use of pediatric regional anesthesia has become established. Regional anesthesia provides perioperative analgesia minimizing the risk of respiratory depression, modifies the metabolic responses to anesthesia and surgery, and may improve patient outcomes.[136-138] Although the popularity of combined regional anesthetic techniques for adults has increased, the use of pediatric regional anesthesia has been more limited. Regional anesthesia is generally performed during general anesthesia, and the detection of intravascular injection and the signs of local anesthetic toxicity are masked during general anesthesia. Also, there is a limited ability to properly assess the sensory level of block in the sedated preverbal child and the consequences of accidental dural puncture are more difficult to assess and treat.

Unlike the adult patient, the pediatric patient will generally receive a peripheral or centrally administered regional anesthetic after the induction of general anesthesia. The inherent fear of needles and pain, the fear of neurologic injury in a combative child, and the difficulty in providing adequate sedation to ensure patient mobility during the introduction of the block often necessitates the safe execution of the regional anesthetic during general anesthesia. Perhaps the risk of neurologic injury is lower in the anesthetized child who is not resistant and combative during attempted epidural or caudal anesthesia now that the use of ultrasound-guided blocks are routine.[139] See Chapter 47 for a complete description of caudal anesthesia in children.

OUTPATIENT ANESTHESIA

Outpatient surgery is now the mainstay of modern surgical and anesthesia practice.[140] Many specialties are performing procedures in the ambulatory surgery center including otolaryngology, ophthalmology, general surgery, urology, plastic surgery, orthopedics, radiology, dentistry, and others. The postoperative goals are the same for all surgeries: normal vital signs, minimal pain and nausea, and return of preoperative level of consciousness. However, with ambulatory surgery, the discharge criteria are more rigid due to the fast-paced nature of the perioperative process. It is of the utmost importance that the patient be able to take oral medications without nausea when he or she leaves the surgery center. The typical surgery does not have a large amount of planned blood loss or large fluid shifts.

There are few absolute contraindications to ambulatory surgery for the pediatric patient. Children who were previously premature, either less than 35 weeks' gestation, or those less than 60 weeks' postconceptual age, are at risk for postoperative apnea.[141,142] These children require an overnight stay in the hospital for observation. Those children with obstructive sleep apnea (OSA) are also not candidates for a surgery center. However, this topic is controversial. Tonsils and adenoids are frequently removed for obstructive sleep apnea in the pediatric patient. After removal, the anatomy returns to its normal state after a couple of weeks; therefore, obstruction is a risk in the immediate postoperative period. Patients need to be carefully screened in the preoperative period by the surgeon and anesthesia provider to determine whether they are at high risk for hypoxia and hypercarbia postoperatively. Careful questioning of the patient and parents can help determine whether the patient is suitable for same-day surgery.

Patients that are not candidates for an outpatient surgery are those with a personal or familial history of malignant hyperthermia (MH). These patients need careful attention to avoid the triggers of MH. Although administering anesthesia can be routine, these patients need to be observed closely for increases in temperature postoperatively. If the patient develops MH in the surgery center, transfer to a higher level of care becomes an urgent issue.

Induction, airway management, and maintenance of anesthesia are similar when giving anesthesia in the hospital and surgery

center. Laryngeal mask airways may be used more often in surgery centers due to the generally short, simple procedures and healthier patients. When the patient is spontaneously breathing, the anesthesia provider can decide to extubate the patient deep or awake. Other factors that influence procedures and patient selection for a surgery center are the need for postoperative analgesia and minimizing postoperative nausea and vomiting (PONV). Local anesthesia injection by the surgeon or regional anesthesia is imperative, if applicable, for multimodal pain management. Patients also may be given acetaminophen before or during surgery. Nausea can be managed by using multimodal techniques and indentifying high-risk patients.[143,144]

PEDIATRIC ANESTHETIC MORBIDITY AND MORTALITY

Anesthetic morbidity and mortality differ between the pediatric patient and the adult patient. Accordingly, children require individualized and specialized anesthetic care. When compared with adults, children often present for surgery with unique symptoms. Their lack of ability to communicate effectively further complicates proper diagnosis and interventions. Fortunately, with a well-conducted history and physical and effective caregiver communication, a safe anesthetic may be planned and executed.

The Pediatric Perioperative Cardiac Arrest Registry (POCA), an ongoing database of pediatric cardiac arrest established in 1994, is a self-reporting, voluntary registry recording institutional cardiac arrests in children up to 18 years of age from as many as 80 participating institutions in Canada and the United States. The POCA data provides a retrospective assessment of contributing factors rather than determining causation of cardiac arrest. The initial registry results for the years 1994 to 2005 found 373 cardiac arrests in more than 1 million pediatric anesthetic experiences. One hundred and ninety three arrests (49%) were judged to be anesthesia related.[145] When cardiac arrest occurred, children with congenital or acquired heart disease (HD) were more likely to progress to cardiac arrest as compared with those without HD (50% vs 38%).[146] The patients with HD had higher ASA classifications (ASA III or above) and were more difficult to successfully resuscitate. Hyperkalemia from blood transfusions and hypovolemia were additional cardiovascular-related causes for cardiac arrest. Other reasons for cardiac arrest included respiratory-related causes (most often laryngospasm) and vascular injuries from central line placement. Medication-induced cardiac arrest has decreased since sevoflurane has replaced halothane as the inhalation agent of choice during perioperative management. Figure 48-5 shows the causes of anesthesia-related cardiac arrest associated with heart disease versus non–heart disease.

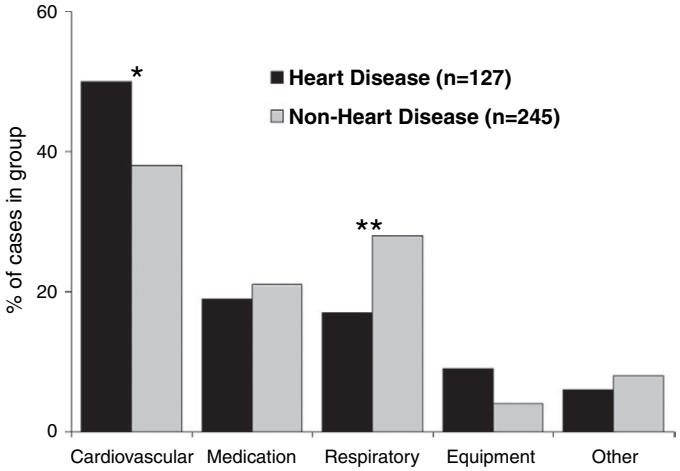

FIGURE **48-5** Causes of anesthesia-related cardiac arrest associated with heart disease (n = 127) versus non–heart disease (n=245). *P=0.03, **P=0.01. (From Ramamoorthy C, et al. Anesthesia-related cardiac arrest in children with heart disease: data from the Pediatric Perioperative Cardiac Arrest (POCA) registry. *Anesth Analg*. 2010;110[5]:1376-1382.)

SUMMARY

Anesthetic morbidity and mortality is greater in the pediatric patient and is multifactorial in origin. Pediatric subspecialty practice requires the anesthetist to master the foundations of pediatric growth and development, the anatomic and physiologic changes with maturation, and the influence of anesthetic agents upon immature organ systems. Anesthetic management of the pediatric patient requires integration of this specialized knowledge, refinement of the acquired technical skills of adult anesthetic management, and the ability to apply this knowledge when caring for pediatric patients. This chapter has reviewed pediatric pharmacology, airway management, and fluid and blood product management for the pediatric patient.

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49 CHAPTER Geriatrics and Anesthesia Practice

◆ *Henry C. Talley and Costellia H. Talley*

As a result of health care improvements and progress in overall living conditions, the number of people in the world that are 65 years and older has increased by 300% over the last 50 years. During the next decade, it is estimated that there will be a 39% increase in persons 65 years and older, bringing the number of potential patients within this age group to 55 million. For the first time in history, by the year 2050, the number of individuals 60 years of age and older will exceed the number of younger adults. In the United States (U.S.), it is projected that between 2004 and 2050 the number of older adults 65 years of age or older that are minorities will double. During this time, the population of older adults will become more racially and ethnically diverse with the number of African Americans over the age 65 years doubling, while the number of Asian American and Hispanic American will triple. Furthermore, the composition and characteristics of this population will change. The aging baby boomers (the generation born between 1946 and 1964) will have an influence on the healthcare system, because this generation will have higher levels of education, be more financially stable, be less functionally impaired, more likely to live alone, and will take more time to research anesthesia practices; therefore, anesthesia providers must continue to stay abreast of changing demographics to meet the needs of this population. This demographic shift will have significant implications for anesthesia practitioners and how they approach the surgical and anesthetic management of the geriatric patient. The purpose of this chapter is to provide a resource that reviews normal physiologic changes of the older adult and the perioperative considerations related to managing the older adult.

Definitions of aging are often subjective and place an arbitrary marker on chronologic age; however, this section will operationally define "older adults" as persons 65 years or older. Although aging is not routinely associated with surgical risk, the challenges related to anatomic and physiologic changes that occur with aging impact every aspect of the perioperative course. First, whether or not an anesthesia practitioner is willing to accept an older person as a candidate for anesthesia is one of the most important decisions providers must make. Beginning with the preoperative evaluation of the older patient, providers must understand the heterogeneity of this group, the increased variability of anesthetic response, and the diverse conditions that often occur during the aging process.[1-3] However, the risk of adverse events (i.e., cognitive and functional disorders and cardiac complications) must remain key issues in the decision to proceed.

Perioperative response is difficult to foresee because of progressive decline in baseline physiologic functions, changes in American Society of Anesthesiologists (ASA) physical status classification, and age-related comorbid conditions; all of which also can impact the chance for perioperative complications. Fortunately, most anesthetics can be managed without difficulty given that the provider delivers high-quality care with constant vigilance. Perioperative complications in the older adult are directly related to negative outcomes, including morbidity and mortality in the postoperative period. Cardiac, pulmonary, and neurologic complications are the most commonly occurring postoperative complications in the elderly. Likewise, methods for studying outcome in this diverse population depend, in large part, on what is known about the underlying cause of the presenting problem. Although it is not the intent of this chapter to dictate how the practitioner should practice, every effort has been made to provide a targeted review of the changes that occur with aging and show how these changes might offer the practitioner additional evidence to be considered in their current practice, thus providing a foundation for modifying the current options to improve perioperative outcomes if required.

THE PREANESTHETIC EVALUATION

One of the basic elements of the care of surgical patients requiring anesthesia is the preanesthetic evaluation. Preanesthetic evaluation is thoroughly discussed in Chapter 19; however, the preoperative evaluation of the older adult warrants some special considerations. The preoperative evaluation in the older adult helps reduce the cost of the perioperative course and increases the quality and care in this group. The time spent conducting the preoperative evaluation is usually the anesthesia practitioner's first introduction to the patient.

Although aging is not synonymous with increased surgical risk, progressive decline of baseline functions, age-related comorbid disease, and ASA physical status classification place older adults at greater risk for perioperative complications and death. A speedy recovery, avoidance of functional decline, and maintenance of independence postoperatively are the most important goals in the perioperative care of older adults. The greatest challenge when providing care for older high-risk surgical patients is preventing, detecting, and managing complications. Managing older high-risk patients requires vigilance and rapid and appropriate response to potential problems. Therefore, the significance of a thorough preanesthetic evaluation takes into account the body system changes; likewise, it cannot be overemphasized that pharmacokinetic and pharmacodynamic alterations that accompany aging should be taken into consideration to optimize outcomes.

Three primary factors are associated with perioperative risks in older adults: (1) reduced reserve capacity and functional decline; (2) comorbidities (atypical disease presentations); and (3) untoward reactions to medications, anesthesia, and surgery (outcomes that are difficult to predict).[4,5] These risks are most often associated with age-related physiologic changes. The process of aging is responsible for both the normally accepted chronologic alterations of life and the associated increases in the chance of disease and death.

AGE-RELATED PHYSIOLOGIC CHANGES IN THE OLDER ADULT

Aging is a time-related occurrence during the life cycle of an organism and can be defined as a time-dependent biologic continuum that begins with birth and persists with gradual impairments of organ subsystems, ultimately causing any organism to become more susceptible to illness and death. By the age of 30 years, most age-related physiologic functions in humans have peaked and gradually decline thereafter. Aging is not synonymous with poor physiologic function. Because chronologic age (age in years since birth), which is often used in clinical practice, and biologic age (functional status) differ, chronologic age alone is no longer a reliable indicator of morbidity or of mortality. The degree of functional status that remains with increasing age varies. For example, a 75-year-old patient who bicycles 3 miles every day, has no evidence of coexisting diseases, and lives a healthy lifestyle is considered "physiologically young." Whereas a 75-year-old patient who is sedentary, has a history of hypertension and diabetes mellitus, and is a chronic smoker may be deemed as "physiologically old." In addition, changes in organ function manifest as decreased margins of reserve. Aging patients may be able to maintain homeostasis but become increasingly less able to tolerate changes, or restore homeostasis, when exposed to surgical stress, trauma, or diseases.

In the adult surgical population, it is generally accepted that the older patient has the highest risk of postoperative adverse outcomes. Postoperative adverse outcomes are primarily cardiovascular, neurologic, and pulmonary in origin.[4,6,7] However, 21% of noncardiac surgical patients, age 70 years and older, will have one or more adverse postoperative events;[4,8] of those older patients who experience postoperative adverse outcomes, there is a twofold risk of death within 3 months when compared with older patients who do not have adverse outcomes.[8,9] Likewise, postoperative adverse outcomes dramatically increase in-hospital stay and healthcare costs.

Body Composition and Thermoregulation

Age-related changes to the body composition and its ability to thermoregulate are characterized by loss of lean body mass, increased total body fat, decreased metabolic rate, decreased total body water, and a reduction in blood volume of 20% to 30%.[10] Numerous factors may contribute to the decrease in lean body mass and increased total body fat in the older person. Aging is associated with decreases in all the senses; thus, it is speculated that the decrease in smell and taste may cause foods to be less appetizing. Practitioners must be vigilant because disease and aging cause decreased lean body mass that may mimic or be confused with malnutrition. Even so, malnutrition should not be discounted in the aging patient because it may contribute to decreased albumin levels that can affect protein binding of medications. For the older adult surgical patient, decreases in caloric intake combined with illness depletes body caloric reserves necessary to withstand the stress of anesthesia and surgery. Regrettably, no clearly beneficial preoperative medication has been identified that stimulates the appetite in older adults. As a result of decrease in total body water, older adults are more vulnerable to hypotension and have difficulty compensating for positional changes.

Thermoregulation in the elderly patient is impaired. In the older adult, there is a decrease in the function of the hypothalamus. Hypothermia is more pronounced and lasts longer because of a lower basal metabolic rate, a high ratio of surface to body area mass, and less effective peripheral vasoconstriction in response to cold. It is particularly detrimental in the elderly patient because it also slows anesthetic elimination, prolongs recovery from anesthesia, impairs coagulation, and increases the chance that the patient will shiver.[11] Shivering increases oxygen consumption by up to 400%, which leads to hypoxia, acidosis, and cardiac compromise. It is known that inhaled anesthetics inhibit the temperature regulating centers in the hypothalamus; thus, the aging adult has this added insult to an already inhibited hypothalamus. Thermoregulatory vasoconstriction can cause significant peripheral vasoconstriction, predisposing older adults to produce less heat per kilogram of body weight; therefore, older adults may be unable to maintain their heat in the cooler environment of the operating room. Likewise, once temperature decreases in the elderly patient, it is difficult to restore normal body temperature. Methods to maintain normothermia in the older adult patient should involve prevention of heat loss and active warming initiated in the preoperative area and continued perioperatively. Methods include the administration of all fluids and blood transfusions through a warming device, a thermal mattress or forced air warmer, and an environmental humidity higher than 50%. Age-related changes in the kinetics of medications also occur. The decrease in blood volume will produce a higher-than-anticipated initial plasma concentration when intravenous anesthetic agents are administered. This may be evident upon induction because moderate-to-severe hypotension may result. There is also a decreased volume of distribution with water-soluble medications, leading to plasma concentrations that are higher than normal. Likewise, with the increase in total body fat in older adults, fat-soluble medications have a longer half-life, possibly causing an extension of the pharmacologic properties and a slower excretion from the body.

Cardiovascular System

Age-related changes in the cardiovascular system involve structural and functional changes in the heart, vessels, and autonomic nervous system. In the older adult, the heart and vascular system is less compliant, leading to a faster propagation of the pulse pressure waveform, increase in afterload, and an increase in systolic blood pressure, leading to ventricular thickening (hypertrophy) and prolonged ejection times. The combination of ventricular hypertrophy and slower myocardial relaxation often results in late diastolic filling and diastolic dysfunction. When these changes occur, atrial contraction becomes important in the maintenance of adequate ventricular filling. Even though the elderly have higher amounts of circulating catecholamines, they exhibit decreased end-organ adrenergic responsiveness. Therefore, the older adult has a reduced capacity to increase heart rate in response to hypotension, hypovolemia, and hypoxia. Prolonged circulation time causes a faster induction time with inhalation agents but delays the onset of intravenous drugs. There is calcification of the conducting system with loss of sinoatrial node cells, which predisposes the elderly to atrial fibrillation, sick sinus syndrome, first- and second-degree heart blocks, and arrhythmias. Hence a higher proportion of this population may present with, or require, permanent pacemakers and/or automatic internal defibrillators. Calcification is not limited to the conducting system, but may be present in the valves (primarily aortic and mitral), predisposing elderly patients to valvular stenosis or regurgitation.

Hypertension is a risk factor for perioperative complications, with the risk doubling for every 20-mmHg systolic/10-mmHg diastolic increase in blood pressure. With aging, pulse pressure widens due to a greater proportionate increase in systolic blood pressure compared with diastolic blood pressure. Decreased vein compliance can lead to decreased venous return and reduced atrial filling. Likewise, there is decreased sensitivity of baroreceptors in

TABLE 49-1 Age-Related Cardiovascular Changes and Anesthetic Implications

Age-Related Change	Mechanism	Consequences	Anesthetic Implications
Myocardial hypertrophy	Apoptotic cells are not replaced and there is compensatory hypertrophy of existing cells; reflected waves during late systole create strain on myocardium leading to hypertrophy	Increased ventricular stiffness, prolonged contraction, and delayed relaxation	Failure to maintain preload leads to an exaggerated decrease in CO; excessive volume more easily increases filling pressures to congestive failure levels; dependence on sinus rhythm and low-normal HR
Myocardial stiffening	Increased interstitial fibrosis, amyloid deposition	Ventricular filling dependent on atrial pressure	—
Reduced LV relaxation	Impaired calcium homeostasis; reduced β-receptor responsiveness, early reflected wave	Diastolic dysfunction	—
Reduced β-receptor responsiveness	Diminished coupling of β-receptor to intracellular adenylate cyclase activity, decreased density of β-receptors	Increased circulating catecholamines; limited increase in HR and contractility in response to endogenous and exogenous catecholamines; impaired baroreflex control of BP	Hypotension from anesthetic blunting of sympathetic tone, altered reactivity to vasoactive drugs; increased dependence on Frank-Starling mechanism to maintain CO; labile BP, more hypotension
Conduction system abnormalities	Apoptosis, fibrosis, fatty infiltration, and calcification of pacemaker and His-bundle cells	Conduction block, sick sinus syndrome, AF, decreased contribution of atrial contraction to diastolic volume	Severe bradycardia with potent opioids, decreased CO from decrease in end-diastolic volume
Stiff arteries	Loss of elastin, increased collagen, glycosylation cross-linking of collagen	Systolic hypertension Arrival of reflected pressure wave during end-ejection leads to myocardial hypertrophy and impaired diastolic relaxation	Labile BP; diastolic dysfunction, sensitive to volume status
Stiff veins	Loss of elastin, increased collagen, glycosylation cross-linking of collagen	Decreased buffering of changes in blood volume impairs ability to maintain atrial pressure	Changes in blood volume cause exaggerated changes in cardiac filling

From Sanders D, Dudley M, Groban L. Diastolic dysfunction, cardiovascular aging, and the anesthesiologist. *Anesthesiol Clin*. 2009; 27(3):497-517.
BP, Blood pressure; *CO*, cardiac output; *HR*, heart rate; *LV*, left ventricular.

the aortic arch and carotid sinuses in response to blood pressure changes, which results in increased episodes of hypotension. Age-related changes in the cardiovascular system of the older adult also include changes in the heart's regulation of calcium causing the myocardium to generate force over a longer period after excitation, thereby prolonging the systolic phase of the cardiac cycle.[12]

The myocardium in the older adult has decreased sensitivity to beta adrenergic modulation, physiologically evident as decreased heart rate and lower cardiac dilation at the end of diastole and systole. The combined effect of decreased cardiac reserve and decreased maximum heart rate adversely affects the compensatory mechanisms of the older adult under the stress of anesthesia and surgery. Older adults undergoing noncardiac surgery are at risk of cardiovascular complication as a result of anesthesia and surgery. Although there is evidence supporting the use of beta-blockers as an effective method of reducing adverse perioperative cardiovascular events after noncardiac surgery in select high-risk surgical patient populations, this approach is currently under considerable scrutiny and debate. No matter what approach is taken, complete assessment of the cardiovascular system in the older adult undergoing noncardiac surgery is essential according to the American College of Cardiology/American Heart Association (ACC/AHA) Guidelines for Perioperative Cardiovascular Evaluation for Noncardiac Surgery. According to the ACC/AHA, functional capacity is an objective quantification of the patient's exercise tolerance and can be measured in metabolic equivalents (METs).[13] Research suggests that for every 1 MET that a patient attained, there is a corresponding reduction in annual mortality of 11%.[14] The MET corresponds to the amount of oxygen consumed by a 70-kg male at rest (≈ 3 mL oxygen per kg body weight per minute). Those patients able to perform greater than 4 METs are at decreased risk for perioperative cardiac complications.

In general, older adults may have higher blood pressures caused by increased peripheral vascular resistance, decreased arterial elasticity, and cardiac workload; likewise, older adults may have decreased cardiac output and stroke volume due to decreased conduction velocity and reduction in venous blood flow. Age-related cardiovascular changes and their anesthetic implications are noted in Table 49-1. The preoperative assessment should include the identification of major risk factors for preoperative cardiovascular complications, which include significant exercise intolerance, angina, history of myocardial infarction within the past 6 months, ventricular arrhythmias, acute coronary syndrome, decompensated congestive heart failure, and valvular disease. To assist in the prediction of postoperative cardiac outcome in patients undergoing noncardiac surgery, classic preoperative cardiac risk assessment and guidelines such as the Goldman Cardiac Risk Index (GCI) may be used. The GCI applies nine independent factors to assess the level of hemodynamic stress inflicted upon the vital organs and the risk of adverse cardiac factors are assigned points accordingly (Table 49-2).

The use of beta-blockers is common in older adults with chronic heart failure, hypertension, and ischemic heart disease. However,

TABLE 49-2 Goldman Cardiac Risk Index

History	
Age older than 70 years	5 points
Myocardial infarction within 6 months	10 points
Cardiac	
Signs of CHF: ventricular gallop or JVD	11 points
Significant aortic stenosis	3 points
Arrhythmia other than sinus or premature atrial contractions	7 points
5 or more PVCs per minute	7 points
Medical Conditions	
P_{O_2} < 60; P_{CO_2} > 50; HCO_3 < 20; K < 3; BUN > 50; Creatinine > 3; elevated SGOT; chronic liver disease; bedridden	3 points
Surgery	
Emergency	4 points
Intraperitoneal, intrathoracic or aortic	3 points
Add total points above to find risk index for cardiac complications in table below:	

Points	Class	Range
0-5	I	1%-7%
6-12	II	3%-11%
13-25	III	14%-38%
25-53	IV	30%-100%

Adapted from Fleischer LA, et al. ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery. *J Am Coll Cardiol.* 2007;50(17):1707-1732.
BUN, Blood urea nitrogen; *CHF,* congestive heart failure; *JVD,* jugular venous distension; HCO_3, bicarbonate; P_{CO_2}, partial pressure of carbon dioxide; P_{O_2}, partial pressure of oxygen; *PVC,* premature ventricular contractions; *SGOT,* serum glutamic oxaloacetate transaminase.

for patients that present to the operating room who may not have had the benefit of chronic titration of this class of medication, a practical approach for the anesthesia provider might include the administration of oral medication prior to induction and intraoperative intravenous administration to control heart rate.

Cardiovascular disease is the most common concomitant illness in the older adult and the primary cause for perioperative and postoperative risk in the older adult. The most frequently associated cardiovascular coexisting diseases are hypertension, coronary artery disease, congestive heart disease (CHF), and myocardial ischemia. Myocardial infarction is the most common cardiac complication and the leading cause of death in the postoperative period. Likewise, a patient with preexisting congestive heart failure has a greater than twofold risk of developing postoperative complications.[15]

Respiratory System

There are various age-related alterations of the respiratory system that have an impact on oxygenation in the elderly patient. Older patients develop calcifications of the chest wall, intervertebral joints, and intercostal joints. This, along with decreased intercostal muscle mass, contributes to a decrease in chest wall compliance. In addition, there is a flattening of the diaphragm, a loss of intervertebral disc height, and changes in spinal lordosis, which may further diminish chest wall compliance. Changes also occur with the lung parenchyma. There is a generalized loss of elastic tissue

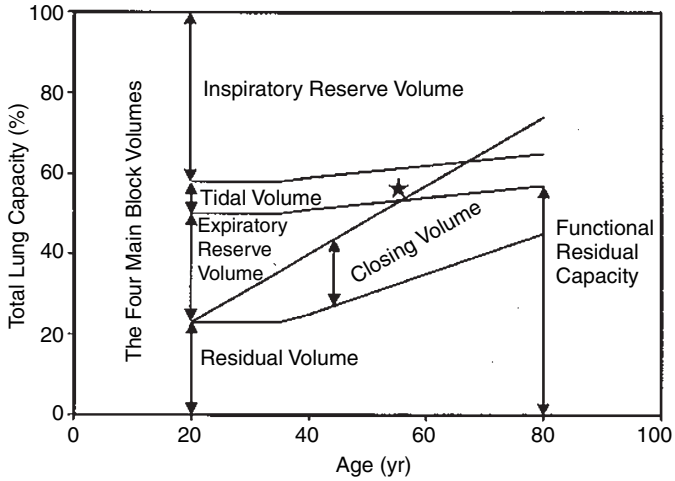

FIGURE 49-1 Changes in lung volumes with aging (erect position). Residual volume (RV) and functional residual capacity (FRC = ERV + RV) gradually increase by aging, whereas expiratory and inspiratory reserve volumes (ERV, IRV) and thus vital capacity (VC = ERV + IRV) decrease. Specific (height-adapted) total lung capacity (TLC) does not change with aging. Forced expiratory volume in 1 second (FEV_1) can be significantly reduced in older people and FEV_1/FVC may be as low as 65% to 55%. Closing volume (CV) is increased and the closing capacity (RV + CV) may even be larger than FRC, thus closing the small airways during normal tidal breathing *(star)*. This may significantly impair pulmonary gas exchange. (From Zaugg M, Lucchinetti E. Respiratory function in the elderly. *Anesthesiol Clin North America.* 2000;18[1]:47-58.)

recoil of the lung. Consequently, there is reduced functional alveolar surface area available for gas exchange. In elderly patients, even in the absence of disease, an increase in lung compliance impairs the matching of ventilation and perfusion, increases physiologic shunt, and results in the reduction of oxygen exchange at the alveolar level. Since lung elastic recoil is necessary for maintaining small airway caliber, an increased lung compliance causes small airway diameter to narrow, and eventually increases the closing volume (i.e., lung volume at which small airways in the dependent parts of the lung begin to close). The closing volume exceeds functional residual capacity (FRC) at approximately 65 years of age in the erect position and at age 45 years in the supine position. Other dynamic and static lung volume changes include a decrease in vital capacity (VC), an increase in residual volume (RV), and an increase in FRC with decreases in inspiratory reserve volume (IRV) and expiratory reserve volume (ERV). Total lung capacity remains unchanged or may slightly decrease due to its correlation with height. There is also a decrease in forced expiratory maneuvers. The forced vital capacity (FVC) and the forced expiratory volume in 1 second (FEV_1) are both decreased due to the loss of lung elastic recoil, decrease in small airway diameter, and subsequent airway collapse with forced expiration (Figure 49-1). Overall, the elderly have impaired efficiency of gas exchange. Impaired oxygenation is reflected by a decline in resting arterial oxygen tension (Pa_{O_2}), which remains somewhat stable, at approximately 83 mmHg, after 75 years of age. This decline in Pa_{O_2} is attributed to the premature closing of small airways and the reduction in the alveolar surface area.[16]

The regulation of breathing is also affected with aging. The central (medulla) and peripheral (carotid and aortic bodies) chemoreceptors affect ventilation with changes in pH, Pa_{O_2}, and Pa_{CO_2}. In the elderly the ventilatory response to hypoxemia and hypercarbia is decreased, predisposing them to increased episodes

TABLE 49-3 Age-Related Pulmonary Changes and Anesthetic Considerations

Structural Changes	Consequences	Anesthetic Considerations
Chest wall	Impaired gas exchange	Risk for respiratory failure
Stiff/decreased compliance	Increased WOB	Careful use of NDMRs, opioids, and benzodiazepines
Flattened diaphragm		
Lung parenchyma	Impaired gas exchange	Risk for respiratory failure
Increased lung compliance	Increased $\dot{V}/\dot{Q}$ mismatch	Avoid high pressure/large TV
Increased small airway closure	Increased anatomic dead space	Consider alveolar recruitment maneuvers (PEEP)
	Decreased alveolar surface area	Limit high inspired O_2
	Decreased PCBF	Maintain $Paco_2$ near normal preoperative value
	Decreased Pao_2	Consider regional/local with sedation
Muscle strength		Risk for respiratory failure
		Risk for aspiration
Decreased	Increased WOB	Adequate hydration
	Decreased protective airway reflexes	Consider RSI with GA
		Ensure fully reversed prior to extubation
		Consider postoperative CPAP or BiPAP
		Vigilant monitoring
		Encourage cough/deep breathing postoperatively
Control of breathing		Risk for respiratory failure
Decreased central/peripheral chemoreceptor sensitivity	Increased hypoventilation	Consider postoperative CPAP or BiPAP
	Increased apnea	Vigilant monitoring
	Decreased ventilator responses	Encourage cough/deep breathing postoperatively
		Supplemental oxygen postoperatively

WOB, Work of breathing; *NDMRs*, nondepolarizing muscle relaxants; $\dot{V}/\dot{Q}$; ventilation-perfusion; *PEEP*, positive end-expiratory pressure; *TV*, tidal volume; *PCBP*, pulmonary capillary blood flow; *GA*, general anesthesia; *RSI*, rapid sequence induction; *CPAP*, continuous positive airway pressure; *BiPAP*, bilevel positive airway pressure.

of apnea. Another challenge associated with oxygenation is the progressive decrease in laryngeal and pharyngeal support that accompanies aging, which can result in airway obstruction. In addition, protective airway reflexes (i.e., coughing and swallowing) are decreased, which increases the risk for pulmonary aspiration. Age-related pulmonary changes and their anesthetic implications are noted in Table 49-3.

Similar to other organ systems, pulmonary changes in the elderly are extremely variable among individuals. Regardless of these variations, an in-depth assessment of the respiratory system and identification of coexisting diseases that affect the pulmonary system is important in order to optimize preoperative respiratory function.

Older patients are at an increased risk for pulmonary-related coexisting diseases (e.g., chronic obstructive pulmonary disease [COPD], pneumonia, sleep apnea), which are associated with increased morbidity and mortality.[17,18] The presence of pulmonary disease increases the risk of hypoxia, pneumonia, and atelectasis. COPD is a significant risk factor for the development of postoperative pulmonary complications.[19] The incidence of postoperative respiratory complications is three- to sixfold in persons who smoke.[17,20] Although smokers have a higher incidence of postoperative pulmonary complications, pulmonary complications may paradoxically increase in patients that quit smoking 2 months or less prior to surgery.[20-23] Despite this, short-term smoking cessation is still advised.

Postanesthesia respiratory complications are common in the older adult, often requiring upper-airway support during the immediate postoperative period. Pulmonary complications account for nearly 40% of perioperative deaths in persons over the age of 65 years. ASA classes of greater than II predict a twofold risk of respiratory complications.[20] Moreover, older patients are more prone to develop atelectasis and pulmonary infection. Therefore, preoperative pulmonary evaluation of the older patient should focus on identifying those persons presenting with limited pulmonary reserve and recognizing factors that aid in maximizing performance status. In patients over 70 years of age, the number of stairs a patient can climb before the surgery is inversely proportional to cardiopulmonary complication rates after the operation.[24] In addition to age, pulmonary complications are increased based on length of surgery, obesity, and sex (females slightly higher).

Renal Function

Age-related changes in renal function are particularly significant because of the many roles of the kidneys. Older adults have a significant baseline decrement in renal function relative to their younger counterparts. Changes in renal function in the older patient are characterized by a progressive atrophy of kidney parenchymal tissues, deterioration of renal vascular structures, decreased renal blood flow, and an overall decrease in renal mass. The cumulative effect is a decrease in the glomerular filtration rate resulting in decreased renal drug clearance and decreased renal blood flow from age 20 years to age 90 years (approximately a 25%-50% decline). The combined effect is particularly apparent with diminished renal clearance of hydrophilic agents and hydrophilic metabolites of lipophilic agents.

Because of the vital role that the kidneys play in the maintenance of fluid and electrolyte balance, their contribution to acid-base balance, and to the excretion of drugs and their metabolites, it is essential that great consideration is given to the renal function of the aged patient. The decrease in glomerular filtration rate and impairment of the diluting segment of the nephron can easily predispose the patient to fluid overload if overzealous intravenous fluid is administered.[11] The production of renin and aldosterone is decreased with age, causing impairment of sodium conservation. Sodium conservation and hydrogen ion excretion are decreased, resulting in an impaired ability of the kidneys to respond to changes in electrolyte concentrations, intravascular volume, and free water.[11,25] The kidneys do not respond to nonrenal loss of water and sodium and as a result, dehydration can commonly occur. The serum creatinine is often unchanged if there is no renal failure because of decreased creatinine production from the overall declining skeletal muscle mass associated with aging. Creatinine clearance is the best indicator of drug clearance. Estimation of serum creatinine using the Cockroft and Gault creatinine clearance formula is a common method for estimating creatinine clearance in the healthy older adult.[11,26]

$$\frac{(140 - \text{age in yrs}) \times (\text{weight in kg})}{72 \times (\text{serum creatinine in mg/dL})}$$

The factor 0.85 should also be included in the numerator when this formula is applied to females; however, when this formula is applied to the critically ill or those patients on medications that directly affect renal function, caution must be employed. This formula often overestimates creatinine clearance. Therefore, older patients with renal impairment may be at increased risk for (1) fluid overload; (2) accumulation of metabolites and drugs that are excreted by the kidneys; (3) decreased drug elimination, which can prolong the effects of a wide range of anesthetic drug and adjuncts; and (4) electrolyte imbalances, which can lead to arrhythmias by affecting cardiac conduction.[11,27] Furthermore, overhydration in a compromised heart with marginal reserves must be cautiously avoided because the physiologic changes in the kidneys of older adults decrease the ability to excrete a large-volume load.[11] Perioperative management of renal function should be geared toward preventing acute renal failure during the preoperative planning phase.

Hepatic Function

The age-related physiologic changes in hepatic function may cause decreased clearance, prolonged half-life, and either increased or decreased volume of distribution of the drugs. After the age of 50 years, there is a steady decline in the weight of the liver, which is about 2.5% of the total body weight throughout adulthood until age 50. By the age of 90 years, the liver is approximately only 1.6% of the total body weight.[28,29] The changes in hepatic function may affect hepatic drug clearance, particularly if the patient has a concomitant disease, smokes, or is consuming multiple medications that alter blood flow or up- or down-regulate hepatic functional biochemistry. Furthermore, increased body fat and decreased water content in the older patient has considerable impact on the volume distribution (Vd) of many drugs. The Vd of hydrophilic drugs in the older patient may be decreased, causing an increase in plasma concentration. The Vd of lipophilic drugs in the older adult may be increased, causing a decrease in their plasma concentration.

Age-related physiologic changes in hepatic function and disease processes can produce kinetic changes to anesthetic agents in older adults. The effect of age on phase I drug metabolism is somewhat variable. Phase I drug metabolism involves oxidation, reduction, and hydrolysis and is primarily mediated by the cytochrome P450 system. Phase II drug metabolism involves conjugation reactions, sulfonic acid, or acetylation. Age has been identified as an insignificant factor during phase II drug metabolism. Changes in pharmacologic responses are discussed later.

Because of the high prevalence of concomitant illnesses, the older adult is more likely to take multiple prescriptions, over-the-counter medications, and herbal remedies, which also increases the risk of adverse reactions. Therefore, the potential for drug interactions is increased as a result of age-related changes in hepatic function.

As previously stated, age-related changes in hepatic function are characterized by a decrease in liver mass, a decrease in portal and liver blood flow, decreased serum albumin, and decreased enzyme activity; therefore, the dosing of drugs dependent on hepatic metabolism must be carefully considered. The decrease in overall liver mass results in a reduction in the rate of plasma clearance and a prolongation of the effects of opiates. Furthermore, the delivery of drugs to the liver is highly influenced by hepatic blood flow. Age-related changes in hepatic function should be presumed to modify the metabolism of most of the anesthetic agents as well as the nondepolarizing neuromuscular blocking agents.[10] In general, we can anticipate an increase in duration of activity of the drugs that are most commonly used in anesthesia care.

Endocrine System

Age-related changes of the endocrine system have widespread effects on other body systems and processes. The endocrine system has multiple feedback loops and is strongly influenced by anesthesia and surgical stress. Anesthesia and surgery cause a neuroendocrine stress response that is reflected by increased secretion of many hormones including epinephrine, norepinephrine, adrenocorticoids, and growth hormone (insulin antagonist), which causes insulin resistance at the tissue level. [30] Furthermore, increased hepatic production of glucose, impaired insulin secretion, and impaired breakdown of fats and proteins have widespread consequences.[31]

Although risk stratification of patients exists (e.g., ASA Physical Status, Goldman's cardiac risk index, and Lee's revised Cardiac Risk Index), defective glucose/insulin control further increases the risk for adverse reactions in patients with cardiovascular disease and increases the risk of perioperative complications. Older adults are more susceptible to the effects of increased glucose due to hyperglycemia-induced immune defects and age-related immune senescence.[32] Diabetes affects perioperative cardiovascular risk and autonomic dysfunction and is associated with an increased risk for stroke, myocardial infarction, ketoacidosis, and deterioration in renal function. Patients with long-term diabetes often have compromise in one or more organ systems.[33] These factors place patients with diabetes at increased risk for developing complications during the perioperative and postoperative period. The extent of endocrine and metabolic changes experienced is influenced by preoperative diabetes control, type of diabetes, magnitude of surgery, and perioperative complications.

Assessment of the older patient with diabetes includes identification of the type of diabetes, diabetes control (hemoglobin A1c), length of disease, and complications from diabetes. Patients with a history of diabetes for greater than 10 years are particularly at increased risk for complications.[30] Perioperative assessment of the degree of endocrine dysfunction is essential, along with ongoing monitoring and timely intervention when appropriate.

Central Nervous System

Age-related physiologic changes of the central nervous system (CNS) are characterized by a progressive loss of neurons and neuronal substance, decrease in neurotransmitter activity, and decreased brain mass. These losses are most prominent in the cerebral cortex, particularly the frontal lobes. The associated physiologic changes cause a decrease in cerebrospinal fluid, a decrease in nerve conduction velocity, and degeneration of peripheral nerve cells. In addition, there is a decreased number of myelinated nerve fibers. The regulation of brain function, including neuronal membranes, receptors, ion channels, neurotransmitters, cerebral blood flow, and metabolism, is affected by general anesthetics at all levels. Consequently, there are changes in mood, memory, and motor function. In addition, cellular processes that participate in neurotransmitter synthesis and release, such as intraneuronal signal transduction and the second messenger system, may be altered.[34] The CNS changes experienced by the older patient results in an increased sensitivity to anesthetic agents; as a result, there may be an increased risk for postoperative delirium or cognitive dysfunction.

The older patient may experience increased sensitivity to drugs because the number of receptors available are decreased.[35] As a rule, older patients frequently experience an exaggerated response to CNS-depressant drugs with particular sensitivity to general anesthetics, hypnotics, opioids, and benzodiazepines.[29] The dose of induction agents should be decreased by as much as 30% to 40% in older patients, arguing for very meticulous titration.

CNS changes in the elderly also affect neuraxial anesthesia. Because the number of myelinated nerve fibers are decreased, this poses a risk for neural damage with regional anesthetics. Likewise, anatomic changes in the aging patient, such as decreased intervertebral disc height, narrowing of the intervertebral foramina, decreased space between the posterior spinous processes, presence of calcifications, and changes in normal lordosis, contribute to difficulties associated with patient positioning and spinal or epidural needle placement. It is also postulated that the dura is more permeable to local anesthetics and that the CSF specific gravity increases whereas its volume decreases. All of these alterations in the nervous system may produce a more enhanced spread of local anesthetics for subarachnoid blocks.[36] Because elderly patients have an impaired baroreceptor response, severe hypotension refractory to adrenergic stimulation may result from postsubarachnoid sympathectomy. This could potentially be detrimental in the presence of impaired cardiac function. There is also an enhanced spread of local anesthetics with epidural blockade. In addition, the use of an epinephrine "test dose" for identification of intrathecal injection is less reliable in the elderly because of the decreased end-organ adrenergic responsiveness.[37] Therefore, a decreased dose of local anesthetic is recommended for subarachnoid and epidural blockade. Overall, subarachnoid and epidural blockade are generally not contraindicated in the elderly patient. A plan of anesthesia should be developed based on patient history and surgical procedure while considering the risks and benefits in an effort to decrease postoperative morbidity and mortality.

POSTOPERATIVE DELIRIUM

The most common type of complication in older adults is neurologic.[38] The most frequently occurring neurologic complication in older adults is postoperative delirium. Depending on the type of procedure, the rate of postoperative delirium ranges from 15% to 53%.[39] In older adults, other common neurologic postoperative complications are stroke and peripheral nerve damage.

Although normal intellectual function peaks between the ages of 20 and 30 years, it reaches a relative level of stability and remains so until 83 to 87 years, and then begins to decline. General anesthesia may deteriorate the mental capacity in those with preexisting problems and may have a strong association with postoperative cognitive dysfunction.[27] Although often used interchangeably, delirium and cognitive dysfunction are distinct conditions that occur in the older adult. Cognitive dysfunction is often subtle and comprised of an extensive range of psychoneurologic changes that occur in several functional domains. However, some older adults experience a transient reversible state of cognitive alteration after surgery: postoperative delirium, a common postoperative complication associated with the older adult. Delirium is associated with several adverse events that include depression, function decline, prolonged hospitalization, increased healthcare costs, and death.

Postoperative delirium is characterized by disruption of perception, thinking, memory, psychomotor behavior, sleep-wake cycle, consciousness, and attention.[40,41] Delirium occurs in 10% to 26% of patients over the age of 65.[42,43] The exact cause of delirium is not known but is likely multifactorial. Risk factors that have been associated with the development of delirium are older age, male gender, dementia, history of alcohol abuse, depression, duration of anesthesia, poor functional status, abnormal electrolytes and glucose, Parkinson's disease, cardiovascular disease, dehydration, metabolic diseases (e.g., diabetes, hyperthyroidism), anticholinergic drugs used intraoperatively, patients requiring admission to the intensive care unit, inadequate pain control, and type of surgery.[44-50] Postoperative delirium is believed to be related to anesthesia-stimulated vasodilation with a resultant hypermetabolic state in the brain. This hyperbolic state leads to oxidative stress and irregularities in the cholinergic, dopaminergic, histaminergic, and noradrenergic neuronal systems. Hence, synthesis and release of acetylcholine from cholinergic cells may be reduced, causing disorientation and memory impairment or agitation and hallucinations.

Symptoms associated with delirium typically begin early during the postoperative period and can last for several days or weeks. Delirium is associated with increased risk of postoperative adverse reactions (i.e., pulmonary edema, myocardial infarction, respiratory failure, pneumonia, and death), increased length of hospital stay, increased healthcare cost, and poor functional and cognitive recovery.[27,47,51-53] Delirium is more common in patients having orthopedic procedures (i.e., femoral fractures) and patients undergoing cardiac surgery, with incidence rates of 28% to 60% and 32% to 47% in these surgical populations, respectively.[47,54-56] In cardiac surgery patients, the presence of four preoperative factors (depressive symptoms, impaired cognitive function, prior stroke or transient ischemic attacks [TIA], and abnormal albumin) has been independently associated with postoperative delirium.[56-59]

For practical clinical purposes, the most common CNS disorder in the older patient is delirium. A history of neurologic deficits and neurologic diseases are most often associated with risk of delirium; therefore, symptomatology related to these disorders should be included in the preoperative evaluation and consultation requested when needed.[60]

POSTOPERATIVE COGNITIVE DYSFUNCTION

Postoperative cognitive dysfunction (POCD) is often reported as being part of the same continuum as postoperative delirium. Even though they are both neurocognitive disorders that contribute to increased hospital costs, morbidity, and mortality, there are differences. POCD is characterized by an array of cognitive impairments such as memory deficits, difficulty with concentration, impaired comprehension, and delayed psychomotor speed.

BOX 49-1

Risk Factors for Postoperative Cognitive Dysfunction

- Genetic disposition
- Lower educational level
- High alcohol intake or alcohol abuse
- Increasing age
- High ASA status
- Preexisting mild cognitive impairment
- History of cerebrovascular accident
- Major operations, redo operations
- Cardiac surgery
- Longer duration of surgery and anesthesia
- Intraoperative cerebral desaturation
- Postoperative delirium
- Postoperative infection

From Grape S, et al. Postoperative cognitive dysfunction. *Trends Anaesth Crit Care*. 2012;2(3):98-103.
ASA, American Society of Anesthesiologists.

Unlike postoperative delirium, the onset of POCD is subtle and neurocognitive deficits may not present themselves until weeks to months after surgery. This ultimately results in the inability to work, a decline in activities of daily living, and perhaps a need for assisted care.

Currently, there are no universally accepted diagnostic criteria for POCD, nor is there a standard definition. In order to diagnose POCD, a battery of time-consuming and sophisticated neurocognitive tests must be done preoperatively as well as postoperatively in identifying cognitive decline after surgery and anesthesia. Establishing baseline cognitive function is critical because preoperative cognitive impairment may be present prior to surgery. However, preoperative test timing, specific test(s), and test interpretations remain inconsistent and debatable. Risk factors for POCD are also controversial, with advanced age being the most agreed upon. Other risks may include lower educational level, longer duration of anesthesia, preoperative depression, preoperative cognitive decline, postoperative infection, and second operation[61] (Box 49-1). The cause of this neurocognitive postoperative complication is still unknown and appears to be multifactorial. However, several theories have been postulated. Common theories include cerebral hypoperfusion (severe hypotension and embolic events), the inflammatory process associated with surgery, and general anesthetics.[62] In a recent study on mice, Freche et al.[63] purported that repeated exposure to sevoflurane resulted in an increase in the hippocampal phosphorylation of the protein tau and memory impairment. However, with human studies, a link between the tau phosphorylation and memory impairment is yet to be reported.

Presently, there is no cure for POCD. Patients who suffer from POCD may or may not recover to their preoperative cognitive state. Because POCD pathogenesis is multifactorial and unclear, strategies should be aimed at prevention. Unfortunately, there are no proven effective strategies. However, based on the knowledge that the elderly have decreased nervous system function and decreased cognitive reserve, efforts should consist of identifying risk factors and tailoring anesthetic management to minimize them. Recommendations are aimed at maintaining oxygenation and cerebral perfusion. Because it is speculated that POCD may be caused by general anesthesia and/or surgery, it is only prudent that surgeries should be as short or as minimally invasive as possible. Other recommendations for the prevention of POCD are listed in Box 49-2.

BOX 49-2

Recommendations for the Prevention of Postoperative Cognitive Dysfunction

- Keep anesthesia and surgery as short and as minimally invasive as possible
- Use short-acting and rapidly metabolized drugs
- In patients at risk, prefer inhaled over intravenous anesthetics
- Neuroprotective drugs currently under investigation:
  - Piracetam
  - Ketamine
  - Pexelizumab
  - Remacemide

It is apparent that further research is needed regarding the pathophysiology, prevention, and treatment of POCD. Furthermore, standardized preoperative neurocognitive assessment, especially in the elderly population, needs to be initiated to help identify patients with cognitive impairment. The elderly surgical population is increasing, and there must be an increased focus on the risk for postoperative neurologic events, specifically, postoperative delirium and POCD.

AGE-RELATED PHARMACOLOGIC IMPLICATIONS IN THE OLDER ADULT

Exaggerated responses to anesthetic drugs and a prolonged duration of action are often seen in the elderly. These differences in drug response are due to both pharmacokinetic and pharmacodynamic changes associated with aging. Pharmacokinetic alterations occur in the volume of distribution, renal and hepatic clearance rates, compartmental redistribution, and elimination half-lives. A decreased blood volume results in a decrease in initial volume of distribution, which produces a higher-than-expected initial concentration of drug with an intravenous bolus injection. Changes in steady-state volumes of distribution (Vd_{ss}) vary. In aging patients who have an increase in body fat, decrease in lean body mass, and a decreased total body water, there is an increased Vd_{ss} for lipophilic drugs and a decrease for hydrophilic drugs.[64] Decreased plasma protein binding in the elderly theoretically results in an increase in the free plasma concentration for drugs that are highly protein bound. A decrease in renal function resulting from lower renal blood flow, glomerular filtration, and tubular secretion leads to increased serum concentration and prolonged effects of drugs dependent on renal elimination. The elimination of hepatic-dependent drugs varies. Phase I metabolism may be reduced, but phase II metabolic pathways are not affected by age.[65]

Pharmacodynamics changes in the elderly include altered receptor density and binding, changes in signal transduction, and impaired cellular responses. Drug-induced changes tend to be longer lasting and require a greater length of time for recovery to preanesthetic steady state. The minimal alveolar concentration (MAC) of inhalational agents decreases roughly 6.7% per decade from the MAC value of 40-year-old adults.[66-68]

COMORBIDITY

Comorbidity, the co-occurrence of more than one disease, is higher in older adults.[69,70] Over 50% of individuals over the age of 70 years will have at least one chronic illness, and 30% will have two or more.[4] Hypertension is the most common comorbidity in the elderly, followed by coronary artery disease. Other common conditions are diabetes, arthritis, and chronic obstructive pulmonary disease (COPD).

Congestive heart disease, COPD, and/or malignancy are the strongest predictors of mortality in older adults with hip fracture repair at 1 month and at 1 year postoperative.[71,72] In a sample of patients undergoing noncardiac surgery, congestive heart failure and decreased functional status were the greatest predictors of postoperative neurologic and cardiac adverse outcomes.[15]

FRAILTY

Frailty is an emerging concept in terms of a perioperative risk factor for complications and mortality. Frailty rates of 4.1% to 50.3% have been reported in surgical patients.[73-76] Frail older adults are more likely to have complications postoperatively.[8,76] In addition, frail older adults are also at increased risk for longer length of hospital stay and discharge to a skilled or assisted living facility.

There is no agreed upon definition of frailty. This may be related to the complexity of the syndrome and the fact that frailty often overlaps with other syndromes. However, most agree that frailty is a biologic state associated with increased vulnerability to adverse outcomes that result from decreased resistance to stressors as a result of deterioration in multiple physiologic systems. Frailty is classified as primary or secondary. Primary frailty occurs as part of the intrinsic process of aging. Secondary frailty is related to the end stage of chronic illnesses and is caused by inflammation and wasting, for example, heart failure, COPD, inflammation, and wasting associated with cancer. Frailty markers include older age, age-associated declines in lean body mass, endurance, strength, balance, walking performance, and reduced activity.[77] Fried et al.[77] defined frailty as meeting three of five phenotypic criteria: low energy, slowed waking speed, low grip strength, low physical activity, and/or unintentional weight loss. Frailty also has been operationalized as a frailty index.[78] The frailty index defines frailty as the proportion of accumulated deficits over time, including diseases, disability, geriatric syndromes, psychosocial risk factors, and physiologic and cognitive impairment. It is suggested that the frailty index may be more sensitive to the identification of adverse outcomes than Fried's frailty phenotype.

ETHICAL ISSUES IN THE TREATMENT OF THE OLDER ADULT

Changes in the healthcare system and advances in medical treatment have resulted in a number of ethical dilemmas for healthcare providers. Research on health services delivery has found confounding variations in the quality and quantity of care provided to patients with severe chronic illness across the United States as they age and approach the end of life; more care does not necessarily lead to better quality of care, patient satisfaction, or outcomes.[79] Discrepancies between withholding versus withdrawing care or ordinary versus extraordinary treatments can complicate clinical decision making by healthcare providers. These findings raise three very important ethical issues for the healthcare provider: (1) impartiality in the delivery of limited resources across health service areas; (2) the promise to "do no harm" in providing of appropriate amounts of care to patients; and (3) transparency regarding local healthcare practice to facilitate informed decisions about healthcare choices. In this era of healthcare accountability, educators, clinicians, and employers must remain steadfast when addressing those ethical principles that drive change while simultaneously providing more efficient, more effective, and more patient-centered care to our older patients.[79,80] It is widely accepted that chronologic age is possibly an independent risk factor for anesthesia and surgery; its specific role as a risk factor is difficult, at best, to ascertain. Therefore, age, as an independent factor, should not be regarded as a reason to exclude an older adult for any procedure.

SUMMARY

Integrating care across the lifespan continuum can improve the anesthetic outcome of the geriatric patient and may minimize the physical structure and functional complications encountered in this population. Emphasis on biologic age as it relates to chronologic age requires the anesthetic practitioner to sometimes make alterations in the perioperative course. The goal of anesthesia for the older adult patient is the same as any other patient; however, strategies to ensure success in this immensely heterogeneous group are often more complex than with younger patients. Anesthesia for the elderly patient is no longer an empiric specialty; the practice of anesthesia for elderly patients is built on evidence-based concepts.

Physiologic, psychological, and functional status changes such as normal and anesthesia-related thermoregulation can be impaired in the older adult and are major contributors to perioperative outcome.

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CHAPTER 50

Postanesthesia Recovery

◆ *Jan Odom-Forren*

The term *perianesthesia patient care* reflects a continuum of care, because the patient is moved from the preanesthesia holding or admitting area to the operating room (OR) and then to the postanesthesia care unit (PACU). *Postanesthesia recovery* refers to those activities undertaken to manage the patient after completion of a surgical or nonsurgical procedure in which anesthesia, analgesia, or sedation was administered. The primary purpose of postanesthesia recovery is critical assessment and stabilization of patients after these procedures, with an emphasis on prevention and detection of complications.[1] Care in the postanesthesia Phase I unit centers on providing postanesthesia nursing care and transitioning the patient to the intensive care setting, the surgical floor setting, or Phase II outpatient care.[2] The focus of this chapter is on the postanesthesia care of patients with the goals of improving postanesthetic safety and quality of life, reducing postoperative adverse events, providing a uniform assessment of recovery, and streamlining postoperative care and discharge criteria.

POSTANESTHESIA CARE UNIT ADMISSION

Before the patient is transferred, PACU personnel should be notified not only to expect the transfer but also to have any necessary equipment (e.g., ventilator, nebulizer, invasive monitoring equipment, pharmacologic infusions, capnograph) ready and waiting. Knowledge of the patient's acuity enables the PACU staff to best plan the patient's care and assign that care to an appropriately experienced practitioner.

Both the anesthesia provider and the PACU nurse should collaborate in the patient's admission to the PACU. The immediate priority is evaluation of respiratory and circulatory adequacy. During this initial assessment, any signs of inadequate oxygenation or ventilation are identified, as well as the cause (Boxes 50-1 and 50-2). Although many of the signs of respiratory compromise could have multifactorial explanations, assessment of the adequacy of oxygenation and ventilation ensures that respiratory inadequacy is not contributory. Any evidence of respiratory compromise requires immediate correction.

Electrocardiographic (ECG) monitoring is initiated for determination of cardiac rate and rhythm. Any deviation from preoperative or intraoperative findings is noted and evaluated. Also, blood pressure is measured, and adequacy of organ perfusion is determined. Any necessary invasive monitoring, such as an arterial line, is initiated. Any evidence of cardiocirculatory compromise requires immediate correction.

The anesthesia provider should be active during the patient's transfer and stabilization in the PACU. Assistance in the initiation of oxygen therapy, maintenance or verification of airway adequacy, and assessment of circulatory status familiarizes PACU personnel with the patient and fosters a smooth transfer of care. After initially stabilizing the patient, the anesthesia provider can communicate relevant preoperative and intraoperative data to the PACU nurse.

ANESTHESIA REPORT

To ensure patient safety and continuity of care, the anesthesia provider must give a verbal handoff report to the PACU nurse that specifies the details of the surgical and anesthetic course, the preoperative conditions that warrant or influence the surgical and anesthetic outcome, and the PACU treatment plan, including suggested interventions and end-points. Transfer of the patient from the OR to the PACU is a critical patient handoff and should include an opportunity for the PACU nurse to ask questions and the anesthesia provider to respond. Communication errors can occur during the process of a handoff. To decrease these communication errors, handoff information needs to be standardized and communicated in a logical and meaningful manner.[3] A coherent order for the presentation of this information is presented in Box 50-3.

The importance of the anesthesia report is reflected in the American Association of Nurse Anesthetists (AANA) guideline from the *AANA Scope and Standards for Nurse Anesthesia Practice*: "Standard VII: Transfer the responsibility for care of the patient to other qualified providers in a manner which assures continuity of care and patient safety."[4] The American Society of Anesthesiologists (ASA) points to the importance of a verbal report to the responsible PACU nurse but also goes on to state, "The member of the Anesthesia Care Team shall remain in the PACU until the PACU nurse accepts responsibility for the nursing care of the patient."[5]

INITIAL POSTANESTHESIA CARE UNIT ASSESSMENT

Many postanesthesia assessment approaches (e.g., head-to-toe, major body systems assessments, and scoring systems) are currently used in PACUs, and each approach has its benefits and limitations. The assessment approach should accomplish the following:

- Determine the patient's physiologic status at the time of admission to the PACU
- Allow the periodic reexamination of the patient so that physiologic trends become obvious
- Establish the patient's baseline level so that the effect of previous medical conditions can be assessed and predicted as they affect current physiology
- Assess the ongoing status of the surgical site and its effect on any preexisting conditions and recovery
- Assess the patient's recovery from anesthesia and note residual effects
- Prevent or immediately treat complications that occur
- Provide a safe environment for the patient who is impaired either physically, mentally, or emotionally
- Allow the compilation and trend analysis of patient-specific characteristics that relate to discharge or transfer criteria[1,6]
- Anesthesia personnel must assist in management of the patient until PACU providers secure admission vital signs and attach

BOX 50-1

Signs and Symptoms of Inadequate Oxygenation

Respiratory
- Shallow, rapid respirations or normal, infrequent respirations
- Tachypnea
- Dyspnea
- Oxyhemoglobin saturation less than 90%

Neurologic
- Anxiety, restlessness, inattentiveness
- Altered mental status, confusion
- Dimmed peripheral vision
- Seizures
- Unresponsiveness

Skin
- Diaphoresis
- Cyanosis

Cardiac
- *Early:* Tachycardia
  - Increased cardiac output
  - Increased stroke volume
  - Increased blood pressure
- *Late:* Bradycardia, hypotension
- Dysrhythmias

Modified from Marley RA, Hoyle BL. Respiratory care. In Schick L, Windle PE. *PeriAnesthesia Nursing Core Curriculum*. 2nd ed. St. Louis: Saunders; 2010:625-693.

BOX 50-2

Causes of Hypoxemia

- *Hypoventilation*—Alveolar ventilation is abnormally low in relation to oxygen uptake or carbon dioxide output
- *Diffusion limitation*—Oxygen, carbon dioxide are affected as they cross the blood-gas barrier by simple passive diffusion
- *Shunt*—The entry of blood into the systemic arterial system without going through ventilated areas of lung
- *Ventilation-perfusion relationships*—A mismatch of ventilation and blood flow

Modified from Mason RJ, et al. *Murray and Nadel's Textbook of Respiratory Medicine*. 5th ed. Philadelphia: Saunders; 2010.

appropriate monitors. To optimize safety, the anesthesia provider cannot shift responsibility to PACU personnel until the patient's airway status, ventilation, and hemodynamics are appropriate.

Aldrete Scoring System

The most commonly used assessment approach is a combination of the Aldrete scoring system[7] and the major body systems assessment. The Aldrete scoring system evaluates the patient's activity, respiration, circulation, consciousness, and oxygen saturation level (Box 50-4). Patients receive a numeric score of 0, 1, or 2 in each area, with 2 representing the highest level of function.[8] The Aldrete postanesthetic scoring system is the most widely used scoring system in PACUs, although its predictive value in determining recovery from anesthesia has not been studied prospectively.

Major Body Systems

The major body systems assessment systematically evaluates the body systems that are most affected by anesthesia and the surgical procedure. After the patient is admitted to the PACU, an assessment of cardiorespiratory stability and a more in-depth cardiac assessment are performed. Respiratory assessment comprises rate, depth of ventilation, auscultation of breath sounds, and oxygen saturation level. Type of oxygen delivery system and presence of any artificial airway should be noted.[9] The heart is auscultated,

BOX 50-3

Anesthesia Admission Report

General Information
- Patient name
- Patient age
- Surgical procedure
- Name of surgeon and anesthesia provider(s)
- Type of procedure

Patient History
- Acute (indication for surgery)
- Chronic (medical history, medication use, allergies)

Intraoperative Management
- Anesthetic agents, including dose and technique
- Time of last opioid administration
- Use of reversal agents
- Intraoperative medications (antibiotics, antiemetics, vasopressors)
- Estimated blood loss
- Fluid and blood administration
- Urine output

Intraoperative Course
- Unexpected response to anesthetic administration
- Unexpected surgical course
- Laboratory results (arterial blood gas, glucose, hemoglobin)

Postanesthesia Care Unit Plan
- Potential and expected problems
- Suggested interventions
- Limits of acceptability of laboratory tests
- Discharge criteria
- Responsible contact person

and the quality of heart sounds, the presence of any adventitious sounds, and any irregularities in rate or rhythm are noted. Unexpected findings are compared with preoperative data. Arterial pulses are evaluated for strength and equality. An ECG strip is obtained on admission to the PACU and compared with the preoperative ECG. In addition, body temperature and skin color and condition are assessed and the findings documented.

After respiratory and cardiac assessments are completed, the neurologic system is evaluated, with a focus on the level of consciousness, orientation, sensory and motor function, and pupil size, equality, and reactivity. The patient is assessed on ability to follow commands and move extremities purposefully and equally.[6]

The renal system assessment focuses on fluid intake and output (e.g., blood, crystalloids, and colloids), as well as on volume and electrolyte status. The anesthesia provider relates intraoperative fluid totals in the verbal report, and the PACU nurse notes and documents all intravenous (IV) lines, irrigation solutions, and infusions that enter the patient. All output devices, including drains, catheters, and tubes, are inspected, and the color and consistency of any drainage are noted.

The surgical site is examined. The amount and color of any drainage on the bandage are noted. The patient is also assessed for pain or discomfort, such as nausea, with appropriate interventions administered.

All data obtained in the admission assessment should be documented in a manner that facilitates data collection, trend analysis, and retrieval. Recommended criteria for the initial assessment of a patient in the PACU are included in Box 50-5.

ONGOING ASSESSMENT

Perioperative and postanesthetic management of the patient includes ongoing assessment and monitoring of the following[5]:
- Respiratory function (e.g., obstruction, hypoxemia, hypercarbia)
- Cardiovascular function (e.g., hypotension, hypertension, dysrhythmias)

BOX **50-4**

Postanesthesia Recovery Score

Activity
0 = Unable to lift head or move extremities voluntarily or on command.
1 = Moves two extremities voluntarily or on command and can lift head.
2 = Able to move four extremities voluntarily or on command. Can lift head and has controlled movement. *Exceptions:* Patients with a prolonged block such as with bupivacaine (Marcaine), who may not move an affected extremity for as long as 18 hours; patients who were immobile preoperatively.

Respiration
0 = Apneic; condition necessitates ventilator or assisted respiration.
1 = Labored or limited respirations. Breathes by self but has shallow, slow respirations. May have an oral airway.
2 = Can take a deep breath and cough well; has normal respiratory rate and depth.

Circulation
0 = Has abnormally high or low blood pressure; blood pressure within 50 mmHg of preanesthetic level
1 = Blood pressure within 20-50 mmHg of preanesthetic level
2 = Stable blood pressure and pulse. Blood pressure 20 mmHg of preanesthetic level (minimum 90 mmHg systolic). *Exception:* Patient may be released by anesthesia provider after drug therapy.

Neurologic Status
0 = Not responding or responding only to painful stimuli.
1 = Responds to verbal stimuli but drifts to sleep easily.
2 = Awake and alert; oriented to time, place, and person.

O_2 Saturation
0 = O_2 saturation less than 90%, even with O_2 supplement.
1 = Needs O_2 inhalation to maintain O_2 saturation greater than 90%.
2 = Able to maintain O_2 saturation greater than 92% on room air.

Modified from Ead H. From Aldrete to PADSS: reviewing discharge criteria after ambulatory surgery. *J Perianesth Nurs*. 2006;21:259-267.

BOX **50-5**

Criteria for Initial Assessment: Phase I Postanesthesia Care Unit

Initial assessment and documentation include:
1. Integration of data received at transfer of care
   a. Relevant preoperative status
   b. Anesthesia/sedation technique and agents
   c. Length of time anesthesia administered
   d. Pain and comfort interventions and plan
   e. Medications administered
   f. Type of procedure
   g. Estimated blood loss and replacement
   h. Complications during course of anesthesia and response to treatment
2. Vital signs
   a. Respiratory status—airway patent, breath sounds, type of artificial airway, mechanical ventilatory settings, oxygen saturation, end-tidal CO_2 (if ordered)
   b. Blood pressure—cuff or arterial line
   c. Pulse—apical, peripheral
   d. Cardiac monitor, rhythm documented
   e. Temperature/route
   f. Hemodynamic pressure readings: central venous, pulmonary artery, and wedge; intracranial pressure as indicated
3. Pain level, level of emotional comfort
4. Neurologic function to include level of consciousness; pupillary response as indicated
5. Sensory and motor function as appropriate
6. Position of patient
7. Condition and color of skin
8. Patient safety needs
9. Neurovascular: Peripheral pulses and sensation of extremity(ies) as applicable
10. Condition of dressings and visible incisions
11. Type and patency of drainage tubes, catheters, and receptacles; effectively secured
12. Amount and type of drainage
13. Hydration status/fluid therapy: Location of lines, condition of IV site, and amount of solution infusing
14. Procedure-specific assessment (i.e., firmness of abdomen)
15. Postanesthesia scoring system if used

Modified from American Society of Perianesthesia Nurses (ASPAN). *Perianesthesia Nursing Standards and Practice Recommendations 2010-2012*. Cherry Hill, NJ. ASPAN; 2010.

- Neuromuscular function (e.g., inadequate reversal of neuromuscular blockade)
- Mental status (e.g., delayed awakening, emergence delirium)
- Pain
- Temperature (e.g., hypothermia)
- Nausea and vomiting
- Fluids
- Urine output and voiding

Respiratory Function

In postoperative patients, airway problems that interfere with oxygenation and ventilation are always related to an increase in the resistance to gas flow in the airway.[10] However, the most common cause of airway obstruction in the immediate postoperative phase is the loss of pharyngeal muscle tone in a sedated or obtunded patient.[11]

Obstruction

In postanesthesia patients, the tongue causes most upper airway obstructions. Obstruction occurs when the tongue falls back into a position that occludes the pharynx and blocks the flow of air into and out of the lungs. Signs and symptoms of an upper airway obstruction include snoring and activation of accessory muscles of ventilation. Intercostal and suprasternal retractions may be noted. However, patients are usually somnolent and may be difficult to arouse. Risk factors for an upper airway obstruction include anatomy (e.g., obesity, large neck, or short neck), poor muscle tone (secondary to opioids, sedation, residual neuromuscular blockade, or neuromuscular disease), or swelling (secondary to surgical manipulation, edema, or anaphylaxis).

The goal for the relief of a tongue obstruction is a patent airway. Treatment consists of a series of interventions. The initial intervention may be as simple as stimulating the patient to take deep breaths, or it may require repositioning of the airway via a jaw thrust or a chin lift. Placement of an oral or a nasal airway may be required. The nasal airway is tolerated much better by patients emerging from general anesthesia, and unlike the oral airway, it is unlikely to cause gagging or vomiting. If the obstruction remains unrelieved, reintubation may be required, with or without adjunctive mechanical ventilation.

Laryngeal obstruction may occlude the airway as a result of partial or complete spasm of the intrinsic or extrinsic muscles of the larynx. Laryngospasm may be the result of a reflex closure of the glottis (intrinsic muscles) or the larynx (extrinsic muscles).[10] Glottic closure usually manifests as intermittent obstruction; laryngeal closure manifests as complete obstruction. Airway irritation that predisposes a patient to laryngospasm may be the result of laryngoscopy, secretions, vomitus, blood, artificial airway placement, coughing, bronchospasm, or frequent suctioning. Symptoms that suggest laryngospasm include agitation, decreased oxygen saturation, absent breath sounds, and acute respiratory distress. Incomplete obstruction may manifest as a crowing sound or stridor.

Treatment of laryngospasm must be immediate. Positive-pressure ventilation with 100% oxygen is the initial intervention. If this intervention is ineffective, a subparalytic dose of IV succinylcholine (0.1 mg/kg) may be given by the anesthesia provider. If succinylcholine is administered, assisted ventilation for 5 to 10 minutes is required, even if the obstruction has been relieved. Reintubation should be performed if severe airway edema is present or if the obstruction persists despite treatment interventions. During the crisis, the anesthesia provider should consider medication for sedation, such as midazolam, to alleviate the possibility of an awake or partially awake patient.

Steroids and topical or IV lidocaine have been included in the prevention and management of airway irritability. Other preventive strategies include obtaining meticulous hemostasis during surgery, suctioning the oropharynx before extubation to clear any retained blood or secretions, and extubating the patient when he or she is in either a very deep plane of anesthesia or the awake state.[10] When obstruction occurs, rapid intervention is imperative because the arterial carbon dioxide pressure ($PaCO_2$) increases 6 mmHg in the first minute of total obstruction and an additional 3 to 4 mmHg each minute thereafter.[11]

Hypoxemia

Hypoxemia, defined as low arterial oxygen pressure (PaO_2) (usually less than 60 mmHg), is characterized by nonspecific signs and symptoms ranging from agitation to somnolence, hypertension to hypotension, and tachycardia to bradycardia. Pulse oximetry may confirm low oxygen saturation (less than 90%); arterial blood gas analysis may confirm a PaO_2 of less than 60 mmHg. Hypoxemia, if untreated, can result in organ ischemia.

Hypoxemia can be the result of a delivered airway obstruction, low concentration of oxygen, hypoventilation, impaired alveolar-capillary diffusion, ventilation-perfusion mismatches, or increased intrapulmonary shunting.[11,12] The most common causes of hypoxemia in the PACU include atelectasis, pulmonary edema, pulmonary embolism, aspiration, bronchospasm, and hypoventilation. A brief explanation of these pathologic states follows.

Clinical issues with pulse oximetry have to be considered when used to determine oxygen saturation levels. The relationship between percent of hemoglobin saturated with oxygen (SaO_2) and the partial pressure of oxygen in the blood (PaO_2) is symbolized by the oxyhemoglobin dissociation curve (see Figure 26-8). Shifts in the curve are caused by abnormal values of pH, temperature, partial pressure of carbon dioxide, and 2,3-diphosphoglycerate. The patient's level of hemoglobin must also be considered, because if too low, even fully saturated hemoglobin is not adequate to meet tissue needs.[1]

Atelectasis

Atelectasis is the most common cause of postoperative arterial hypoxemia and can lead to an increase in right-to-left shunt. Atelectasis may be the result of bronchial obstruction caused by secretions or decreased lung volumes. Hypotension and low cardiac output conditions can also contribute to the development of decreased perfusion and atelectasis. Treatment includes the use of humidified oxygen, coughing, deep breathing, postural drainage, and increased mobility. Incentive spirometry and intermittent positive-pressure ventilation also may be used.[13]

Pulmonary Edema

Pulmonary edema, which is caused by fluid accumulation within the alveoli, may be the result of an increase in hydrostatic pressure, a decrease in interstitial pressure, or an increase in capillary permeability.

An increase in hydrostatic pressure is usually the result of fluid overload, left ventricular failure (especially in the presence of systolic hypertension), mitral valve dysfunction, or ischemic heart disease. Increased capillary permeability may be the result of sepsis, aspiration, transfusion reaction, trauma, anaphylaxis, shock, or disseminated intravascular coagulation and is frequently referred to as *adult respiratory distress syndrome*.[10]

A decrease in interstitial pressure is often seen after prolonged airway obstruction, such as laryngospasm. Acute pulmonary edema that occurs shortly after relief of severe upper airway obstruction is called *postobstruction* or *negative-pressure pulmonary edema* or *noncardiogenic pulmonary edema*. The airway obstruction causes extreme negative intrapleural pressure that increases the pulmonary transvascular hydrostatic pressure gradient. The rapid movement of fluid from pulmonary vasculature to interstitium exceeds the clearing capacity of the pulmonary lymphatic system, and the alveoli become flooded.[14] Other causes of noncardiogenic pulmonary edema are bolus dosing with naloxone, incomplete reversal of neuromuscular blockade, or a significant period of hypoxia.[15]

Pulmonary edema is characterized by hypoxemia, cough, frothy sputum, rales on auscultation, decreased lung compliance, and pulmonary infiltrates seen on chest radiography. Treatment of pulmonary edema is directed toward identification of the cause and reduction of hydrostatic pressure within the lungs. Oxygenation must be maintained (particularly in the presence of profound hypoxemia) via oxygen mask or continuous positive airway pressure (CPAP) with mask, or if necessary, intubation, mechanical ventilation, and the addition of positive end-expiratory pressure (PEEP) ventilation. Diuretics (most commonly furosemide) and fluid restriction are a part of treatment. Dialysis may be used if the fluid retention results from renal failure. Afterload reduction, which is achieved through the use of nitroglycerin or sodium nitroprusside, may be used to decrease myocardial work.[10] Patients with noncardiogenic pulmonary edema usually recover quickly after the acute phase and have no permanent sequelae.[15]

Pulmonary Embolism

Pulmonary embolism is a leading cause of morbidity and mortality, accounting for 50,000 to 90,000 deaths annually in the United States. Most cases of pulmonary embolism are not fatal; however, two thirds of all deaths caused by a pulmonary embolism occur within 30 minutes of an acute event.[16]

Patients can be considered to be at risk for pulmonary embolism if three conditions, known as *Virchow's triad*, exist: venous stasis, hypercoagulability, and abnormalities of the blood vessel wall. These conditions are accentuated in the presence of obesity, varicose veins, immobility, malignancy, congestive heart failure, and increased age and after pelvic or long-bone surgery or injury. However, 90% of all pulmonary emboli arise from deep veins in the legs.[16,17] Thrombosis in postoperative patients seems to be related

BOX **50-6**

Surgery-Induced Hemostatic Changes

Increased Platelet Reactivity
↑ Aggregation
↑ Dense granule release

Increased Leukocyte Reactivity
↑ Free-radical release
↑ Surface adhesion molecules

Increased Coagulation Cascade Activation
↑ Fibrinogen
↑ Factor VIII
↑ Von Willebrand factor
↑ Thrombin formation

Decreased Endogenous Anticoagulants
↓ Antithrombin III
↓ Heparin cofactor II
↓ Tissue factor pathway inhibitor
↓ Protein C, protein S

Decreased Fibrinolysis
↑ Plasminogen activator inhibitor-1

From Patel K, Chaney MA. Hypercoagulable states: thrombosis and embolism. In Atlee JL. *Complications in Anesthesia*. 2nd ed. Philadelphia: Saunders; 2007:363.

to surgical tissue trauma and liberation of tissue factor that leads to thrombin formation. Leukocyte reactivity and surgery-induced hemostatic changes also may contribute[18] (Box 50-6).

A pulmonary embolism should be suspected in a patient who complains of or whose presenting signs include acute-onset tachypnea, dyspnea, and tachycardia, particularly when the patient is already receiving oxygen therapy. Signs and symptoms also may include chest pain, hypotension, hemoptysis, dysrhythmias, and congestive heart failure. Although the clinical symptomatology may be suggestive of a pulmonary embolism, confirmation requires pulmonary angiography. Pulmonary angiography is infrequently performed because of its high risk and associated mortality. A ventilation-perfusion scan may also prove useful.

Treatment of a pulmonary embolism is directed toward the correction of hypoxemia and support of hemodynamic stability. Preventive measures may include the use of antiembolic stockings or sequential compression devices. Subcutaneous heparin therapy also may be initiated. Once the occurrence of a pulmonary embolism has been confirmed, IV heparin therapy is started for the prevention of further clot formation. The goal of heparin therapy is an activated partial thromboplastin time that is 1.5 to 2 times the control value. Several new drugs are under development that will have fixed doses and not require laboratory monitoring.[19]

Aspiration

Aspiration is a potentially serious airway emergency that can compromise patient safety and stability on the induction of, or the emergence from, anesthesia. Aspiration may occur in the OR, in the PACU, or at any time during transfer. Patients may aspirate foreign matter (e.g., a tooth, food), blood, or gastric contents. Each type of material is associated with a characteristic clinical presentation.

Foreign matter aspiration may result in cough, airway obstruction, atelectasis, bronchospasm, and pneumonia. A profound reflex sympathetic nervous system (SNS) response might also cause hypertension, tachycardia, and dysrhythmias. In the absence of complete upper airway obstruction, complications are often localized and treated with supportive care once the foreign matter has been expelled or removed by bronchoscopy.[16]

Aspiration of blood may result from trauma or surgical manipulation and also may cause minor airway obstruction that is rapidly cleared by cough, resorption, and phagocytosis. Massive blood aspiration interferes with gas exchange through mechanical blockage of airways and leads to chronic fibrinous changes in air spaces or pulmonary hemochromatosis from iron accumulation in phagocytic cells. Aspiration of blood may result in infection, particularly if particles of soft tissue are aspirated along with the blood. Treatment involves correction of hypoxemia, maintenance of airway patency, and initiation of antibiotic therapy, if indicated.[15]

Aspiration of gastric contents is the most severe form of aspiration and may result in a chemical pneumonitis. Patients have diffuse bronchospasm (secondary to reflex airway closure), hypoxemia (compromised alveolar-capillary membrane), atelectasis (loss of surfactant), interstitial edema (loss of capillary integrity), hemorrhage, and adult respiratory distress syndrome. Gastric aspiration also may cause laryngospasm, infection, and pulmonary edema.

For this reason, the prevention of gastric aspiration, rather than its treatment, is the goal. Patients who are at risk for gastric aspiration (e.g., obese or pregnant patients or those with a history of hiatal hernia, peptic ulcer, or trauma) may be given histamine-2 (H_2) blockers, gastrokinetic agents, nonparticulate antacids, or anticholinergics before anesthesia induction. Prophylactic medications are not recommended for those patients who are not at risk.[20] Rapid-sequence induction is likely used. Intraoperatively a nasogastric tube may be inserted and is usually then removed to decrease gastric volume and decompress the stomach. Postoperatively the patient should be left intubated until airway reflexes return.

Treatment of gastric aspiration is directed toward correction of hypoxemia and maintenance of hemodynamic stability. Antibiotics are indicated only if signs of infection (e.g., fever, leukocytosis, positive culture results) are present. No beneficial effect of corticosteroids has been determined. Administration of corticosteroids may be indicated with the presence of inflammatory pneumonitis, but the immunosuppressant effect may exacerbate any secondary bacterial pneumonia.[21]

If aspiration causes hypoxemia, increased airway resistance, atelectasis, or pulmonary edema, institution of support with supplemental oxygen, PEEP, or CPAP and mechanical ventilation is often necessary. Pulmonary edema is usually secondary to increased capillary permeability, so diuretics should not be used to decrease intravascular volume. Bacterial infection does not always occur, so prophylactic antibiotics might merely promote colonization by resistant organisms. If evidence of secondary bacterial infections appears, specific antibiotic therapy is instituted, based on sputum samples obtained for Gram stain and culture or on prevailing colonization experience within the institution.[15]

Bronchospasm

Bronchospasm results from an increase in bronchial smooth muscle tone, with resultant closure of small airways. As a result of the strong increase in inspiratory force against these closed airways, airway edema develops, causing secretions to build up in the airway. Clinically, the patient demonstrates wheezing, dyspnea, use of accessory muscles, and tachypnea. Airway resistance is increased, and increased peak inspiratory pressures are noted if the patient is receiving mechanical ventilation.[10,22]

Bronchospasm may result from aspiration, pharyngeal or tracheal suctioning, endotracheal intubation, histamine release secondary to medications, or an allergic response, and it may be seen in greater frequency in patients with a history of asthma or chronic obstructive pulmonary disease.

Treatment of bronchospasm requires confirmation and removal of the precipitating cause. Pharmacotherapy is instituted, with the goals of decreasing airway irritability and promoting

bronchodilation. Medications used in the management of bronchospasm include salmeterol (Serevent) and β_2-agonists such as albuterol (Proventil, Ventolin), salbutamol, and terbutaline and, if the condition is life threatening, IV epinephrine. Anticholinergics such as atropine sulfate and glycopyrrolate have been given via nebulization to decrease secretions. Both IV and inhaled lidocaine attenuate histamine-induced bronchospasm; however, inhaled lidocaine works at a lower serum level than IV lidocaine.[22] Steroids have been used if the underlying cause is an inflammatory disease such as asthma.[15]

Hypoventilation

Hypoventilation is a common, easily recognizable complication in the PACU. It is manifested clinically by a decrease in respiratory rate that results in an increase in $Paco_2$ secondary to a decrease in alveolar ventilation. This may occur because of a decrease in central respiratory drive, poor respiratory muscle function, or a combination of both.[11]

Depression of central respiratory drive can occur with both IV and inhalation anesthetics. Central respiratory depression is most profound on admission to the PACU, although the time and route of anesthetic administration may suggest otherwise. For example, an IV dose of fentanyl given just before the patient emerges from anesthesia may not peak until later in the PACU. An intramuscular dose of an opioid takes substantially longer to peak than does an IV dose.[16]

Patients also may demonstrate a secondary stage of respiratory depression once certain stimuli are removed. For example, a patient may be admitted awake and breathing to the PACU with an endotracheal tube in place. After extubation, because of the loss of stimulation from the endotracheal tube, the patient may become hypercarbic secondary to residual opioid effects and hypoventilation.[10] Verbal and tactile stimulation, deep breaths, and repositioning the patient may increase ventilatory function and decrease carbon dioxide. Capnography may be of use in patients at risk.[15]

Poor respiratory muscle function can result from many conditions. Some of the most common situations are inadequate reversal of neuromuscular blocking agents, surgery involving the upper abdomen, positioning, obesity, and diseases involving the neuromuscular system.

Inadequate reversal of neuromuscular blocking agents can result in hypoventilation secondary to respiratory muscle weakness. Factors that can adversely affect neuromuscular blockade and reversal include certain medications, hypokalemia, hypermagnesemia, hypothermia, and acidosis.[23]

Medications that have been associated with prolongation of blockade include the aminoglycoside antibiotics (e.g., gentamicin, clindamycin, and neomycin), as well as magnesium and lithium. Hypermagnesemia and hypothermia may potentiate neuromuscular blockade. Hypokalemia and respiratory acidosis inhibit reversal.[23]

Upper abdominal surgery also can affect respiratory muscle function. Hypoventilation occurs because of a reduced vital capacity secondary to poor diaphragmatic function. A reduction in vital capacity of up to 60% has been noted on the first postoperative day.[11] Obesity, especially when combined with upper abdominal surgery, further contributes to hypoventilation because of the increased intraabdominal pressure in obese patients.

Diseases of the neuromuscular system also can affect ventilation. Patients with muscular dystrophy, myasthenia gravis, Eaton-Lambert syndrome, Guillain-Barré syndrome, or other muscle diseases can exhibit postoperative muscle weakness. Patients with severe scoliosis also exhibit poor respiratory muscle function. It is often in the best interests of patients with these disorders that they remain intubated in the PACU until complete return of function occurs, and any residual anesthetic effects are absent.

Cardiovascular Function

Hypotension

Classically, *hypotension* has been defined as a blood pressure of less than 20% of the baseline or preoperative blood pressure. However, the clinical signs of hypoperfusion, rather than numeric values, should be the indicators of compromise. Because the autonomic nervous system preferentially maintains blood flow to the brain, heart, and kidneys, signs of hypoperfusion to these organs (including disorientation, nausea, loss of consciousness, chest pain, oliguria, and anuria) reflect the failure of physiologic compensation. Hypoxia, which results from hypoperfusion, may cause lactic acidosis. Intervention must be implemented in a timely fashion so that cerebral ischemia, cerebrovascular accident (CVA), myocardial infarction or ischemia, renal ischemia, bowel infarction, and spinal cord damage do not develop.[24]

Hypotension in the PACU is most commonly caused by hypovolemia secondary to inadequate replacement of intraoperative fluid and blood loss. As a result, initial treatment should focus on restoring circulating volume. The patient should be assessed for active bleeding and a 300- to 500-mL fluid bolus of physiologic saline or lactated Ringer's solution should be given. If no response is noted, myocardial dysfunction should be considered the cause of hypotension.

Primary cardiac dysfunction, as is the case with myocardial infarction, tamponade, or embolism, results in an acute fall in ventricular emptying and cardiac output. Secondary cardiac dysfunction occurs as a result of the negative chronotropic and negative inotropic effects of medications.

Low systemic vascular resistance (SVR) also can contribute to hypotension. Numerous anesthetic agents cause histamine release with subsequent vasodilation (e.g., morphine, atracurium), whereas others cause vasodilation by directly relaxing arterial smooth muscle (e.g., volatile inhalation anesthetics, local anesthetics used for producing spinal anesthesia). Sensitivity to vasodilators such as hydralazine, sodium nitroprusside, and nitroglycerin also can produce profound hypotension. Sepsis may be another cause of low SVR.

Dysrhythmias that interfere with cardiac conduction and subsequently compromise cardiac output also can produce hypotension. Tachydysrhythmias prevent optimal ventricular filling and emptying. Conduction blocks compromise myocardial effectiveness, resulting in a lowered cardiac output and hypotension. See Box 50-7 for a differential diagnosis of hypotension in the postoperative patient.

Intervention should always include supplemental oxygen therapy while the cause of the hypotension is being investigated. Volume status should be evaluated, and preoperative and intraoperative fluid administration should be considered. Hypotension caused by artifact of the measurement system also should be considered—for example, a blood pressure cuff that is too large or too small or an inappropriate transducer height. The presence of hypotension secondary to myocardial dysfunction suggests the need for coronary vasodilators, inotropic therapy, and afterload reduction (e.g., through nitroglycerin therapy, dobutamine therapy, or both). Secondary myocardial dysfunction may require that administration of the causative medications be discontinued. Vasodilation resulting in lower SVR and symptomatic hypoperfusion can be treated with vasoconstrictive agents, either by IV bolus (ephedrine) or by infusion (dopamine or epinephrine).

BOX **50-7**

Differential Diagnosis of Hypotension in the Postanesthesia Care Unit

Intravascular Volume Depletion
- Persistent fluid losses
- Ongoing third spacing of fluid
- Bowel preparation
- Gastrointestinal losses
- Surgical bleeding

Increased Capillary Permeability
- Sepsis
- Burns
- Transfusion-related acute lung injury

Decreased Cardiac Output
- Myocardial ischemia/infarction
- Cardiomyopathy
- Valvular disease
- Pericardial disease
- Cardiac tamponade
- Cardiac dysrhythmias
- Pulmonary embolus
- Tension pneumothorax
- Drug induced (β-blockers, calcium channel blockers)

Decreased Vascular Tone
- Sepsis
- Allergic reactions (anaphylactic, anaphylactoid)
- Spinal shock (cord injury, iatrogenic high spinal)
- Adrenal insufficiency

From Nicholau D. The postanesthesia care unit. In Miller RD, et al, eds. *Miller's Anesthesia*. 7th ed. Philadelphia: Churchill Livingstone; 2009:2717.

BOX **50-8**

Factors Leading to Postoperative Hypertension

- Preoperative hypertension
- Arterial hypoxemia
- Hypervolemia
- Emergence excitement
- Shivering
- Drug rebound
- Increased intracranial pressure
- Increased sympathetic nervous system activity
  - Hypercapnia
  - Pain
  - Agitation
  - Bowel distention
  - Urinary retention

From Nicholau D. The postanesthesia care unit. In Miller R, et al, eds. *Miller's Anesthesia*. 7th ed. Philadelphia: Churchill Livingstone; 2009:2717.

Hypertension

Hypertension, defined as a 20% to 30% increase relative to the baseline blood pressure, is a common finding in the PACU and can be caused by stimulation of the SNS and pain, respiratory compromise, visceral distention, and significant increases in plasma catecholamine levels that produce vasoconstriction (Box 50-8).

Pain remains the leading cause of hypertension and tachycardia in the PACU and results in stimulation of the somatic afferent nerves, producing a pressor response known as the *somatosympathetic reflex*.[24] The use of analgesics attenuates the sympathetic response, thereby normalizing blood pressure.

Hypoxemia and hypercarbia cause direct stimulation of the vasomotor area of the medulla, resulting in increased vasomotor tone, increased arteriolar constriction, and increased blood pressure.[24] Correction of the respiratory compromise should result in normalization of blood pressure.

Distention of the bladder, bowel, or stomach causes stimulation of afferent fibers of the SNS, producing an increase in plasma catecholamine levels. Catheterization of the bladder and decompression of the bowel or stomach remove the offending stimulus.

Hypertension also may develop as a sequela of hypothermia. Increased catecholamine secretion is an important endocrine response to cold.[24] As cooling occurs, blood vessels become more sensitive to catecholamines, resulting in arteriolar and venous constriction. Rewarming reverses the process. As vasodilation occurs, reperfusion of the extremities and skin decreases systemic elevations in pressure.

Preexisting hypertension exists in many of the patients who develop hypertension in the PACU. The degree of elevation in pressure is greater if preoperative antihypertensive medications are withdrawn suddenly. Ideally, patients receive their antihypertensive medications on the day of surgery.

Hypertension also may be seen secondary to revascularization and baroreceptor stimulation after vascular or cardiac surgery, including carotid endarterectomy. Pharmacologic intervention is required for the protection of graft sites and the prevention of hemorrhage. Sodium nitroprusside and nitroglycerin are agents of choice for vasodilation.

A significant number of patients, especially those with a history of essential hypertension, will require pharmacologic blood pressure control in the PACU.[11] Agents that may be used for the reduction of blood pressure include hydralazine and labetalol hydrochloride. Hydralazine relaxes vascular smooth muscle, preferentially favoring the arteriolar circulation. Labetalol is both an α- and a β-blocking agent, causing peripheral vasodilation and slowing of the heart rate. Other beta blockers used postoperatively include metoprolol and esmolol. Beta-blockers assist in controlling the sympathetic responses of patients during recovery. α-2-agonists also can be used postoperatively to assist when needed. Many other agents are available and may include the patient's usual prescription antihypertensive for mild increases. Patients who were on β-blockers prior to surgery should be given a β-blocker the day of surgery. One of the surgical care improvement measures (SCIP) that is evaluated during the perioperative period is SCIP-cardiovascular-2. SCIP cardiovascular-2 measures the number of "surgery patients on a beta blocker prior to arrival who received a beta blocker during the peri-operative period."[25]

Dysrhythmias

Dysrhythmias seen in the PACU most commonly have an identifiable cause that is not an actual myocardial injury. The major postanesthetic and surgical factors that lead to a relatively high incidence of perioperative dysrhythmias include hypokalemia, hypoxia, hypercarbia, altered acid-base status, circulatory instability, and preexisting heart disease.

Arterial desaturation is a common postoperative complication that may result from obstruction or hypoventilation or less commonly from pulmonary embolism, pulmonary edema, or aspiration. A direct consequence of hypoxia is myocardial ischemia and depression of cardiac contractility. Signs of cardiac irritability may be manifested by atrial and ventricular dysrhythmias, conduction delays, and heart block.

Hypercarbia caused by reduced alveolar ventilation results in elevation of the arterial carbon dioxide tension, which in turn stimulates the SNS and sensitizes the myocardium to the arrhythmic effects of endogenous catecholamines. Among the earliest signs of hypercarbia are tachycardia and hypertension, which may progress to ventricular dysrhythmias.

Hypokalemia may occur secondary to hyperventilation, respiratory alkalosis, gastric suctioning, insulin administration, and

diuretic use. The ECG may demonstrate widening of the QRS complex, U waves, and ST-segment abnormalities that may progress into premature ventricular complexes, ventricular tachycardia, and ventricular fibrillation.

Acid-base disturbances may occur as a result of alterations in ventilation, gastrointestinal losses, and lactic acid production during hypotension or shock. The cardiovascular effects include increased cardiac excitability and irritability.

Hypotension may result in impaired oxygen transport and compromised coronary circulation, leading to myocardial ischemia with associated conduction deficits. The use of vasoconstrictive medications designed to treat the hypotension also may contribute to the development of dysrhythmias. Patients with preexisting heart disease, particularly those who have a history of myocardial infarction, are at continued risk for myocardial ischemia throughout the perioperative period.

Hypothermia prolongs the refractory period, contributing to the development of sinus bradycardia and atrial fibrillation. Conduction deficits may progress to atrioventricular block and eventually to ventricular fibrillation.[26]

Vagal reflexes are usually transient and are produced by the Valsalva maneuver or direct eye, vagal nerve, or carotid sinus pressure. Severe sinus bradycardia with possible ventricular escape beats may occur. Vagotonic medications such as neostigmine also can produce these dysrhythmias.

The presence of residual anesthetics in both blood and tissue in patients admitted to the PACU may contribute to dysrhythmias. Ketamine may contribute to sympathetic stimulation, resulting in tachyarrhythmias and hypertension, as can vagolytic drugs such as atropine and glycopyrrolate. Opioids such as morphine, fentanyl, and sufentanil may result in the indirect development of dysrhythmias. Respiratory depression, a potential side effect of opioids, may result in hypoxemia and hypercarbia, both of which are known to be dysrhythmogenic. Anticholinesterase agents may produce severe bradyarrhythmias or heart block.[27]

Surgical stress and pain can significantly increase plasma catecholamine levels. Although this sympathetic response may be mitigated by anesthetic administration, norepinephrine and epinephrine concentrations are consistently elevated in PACU patients who are in pain. Administration of analgesic medications may blunt this sympathetic response; however, cardiac irritability, tachycardia, and conduction dysrhythmias may occur.

Neuromuscular Function

Reversal of Neuromuscular Blockade

Incomplete reversal of neuromuscular relaxation can lead to postoperative airway obstruction and hypoventilation. Residual paralysis compromises cough, airway patency, ability to overcome airway resistance, and airway protection. Intraoperative use of shorter-acting relaxants might decrease the incidence of residual paralysis but does not eliminate the problem. Reversal agents such as neostigmine and edrophonium chloride will be given in conjunction with either atropine or glycopyrrolate.[23] A new reversal agent, sugammadex, is designed specifically to reverse rocuronium. The main advantage of sugammadex is reversal of neuromuscular blockade without relying on inhibition of acetylcholinesterase.[28] Marginal reversal can be more dangerous than near-total paralysis, because an agitated patient exhibiting uncoordinated movements and airway obstruction is more easily identified. A somnolent patient exhibiting mild stridor and shallow ventilation from marginal neuromuscular function might be overlooked. Insidious hypoventilation leading to respiratory acidemia or regurgitation with aspiration can occur later into recovery. Patients with coexisting neuromuscular abnormalities such as myasthenia gravis, Eaton-Lambert syndrome, or muscular dystrophies exhibit exaggerated or prolonged responses to muscle relaxants. Even without muscle relaxant administration, such patients can exhibit postoperative respiratory insufficiency from inadequate neuromuscular reserves.

Simple bedside tests help assess mechanical ability to ventilate. Forced vital capacity of 10 to 12 mL/kg and inspiratory pressure more negative than −25 cm H_2O imply that strength of ventilatory muscles is adequate to sustain ventilation. Sustained head elevation in a supine position, hand grip, and ability to bite down, swallow, and stick out the tongue are easily assessed parameters. These measures, along with tactile train-of-four and double-burst stimulation assessment, more accurately predict a patient's ability to maintain sustained ventilation.

Mental Status

Emergence Delirium

Postoperatively, emergence delirium is the alteration in neurologic functioning that causes the most concern to the practitioner. *Delirium* is defined as a condition that is characterized by extreme disturbances of arousal, attention, orientation, perception, intellectual function, and affect and is most commonly accompanied by fear and agitation.[29] There have been recent attempts to differentiate emergence delirium from agitation,[30,31] with *agitation* defined as mild restlessness and mental distress. Agitation can be due to pain, physiologic compromise, or anxiety. Delirium can be confused with agitation or be the source of agitation, and the two conditions can be very difficult to differentiate.[31] The incidence of postoperative delirium has been described to be 3% to 20%; with some procedures, the incidence may be as high as 75%. A recent study found an incidence of 4.7% in adult PACU patients.[32] Emergence delirium also appears to occur with greater incidence among combat veterans compared with the general military population of the same age.[33] The causes of postoperative delirium have been classified into four categories: withdrawal psychosis, toxic psychosis, circulatory and respiratory origin, and functional psychosis.[29]

Withdrawal psychosis is caused by withdrawal of various substances such as alcohol and illicit drugs. Alcohol withdrawal can be dangerous because it can cause delirium tremens. Clinical symptoms of delirium tremens may include hallucinations, extreme combativeness, and confusion.[29]

Amphetamine-induced delirium usually appears 1 hour after amphetamine use and disappears within 6 hours of use. Cocaine-induced delirium results from alteration of neurotransmitters. Management of withdrawal psychosis may include protection of patient safety and use of benzodiazepines or other sedatives.[29]

Toxic psychosis is caused by exposure to toxins, including toxic fumes that may occur in the OR, as from a malfunctioning laser. Adherence to the Occupational Safety and Health Administration's regulations and its mandates on monitoring help to limit the occurrence of these events.[34]

Circulatory and respiratory causes of emergence delirium most commonly include hypoxemia and hypercarbia, which may be the result of central respiratory depression, airway obstruction, or perfusion deficits. The primary cause of postoperative emergence delirium is always considered to be hypoxemia until proved otherwise. As a result, sedation of the agitated patient should never be considered until hypoxemia has been ruled out as the cause of agitation.

Functional psychosis is defined as a brief reaction of paranoia and other changes not caused by an organic abnormality. This diagnosis is made by exclusion after known organic causes have been ruled out.[34]

Although this classification is useful, other more frequently occurring causes of emergence delirium may be seen in the PACU. Confusion and agitation are common during recovery from inhalation anesthetics. Sevoflurane in particular has been associated with emergence delirium in children.[30] Many drugs used during the perioperative period have been reported to contribute to postoperative delirium. Ketamine, a phencyclidine derivative, is associated with hallucinations, delirium, and unpleasant dreams, particularly in patients between 16 and 65 years of age. Local anesthetics can cross the blood-brain barrier and may cause postoperative delirium. Nitrous oxide may cause acute mental status changes with prolonged exposure. Other anesthetic adjuncts associated with delirium include butyrophenones (e.g., droperidol), naloxone, and muscle relaxants, which can cause dissociative reactions, heightened pain perception, and hypoxemia, respectively. Delirium also has been reported as a side effect of antibiotic therapy (e.g., cefazoline, penicillin, streptomycin, chloramphenicol), antituberculosis drugs (e.g., isoniazid, cycloserine), antiviral agents (e.g., acyclovir), anticonvulsant medications (e.g., carbamazepine, phenytoin), and antiparkinsonian agents (e.g., levodopa, bromocriptine). Adverse reactions to medications that result in delirium have been reported with digitalis, antidysrhythmics (e.g., amiodarone, flecainide, lidocaine, mexiletine), β-blockers, calcium channel blockers, contrast dye, corticosteroids, chemotherapeutic agents, immunosuppressants, H_1 and H_2 blockers, antipsychotic medications, and clonidine.[33]

Premedicants, including anticholinergics, benzodiazepines, and opioids, may induce untoward reactions. Anticholinergics, specifically atropine and scopolamine, have been noted to cause central anticholinergic syndrome. These drugs cross the blood-brain barrier, altering the neurotransmitter balance and causing agitation, combativeness, and lack of cooperation. Benzodiazepines may contribute to postoperative delirium, especially in the elderly.[35] Flumazenil (Romazicon) remains the only benzodiazepine antagonist available to reverse the effects of benzodiazepine-induced delirium. Flumazenil 0.2 mg should be given over a 15-second interval with a redose after 1-2 minutes if the desired level of consciousness is not achieved. The doses may be repeated up to 1 mg with a 3 mg total to be administered within an hour. Seizures have been known to occur rarely, so the patient should continue to be observed. Opioids, particularly morphine, have been cited as a contributing factor to postoperative delirium secondary to respiratory depression and hypoxemia. In patients with renal failure, meperidine may cause excitation because of accumulation of normeperidine, a neuroexcitatory metabolic by-product. If naloxone is given to reverse the opioid, the dose should be in very small increments until the desired effect.

Metabolic disturbances associated with postoperative delirium include acidosis and alkalosis, electrolyte imbalance (e.g., magnesium, calcium, sodium), and porphyria. Treatment is directed at correction of the cause.

Other causes of postoperative delirium include pain, visceral distention (bowel and bladder), anxiety (including separation anxiety in children), hyperthermia, and hypothermia. Again, treatment is directed at correction of the cause. In a study of adult postanesthesia patients, the most common causes of emergence delirium were presence of an endotracheal tube, pain, and anxiety.[32] In children, determination of cause and treatment of delirium is complex, with pain and anxiety more easily recognized and treated than other anesthetic-related causes. Voepel-Lewis et al.[36] developed an algorithm for assessment, reassessment, and treatment decisions in children with emergence delirium.

Once hypoxemia has been eliminated as a cause of postoperative delirium, and all known causes have been evaluated, sedation may prove useful in controlling the agitation and providing for patient safety. Most events are time limited to the PACU and are resolved before discharge. Figure 50-1 summarizes the factors that contribute to postoperative delirium and treatment options.

Delayed Awakening

Delayed awakening is a common, often easily explained postoperative finding and can be defined as a clinician's expectation in a specific circumstance that the patient "should be awake by now" but is not. Although delayed awakening may slow turnover of PACU beds and delay patient discharge from the PACU, the causes and consequences of delayed awakening are rarely serious. The most common causes of delayed awakening are as follows:

- Prolonged action of anesthetic drugs
- Metabolic causes
- Neurologic injury

Prolonged action of anesthetic drugs is the most common cause of delayed awakening.[11] This may occur secondary to alterations in drug pharmacokinetics and pharmacodynamics. Pharmacokinetic alterations include changes in drug distribution secondary to mobilization of drugs from body tissue stores, redistribution, or decreased protein binding; changes in metabolism; and excretion secondary to renal or hepatic dysfunction. Pharmacodynamic alterations include increased patient sensitivity to drug effects because of extremes of age, hypothermia, or concomitant alcohol and drug use. Other patients at risk for delayed awakening are those with preexisting cognitive or psychiatric disorders, patients who chronically take sedative medications, patients who were intoxicated with alcohol or illicit drugs at the time of anesthesia, and those who were physically exhausted prior to surgery.[37]

Prolonged effects of inhalation anesthetics may be seen secondary to alterations in ventilation. Hypoventilation limits exhalation and prolongs elimination of inhalation agents.[38] Retention of

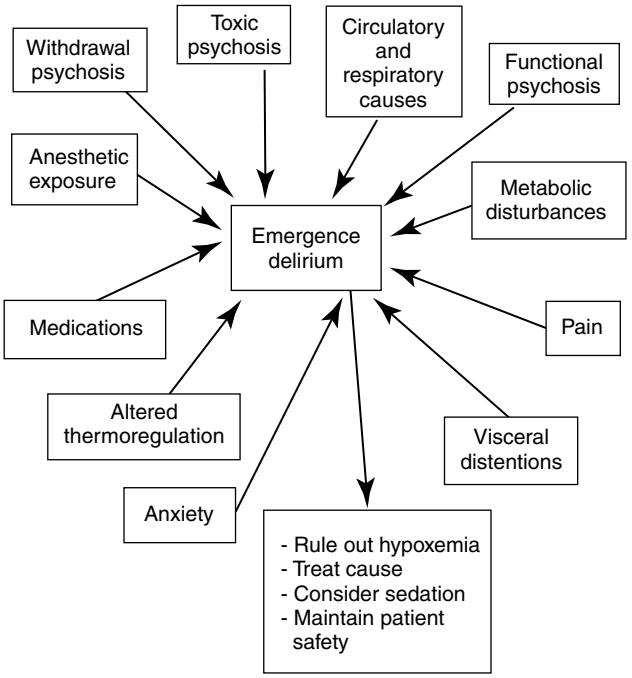

FIGURE **50-1** Emergence delirium in the postanesthesia care unit: contributing factors and treatment.

carbon dioxide contributes to narcosis, particularly in the presence of inhalation agents, and compounds the problem.

The potentiating effects of combining inhalation agents with IV anesthetics and opioids can also contribute to delayed awakening. Premedications, particularly the long-acting benzodiazepines diazepam and lorazepam, may contribute to delayed awakening, especially in the elderly.[39] Prolonged effects of inhalation and IV agents also may occur secondary to multiple drug interactions. Prolonged neuromuscular blockade may mean the patient is awake but unable to move. Some herbal supplements have the potential to cause delayed awakening, especially kava kava, St. John's wort, and valerian.[37]

Metabolic causes of delayed awakening include hypoglycemia, hyperglycemia, and electrolyte disturbances. Diabetic patients have an increased risk of postoperative hypoglycemia. Taking the usual insulin dose (or half the dose) on the morning of surgery, the patient's nothing-by-mouth (NPO) status, and the stress of surgery all contribute to the development of hypoglycemia.[39] It is important to monitor serum glucose levels intraoperatively and postoperatively. The current SCIP measure evaluates the postoperative serum glucose of cardiac surgery patients.[25] Central nervous system changes may occur as blood glucose levels fall below 50 mg/dL.[38] It is good practice to obtain a baseline blood glucose level of all diabetic patients before they are admitted to surgery. Procedures requiring general anesthesia that are longer than 2 hours will have greater glucose variations and require more frequent monitoring and treatment. Blood glucose levels of greater than 600 mg/dL can produce hyperosmolar, nonketotic, hyperglycemic coma. Approximately half of these patients have type 2 diabetes, but the syndrome can occur with severe dehydration (especially in the elderly), uremia, pancreatitis, sepsis, pneumonia, CVA, and large surface burns. Minimizing blood glucose variability during the perianesthesia period should be part of any glycemic control strategy.[39]

Electrolyte disturbances, specifically alterations in sodium, calcium, and magnesium, can prolong awakening. Dilutional hyponatremia, occurring secondary to water intoxication, may develop after transurethral prostate resection surgery, producing sedation, coma, or even hemiparesis. Hypocalcemia, seen after parathyroidectomy and occasionally thyroidectomy, may delay awakening. Hypermagnesemia, which may occur after prolonged administration of magnesium sulfate to women with eclampsia or preeclampsia, may result in sedation and muscle weakness after general or regional anesthesia for cesarean section.[39]

Neurologic injury is a rare cause of delayed awakening of the non-neurosurgical patient. Potential causes of neurologic injury include CVA, intracranial hemorrhage, increased intracranial pressure, uncontrolled extreme hypertension (especially in the anticoagulated patient), air or fat emboli, and uncontrolled hypotension (especially in patients with hypertension or occlusive carotid disease).[38]

Evaluation of the patient who fails to awaken begins with an assessment of the patient's preoperative status and a review of intraoperative events. Oxygenation and gas exchange must be assessed and verified with pulse oximetry, physical assessment, and arterial blood gas analysis. When prolonged drug effects are suspected as the cause of delayed awakening, care must be taken to ensure the adequacy of ventilation and oxygenation through appropriate patient monitoring.

Residual drug effects should be considered. If possible and not contraindicated, reversal of medications should be attempted. Flumazenil reverses benzodiazepines, and naloxone reverses the opioids.[37]

If other contributing factors are found, intervention should be initiated. Hypothermia necessitates rewarming, and electrolyte disturbances require correction. Hypoglycemia and hypocalcemia are treated with the IV administration of glucose and calcium, respectively. Hyperglycemia is treated with IV insulin to lower blood glucose levels and 0.5% normal saline to correct dehydration.

A neurologic cause of delayed awakening is usually either a diagnosis that is initially expected because of patient status or known because of intraoperative events or a diagnosis of exclusion (i.e., suspected after all other causes have been ruled out). At this point, a computed tomography (CT) scan and neurologic consultation are warranted for a more in-depth evaluation.[11,37]

Pain

Relief of surgical pain with minimal side effects is a primary goal of PACU care and a very high priority for both anesthesia provider and patient. Patients should be assessed on admission to PACU and at frequent intervals using a verbal rating scale or visual analog scale to assess for severity of pain (Figure 50-2).[9,40-42] When prioritizing pain assessment, the patient's self-report of pain is the most important measure of pain. Other measures to assess pain intensity include the patient's exposure to painful procedures; behavioral signs, such as crying or agitation; a proxy pain rating by someone who knows the patient well; and physiologic indicators, such as elevated vital signs.[42] Inadequate postoperative analgesia is a major source of preoperative fear and postoperative dissatisfaction in surgical patients. Apfelbaum et al.[41] found that approximately 80% of postoperative patients experienced acute pain, with most of the patients experiencing pain they described as moderate,

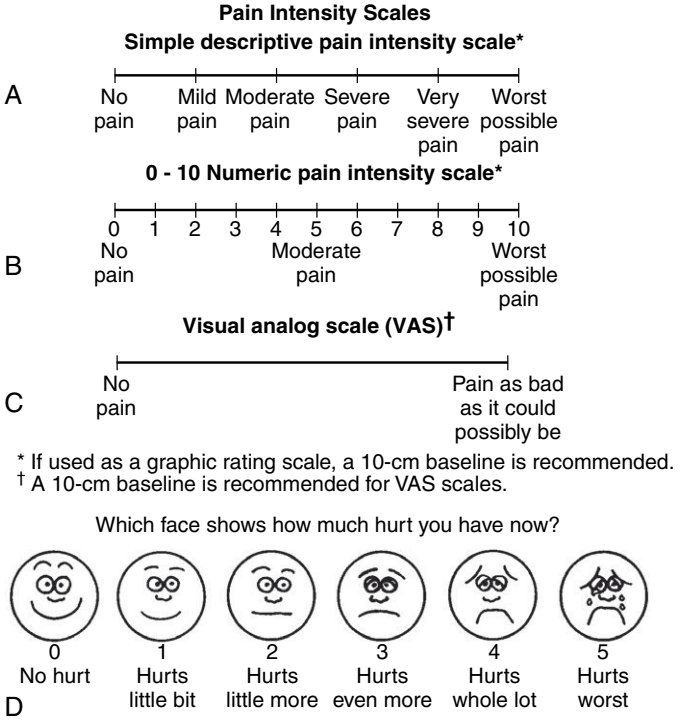

FIGURE **50-2** Pain intensity scales. (**A-C** from Acute Pain Management Guideline Panel. *Acute Pain Management in Adults: Operative Procedures: Quick Reference Guide for Clinicians* [AHCPR Publication No. 92-0019]. Rockville, Md: Agency for Health Care Policy and Research; 1992; **D** from Hockenberry MJ, Wilson D. *Wong's Essentials of Pediatric Nursing*. 8th ed. St. Louis: Mosby; 2009. Used with permission.)

severe, or extreme. In addition to improving patient comfort, relief of pain reduces SNS response and helps avoid hypertension, tachycardia, and dysrhythmias (Table 50-1).

New research is underway to determine other predictors of severe postoperative pain. Yang et al.[42] looked for predictors of acute postoperative pain in 236 female patients. A multiple logistic regression determined that severe postoperative pain occurred significantly more often in patients with the CYP2D6 poor metabolizer (PM) genotype and smokers.

Incisional pain may be effectively treated with careful titration of IV opioids with frequent cardiorespiratory assessments. Short-acting IV opioids are useful to expedite discharge and minimize nausea in ambulatory settings. Ketorolac or IV acetaminophen are effective analgesics with antiinflammatory characteristics that lower opioid requirements.[40]

Other analgesic modalities provide effective pain relief beyond the PACU. IV opioid loading in the PACU is important for smooth transition to patient-controlled analgesia. Injection of opioids into the epidural or subarachnoid space during anesthesia or in the PACU often yields prolonged postoperative analgesia.[40] Epidural opioid analgesia is effective after thoracic and upper abdominal procedures and helps wean patients with obesity or chronic obstructive pulmonary disease from mechanical ventilation. Epidural analgesia also may improve surgical outcomes after orthopedic and urologic procedures. With epidural or intrathecal opioid administration, immediate and delayed ventilatory depression can occur, along with other side effects such as nausea and pruritus.

Patient-controlled analgesia (PCA) allows patients to administer their own pain medication. The most commonly used methods of PCA are intravenous or epidural. Patient therapy should be initiated in the PACU after the patient's initial pain level is under control. Oral opioids are used often with outpatients and have been studied in appropriate orthopedic patients with success. One device called the MOD (Medication on Demand) allows patients to access oral analgesics at the bedside. Medications already in use, such as fentanyl and sufentanil, are currently undergoing development for new drug delivery systems that include intranasal, dry powder inhalation, nebulization, transmucosal, sublingual, and buccal sprays.[43] The newest nonopioid available in intravenous format is acetaminophen (Ofirmev). The onset of analgesia occurs within 5 to 10 minutes of IV administration, with the peak analgesic effect occurring within 1 hour and duration of 4 to 6 hours.[44] Availability of acetaminophen in the postoperative patient adds an effective nonopioid as an option when developing a multimodal plan of pain management.

Placement of long-acting regional analgesic blocks reduces pain, controls SNS activity, and often improves ventilation. For example, interscalene block yields almost complete pain relief from shoulder or upper extremity procedures, with only moderate inconvenience from motor impairment. Paralysis of the ipsilateral diaphragm can impair postoperative ventilation in patients with marginal respiratory reserve. Caudal analgesia is effective in children after inguinal or genital procedures, whereas infiltration of local anesthetic into joints, soft tissues, or incisions decreases the intensity of pain. Other uses of local anesthesia include continuous wound infusion, in which the catheter is inserted at the end of the case by the surgeon, and perineural infusions, in which the anesthesia provider inserts the catheter near the affected peripheral nerves or a nerve plexus.[45] Deposition of long-acting liposomal formulations of bupivicaine (Exparel) to the surgical site can provide pain relief post discharge.

Opioid treatment for postoperative or chronic pain is frequently associated with adverse effects, the most common being dose-limiting and debilitating bowel dysfunction. Postoperative ileus, although attributable to surgical procedures, is often exacerbated by opioid use during and after surgery. Postoperative ileus is marked by increased inhibitory neural input, heightened inflammatory responses, decreased propulsive movements, and increased fluid absorption in the gastrointestinal tract. The current management of opioid-induced bowel dysfunction among patients receiving opioid analgesics consists primarily of nonspecific ameliorative measures. Clinical studies with the agent alvimopan suggest that it may normalize bowel function without blocking systemic opioid analgesia in abdominal laparotomy patients with opioid-related postoperative ileus.[46]

Nonpharmacologic interventions may include positioning for comfort, verbal reassurance, touch, applications of heat or cold, massage, transcutaneous electrical nerve stimulation, relaxation techniques, imagery, biofeedback-controlled breathing, and use of the patient's support system (e.g., parent or significant other),

TABLE 50-1 Harmful Effects of Unrelieved Pain

Domains Affected	Specific Responses to Pain
Endocrine	↑ ACTH, ↑ cortisol, ↑ ADH, ↑ epinephrine, ↑ norepinephrine, ↑ GH, ↑ catecholamines, ↑ renin, ↑ angiotensin II, ↑ aldosterone, ↑ glucagon, ↑ interleukin-1, ↓ insulin, ↓ testosterone
Metabolic	Gluconeogenesis, hepatic glycogenolysis, hyperglycemia, glucose intolerance, insulin resistance, muscle protein catabolism, ↑ lipolysis
Cardiovascular	↑ Heart rate, ↑ cardiac workload, ↑ peripheral vascular resistance, ↑ systemic vascular resistance, hypertension, ↑ coronary vascular resistance, ↑ myocardial oxygen consumption, hypercoagulation, deep vein thrombosis
Respiratory	↓ Flows and volumes, atelectasis, shunting, hypoxemia, ↓ cough, sputum retention, infection
Genitourinary	↓ Urinary output, urinary retention, fluid overload, hypokalemia
Gastrointestinal	↓ Gastric and bowel motility
Musculoskeletal	Muscle spasm, impaired muscle function, fatigue, immobility
Cognitive	Reduction in cognitive function, mental confusion
Immune	Depression of immune response
Developmental	↑ Behavioral and physiologic responses to pain, altered temperaments, higher somatization, infant distress behavior, possible altered development of the pain system, ↑ vulnerability to stress disorders, addictive behavior, and anxiety states
Future pain	Debilitating chronic pain syndromes: postmastectomy pain, postthoracotomy pain, phantom pain, postherpetic neuralgia
Quality of life	Sleeplessness, anxiety, fear, hopelessness, ↑ thoughts of suicide

From Pasero C, McCaffery M. *Pain Assessment and Pharmacologic Management*. St. Louis: Mosby; 2011. Copyright Pasero C, McCaffery M. Used with permission.

ACTH, Adrenocorticotrophic hormone; *ADH*, antidiuretic hormone; *down arrow (↓)*, decreased; *GH*, growth hormone; *up arrow (↑)*, increased.

particularly in children. Nonpharmacologic interventions should supplement and not replace pharmacologic therapy.[9]

Most of the current guidelines for pain management are very general and do not offer specific guidelines associated with different types of surgery.[47] The newest outlook for evidence-based guidelines in the field of pain management are procedure-specific guidelines offered via a web-based program called "PROSPECT" (Procedure-Specific Postoperative Pain Management).[48,49] An international panel of surgeons and anesthesiologists reviews procedure-specific pain research and grades the evidence.[48] Then clinical practice guidelines and recommendations are developed after consensus by the working group (Figure 50-3). The PROSPECT website offers procedure-specific guidelines for managing pain associated with abdominal hysterectomy, herniorrhaphy, open colon resection, laparoscopic cholecystectomy, thoracotomy, total hip arthroplasty, and total knee arthroplasty.[49]

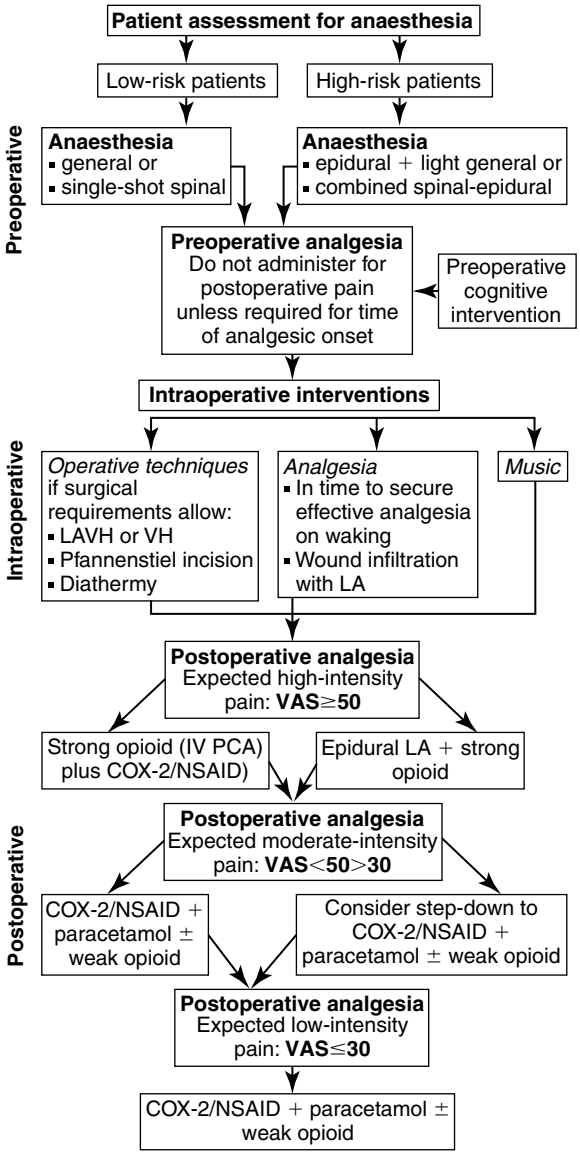

FIGURE **50-3** Algorithm for the management of postoperative pain. *VAS*, Visual analog scale; *LAVH*, laparoscopic-assisted vaginal hysterectomy; *VH*, vaginal hysterectomy; *LA*, local anesthetic; *PCA*, patient-controlled analgesia; COX *2*, cyclooxygenase 2; *NSAID*, non-steroidal antiinflammatory drug; *paracetamol*, acetaminophen (From PROSPECT. Procedure-Specific Postoperative Pain Management website: http://www.postoppain.org.)

Hypothermia

Hypothermia is a condition marked by an abnormally low internal body temperature (below 36° C), that occurs when systemic heat loss exceeds heat production.[50] Many patients are admitted into the PACU with hypothermia, which can prolong recovery, compromise physiologic stability, and contribute to postoperative morbidity. The patient's interaction with the environment determines the degree of heat loss. Heat loss may occur via radiation, convection, conduction, or evaporation.

Radiant heat loss involves the loss of heat from a warm or hot surface (the body) to a cooler one (the environment). It does not require that the two surfaces be in direct contact with each other. Radiant heat loss accounts for 40% to 60% of heat loss to the environment. It is especially profound in the elderly, debilitated, and neonatal populations.[51,52]

Convective heat loss depends on the existence of a temperature gradient between the body and the ambient air. This type of heat loss may occur in the OR, particularly in laminar flow rooms, and accounts for 25% to 50% of heat loss.[31,52]

Conductive heat loss involves loss of heat from a warm surface that comes into contact with a cooler one; it accounts for as much as 10% of heat loss in the OR, where patients lose heat to cooler OR tables, sheets, drapes, skin preparation fluids, and IV fluids or irrigants.[51,52]

Evaporative heat loss involves transfer of heat during the change from a liquid to a gas. Evaporative heat loss occurs via perspiration, respiration, or exposed viscera during surgery. Evaporation accounts for as much as 25% of heat loss in the OR.[51,52]

Patients at high risk for the development of hypothermia can be identified. Elderly patients are at risk because of their decreased subcutaneous fat and alterations in their hypothalamic function. Neonates are at risk because of their immature thermoregulatory center and their high surface-to-volume ratio. Intoxicated individuals are at risk because of vasodilation and depression of their heat regulatory center. Patients taking vasodilators, nonsteroidal antiinflammatory agents, and phenothiazines have alterations in thermoregulation that are caused by either vasodilation or suppression of the thermoregulatory center.[53] Other risk factors are female gender, decreased ambient room temperature, length and type of surgery, preexisting conditions such as peripheral vascular disease or burns, use of cold irrigants, and use of general or regional anesthesia.[50,51,53,54]

General anesthetics depress the thermoregulatory center, with a usual temperature drop of 1° to 3° C. General anesthesia reduces the vasoconstriction threshold; general anesthesia and regional anesthesia both cause peripheral vasodilation, which results in a core-to-peripheral redistribution of heat.[55] Opioids and muscle relaxants depress voluntary shivering as a mechanism for the generation of heat. Any patient in whom a body cavity is entered may lose heat via convection and evaporation. Irrigation solutions used in genitourinary procedures or with cardioplegia in cardiac surgery cause internal cooling.[56]

Physiologically, hypothermia results in decreased oxygen availability by shifting of the oxyhemoglobin dissociation curve to the left. Shivering may increase oxygen demand by 400% to 500%. Metabolically dependent processes slow, thereby decreasing drug biotransformation. Renal transport processes are slowed, thereby decreasing glomerular filtration. Cardiac rate and rhythm disturbances, including bradydysrhythmias and premature ventricular contractions, may occur. Central nervous system depression may

be profound.[57] Other adverse effects of perioperative hypothermia include patient discomfort, increased adrenergic stimulation, coagulopathy, impaired wound healing, surgical site infection, and increased hospital costs.[50,51,54,58,59]

Treatment of hypothermia should ideally be focused on prevention. Assessment of the patient's need for prewarming begins preoperatively, and active warming measures can be instituted for hypothermic patients.[9,50,60] As a result of positioning, operating time, and anesthetic exposure, therapeutic intervention most often begins in the PACU. Every patient in the PACU should be assessed for hypothermia and care provided as suggested in the multidisciplinary American Society of PeriAnesthesia Nurses (ASPAN) evidence-based clinical practice guideline for the promotion of perioperative normothermia (Figure 50-4).[50] Passive rewarming is designed to maximize basal heat production. Active rewarming consists of the use of external rewarming techniques and may include the use of heated blankets, heated water blankets, and radiant warmers. In a systematic review, Moola and Lockwood[60] determined that single strategies such as forced-air warming were more effective than passive warming; however, combined strategies, including using prewarming preoperatively, use of warmed fluids plus forced-air warming as other active

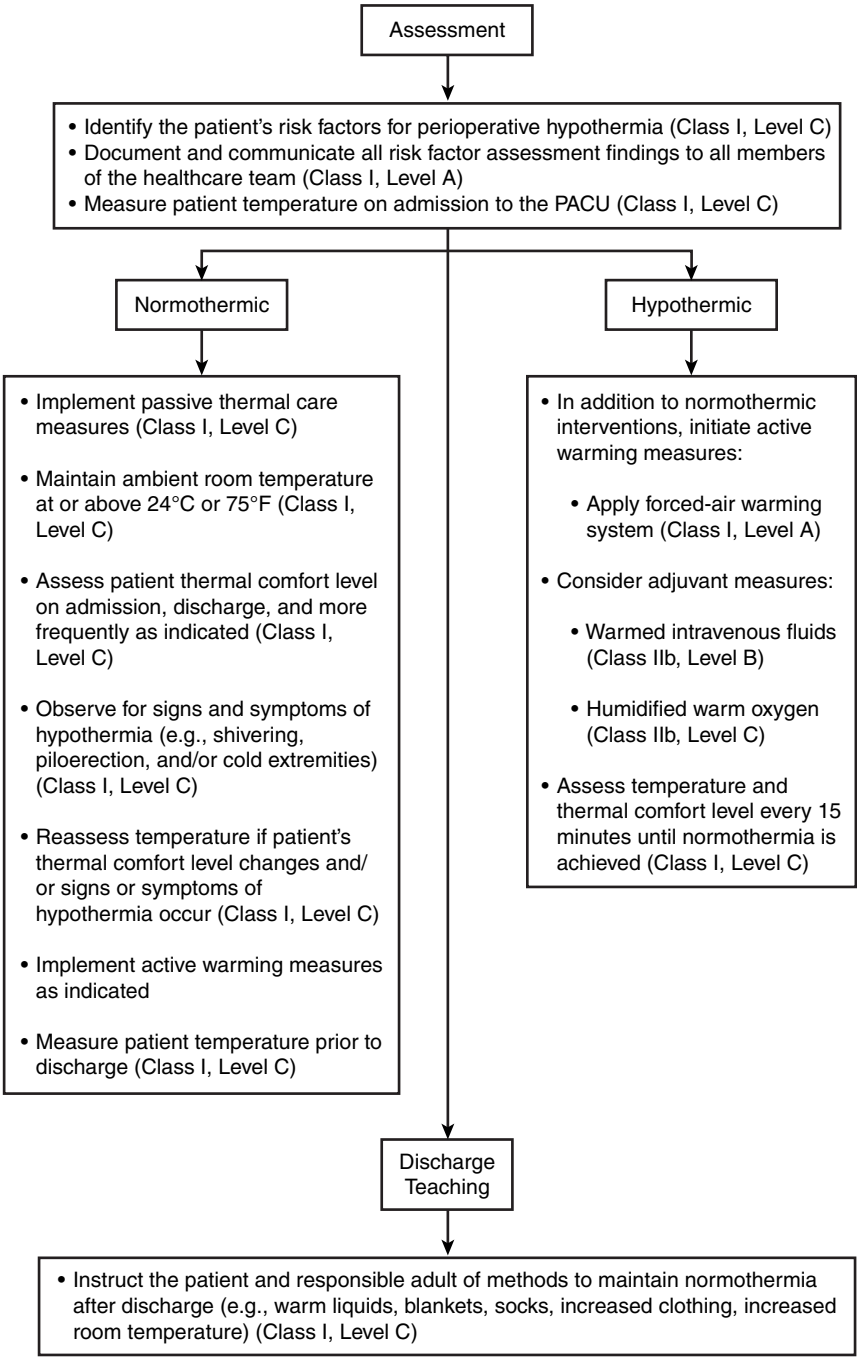

FIGURE **50-4** Preoperative, intraoperative, and postoperative patient management recommendations for promotion of normothermia. *PACU,* Postanesthesia care unit. (From Hooper et al. ASPAN's evidence-based clinical practice guideline for the promotion of perioperative normothermia. 2nd ed. *J Perianesth Nurs*. 2010;25:346-365.)

strategies were more effective in vulnerable groups. Forced-air rewarming systems are the most effective method for treating hypothermia.[5]

Postoperative shivering consists of muscular tremor and rigidity. It is often associated with body heat loss, although hypothermia alone does not fully explain the occurrence of shivering. Shivering is self-limiting, never becomes chronic, and is rarely associated with major morbidity. However, it affects the comfort of patients and may sometimes lead to more serious complications.[61] Treatment is rewarming. However, when clinically indicated, small doses of meperidine, ketamine, dexmedetomidine, hydrocortisone, granisetron, and ondansetron can be effective in the treatment of shivering during emergence and recovery.[62]

Nausea and Vomiting

In 1914 the first journal devoted solely to the topic of anesthesia featured an original article titled "Prophylaxis of Postanesthetic Vomiting."[63] More than 90 years later, postanesthetic vomiting is still one of the major problems faced in the PACU. Postoperative nausea and vomiting (PONV) affects 20% to 30% of all surgical patients, and the chance for PONV can be as high as 70% to 80% for high-risk patients.[64] Post-discharge nausea and vomiting (PDNV) is now being considered as an equally troublesome and all-too-frequent patient complication. The incidence of vomiting is lower than nausea.[65-67] Risk factors can be divided into three categories: patient specific, anesthetic related, and surgery related. Risk factors for PONV are listed in Box 50-9.[68]

The patient-specific risk factors listed in Box 50-9 are independent predictors for PONV. Females experience PONV two to three times more often than males, although these differences do not show up until after puberty. Being a nonsmoker and having a history of motion sickness or PONV are also independent predictors of PONV. Other associated factors are migraines, better health status as defined by the ASA risk classification, and anxiety. Children ages 11 to 14 experience an increased incidence of PONV. The highest rate occurs in young adults but decreases in older adults.[64,68-70]

BOX 50-9

Primary Risk Factors Associated with Postoperative Nausea and Vomiting

Patient Specific
- Female gender
- Age less than 50 years old
- Nonsmoker
- History of PONV
- History of motion sickness

Anesthetic Related
- Use of volatile anesthetics
- Use of nitrous oxide
- Intraoperative and postoperative use of higher doses of opioids

Surgery Related
- Duration of surgery more than 1 hour
- Type of surgery, especially laparoscopy

Data from Murphy MJ, et al. Identification of risk factors for postoperative nausea and vomiting in the perianesthesia patient. *J Perianesth Nurs*. 2006;21:377-384; Gan TJ, et al. Society for Ambulatory Anesthesia guidelines for the management of postoperative nausea and vomiting. *Anesth Analg*. 2007;105:1615-1628; Apfel CC, et al. Who is at risk for postdischarge nausea and vomiting after ambulatory surgery? *Anesthesiology*. 2012;117(3):475-486.
PONV, Postoperative nausea and vomiting.

The choice of anesthetic agent may influence the incidence of PONV. Early vomiting in the PACU is commonly the result of anesthetic agents.[71] PONV occurs more often with inhalation anesthetics than with total intravenous anesthesia (TIVA) techniques, and the risk of PONV decreases significantly after regional anesthesia. The use of nitrous oxide has been associated with PONV, but its relationship may not be as important as originally thought.[68] Desflurane, isoflurane, and sevoflurane have not shown significant differences in the incidence of nausea and vomiting after their use. Propofol, used as an induction agent and IV anesthetic, is associated with a lower incidence of postoperative nausea and vomiting, whereas etomidate and ketamine may increase this adverse effect.[72] Propofol does not appear to reduce the incidence of PDNV possibly due to the short half-life.[67] Postoperative use of opioids is strongly correlated with PONV, although the effect of low doses of intraoperative opioids is less well defined.[68]

The duration of surgery contributes to the incidence of PONV. Longer procedures are associated with a longer exposure to inhalation agents and possibly a larger dose of opioids during the surgery. The type of surgical procedure also has been cited as a contributing factor in PONV, although the evidence is conflicting about site and types of surgeries.[68,70] In children, strabismus and orchiopexy surgery are associated with a higher incidence of PONV. Patients undergoing tonsillectomy and adenoidectomy have a high incidence of nausea and vomiting as a result of swallowed blood.[73] In adults, an increased incidence of nausea and vomiting has been noted in patients undergoing laparoscopy procedures, especially cholecystectomy, breast surgery, gynecologic surgery, intracranial/neurosurgery, and otologic and ophthalmic procedures.[15,68,70]

Simplified risk-assessment instruments are available that identify patients' risk for PONV. One tool in widespread use is Apfel's risk assessment tool.[64] The patient is scored based on four risk factors: gender, smoking status, history of PONV or motion sickness, and postoperative use of opioids. A patient's risk increases with the number of risk factors present. An assessment of risk factors should be done preoperatively and the management of patients at risk guided by the number of risk factors and chance of PONV. The expected incidence of PONV and PDNV based on the number of risk factors is noted in Table 50-2.

The Society for Ambulatory Anesthesia and ASPAN offer clinical practice guidelines and recommendations for antiemetic prophylaxis and treatment of PONV and PDNV.[69,70]

Management of nausea and vomiting should originate from a prophylactic rather than a therapeutic approach, particularly in patients identified as at risk. The patient who experiences PONV may begin with nausea, a subjective feeling of discomfort or need to vomit.[68] Nausea can be rated on a verbal descriptor scale or numeric rating scale to determine its severity. Every individual clinician and anesthesia department has developed techniques to address these issues. Commonly, antiemetic prophylaxis will be given to patients at risk. The number and variety of agents administered will be increased according to the number of risk factors present. This is referred to as a multimodal approach. Smaller doses of drugs with differing mechanisms are chosen to allow for a broader array of potential coverage.[74] If a patient experiences PONV and has already received an antiemetic, a rescue drug or drugs with a different mechanism are chosen.[69,70,75,76] Other rescue interventions should be implemented, including verification of adequate hydration, since supplemental IV crystalloids are

associated with a lower incidence of several PONV outcomes.[77] Appropriate nonpharmacologic therapy, such as aromatherapy, may be instituted.[69]

Drugs that block the serotonin receptors (5-HT_3) are ondansetron, dolasetron, granisetron, and palonosetron. Droperidol blocks the dopamine (D_2) receptor sites (although the Food and Drug Administration [FDA] black box warning about QT prolongation and required ECG monitoring must be kept in mind). Other D_2-blocking agents are prochlorperazine or metoclopramide. For histamine receptors, promethazine or diphenhydramine can be used. Glycopyrrolate or scopolamine patches may be used for the muscarinic receptors. Dexamethasone is often given in conjunction with a 5-HT_3 blocking agent or droperidol. Substance P is another neurotransmitter that belongs to the neurokinin family of neurotransmitters. Substance P has affinity for neurokinin 1 (NK-1) receptors. The only neurokinin antagonist at the present time is aprepitant, which can be given orally as a prophylactic agent.[15,76]

Side effects (e.g., agitation, restlessness, drowsiness) may be associated with the use of some antiemetics. Prophylaxis using a combination of antiemetic drugs has been suggested as an effective strategy for minimizing postoperative nausea and vomiting.[70,76,78] Ephedrine also has been used for maintaining systemic blood pressure, thereby minimizing cerebral ischemia and preventing postoperative nausea and vomiting.[70] The FDA warning for droperidol is intended to increase awareness of the potential for cardiac dysrhythmias during drug administration and to encourage consideration of alternative medications for patients at high risk for cardiac dysrhythmias.[79] Droperidol currently carries a warning about cases of sudden death at high doses (greater than 25 mg) in patients at risk for cardiac dysrhythmias. Recent research has shown QT prolongation (i.e., delayed recharging of the heart between beats) within minutes after injection of a dose of droperidol at the upper end of the labeled dose range. Prolonged QT is dangerous as it may result in a fatal heart arrhythmia known as *torsades de pointes*. Historically the typical dose of droperidol given to adults with symptoms of postoperative nausea and vomiting is in the range of 0.625 to 2.5 mg IV.[80]

Nonpharmacologic interventions also may be appropriate for the patient with PONV in addition to pharmacologic interventions.[15,69,70,81] Acupuncture, transcutaneous electrical nerve stimulation, acupoint stimulation, and acupressure have been shown to be effective in reducing the incidence of PONV and need for rescue medication. P6 stimulation has been shown to be effective, as well as Korean hand acupoints.[69,70,82] Aromatherapy (e.g., isopropyl alcohol or peppermint oil) has been used to treat PONV.[15,81,82] There are limited studies to date, but some show improvement in PONV. Aromatherapy was identified by the ASPAN guideline as an option with limited evidence but little risk to the patient.[69] Some commonly used antiemetics for PONV and PDNV are listed in Table 50-3. The physiologic and pharmacologic effects of drugs, and the brain and peripheral sites that influence vomiting are shown in Figure 12-3.

TABLE 50-2 Incidence of PONV and PDNV Based on the Number of Risk Factors

Number of PONV Risk Factors	Incidence %
1	10-20
2	40
3	60
4 or more	80

PONV risk factors include: female gender, age younger than 50 years, history of motion sickness and/or PONV, nonsmoking, and the use of postoperative opioids.

Number of PDNV Risk Factors	Incidence %
0	10
1	20
2	30
3	50
4	60
5	80

PDNV risk factors include: female gender, history of motion sickness and/or PONV, age less than 50 years, the use of postoperative opioids, and PONV in the PACU.
PONV, Postoperative nausea and vomiting; *PDNV,* postdischarge nausea and vomiting; *PACU,* postanesthesia care unit.
Data from Murphy MJ, et al. Identification of risk factors for postoperative nausea and vomiting in the perianesthesia patient. *J Perianesth Nurs*. 2006;21:377-384; Gan TJ, et al. Society for Ambulatory Anesthesia guidelines for the management of postoperative nausea and vomiting. *Anesth Analg*. 2007;105:1615-1628; Apfel CC, et al. Who is at risk for postdischarge nausea and vomiting after ambulatory surgery? *Anesthesiology*. 2012;117(3):475-486.

Fluids

The goal of fluid management during the perioperative period is to maintain adequate intravascular fluid volume, left ventricular filling pressure, cardiac output, systemic blood pressure, and oxygen delivery to tissues. Appropriate concentrations of body fluid and electrolytes in the perioperative patient is essential to normal physiologic function of all body systems.[83] According to the ASA practice guidelines,[5] routine perioperative assessment of patients' hydration status and fluid management reduces adverse outcomes and improves patient comfort and satisfaction. On the patient's admission to the PACU, intravascular volume is estimated, with consideration given to preoperative status, type and duration of surgery, estimated blood loss, fluid replacement, and hemostasis. Monitoring urine output as an index of intravascular volume can be misleading. Surgery and anesthesia impair renal tubular concentrating ability, and glycosuria causes osmotic diuresis, each falsely indicating that intravascular volume is adequate. Central venous pressure, pulmonary arterial pressure, or transesophageal ultrasound monitoring can help clarify volume status. Symptoms such as poor skin perfusion, for example, cool, pale, and clammy skin, particularly in the feet; oliguria; hypotension; tachycardia; and tachypnea can indicate hypovolemia.[83]

A reduction in circulating intravascular volume decreases ventricular filling and cardiac output. SNS-mediated tachycardia, increased SVR, and venoconstriction might compensate for a 15% to 20% loss of intravascular volume. Greater deficits can cause hypotension. Failure to replace preoperative fluid deficit and fluid or blood lost during surgery frequently causes hypovolemia. In the PACU, ongoing hemorrhage, sweating, and exudation of fluid into tissues (i.e., third-space losses) exacerbate hypovolemia. Blood loss is often occult, as with retroperitoneal bleeding, diffuse oozing related to coagulopathy, or hemorrhage into muscle after trauma or orthopedic procedures. Third-space losses can continue for up to 48 hours after surgery and can be massive during high-permeability pulmonary edema or accumulation of ascites. In a hypothermic, venoconstricted patient, a low intravascular volume might maintain cardiac output on PACU admission but cause hypotension when venous capacity increases during rewarming.[50]

Urinary Output and Voiding

Monitoring kidney function during recovery reduces morbidity in patients with marginal cardiovascular or renal status. The ability to void after spinal or epidural anesthesia should be assessed, because autonomic effects of regional anesthetics or opioids interfere with sphincter relaxation and promote urine retention.[84-86] Urinary retention is common after urologic, inguinal, and genital surgery and frequently delays discharge. It is reasonable to discharge inpatients to a surgical floor and selected ambulatory surgical patients from the facility before they void.[5] However, it is important to ensure that urine output is monitored after discharge from the PACU to avoid urinary retention. A predictor of postoperative urinary retention (POUR) was the presence of greater than 500 mL of urine in the bladder immediately after spinal anesthesia.[84] The amount of urine retained in the bladder can be assessed with use of a bladder scanner.[85] A decision can be made at that time if it is appropriate to do an in-and-out catheterization to drain the urine. The incidence of POUR can contribute to an extra 26 minutes in the length of stay in the PACU. This longer length of stay was not statistically significant, but the authors deemed it clinically significant.[84] It is prudent to give ambulatory patients who are discharged without voiding a specific time interval in which to void (e.g., 6 to 8 hours after discharge). If retention persists, the patient should be instructed to contact a healthcare facility. Patients with indwelling catheters should have urinary output recorded hourly. The Joint Commission added SCIP-9 measure as a required indicator in 2011. That measure requires that the urinary catheter is removed on postoperative day 1 (POD 1) or postoperative day 2 (POD 2) with day of surgery being day zero.[86]

Urine color is not useful for assessment of renal tubular function such as concentrating ability, but color can signal hematuria, hemoglobinuria, or pyuria. Urine osmolarity is a more reliable index of tubular function than specific gravity, which is affected by molecular weight.

Oliguria (less than 0.5 mL/kg/hr) occurs frequently during recovery and usually reflects an appropriate renal response to hypovolemia or systemic hypotension. However, a decreased urine output might indicate abnormal renal function. The acceptable degree and duration of oliguria vary with underlying renal status, the surgical procedure, and the anticipated postoperative course. If events related to the surgical procedure could jeopardize renal function (e.g., aortic cross-clamping, severe hypotension, massive transfusion), oliguria must be aggressively evaluated. In patients without catheters, bladder volume and interval since last voiding should be checked to help differentiate between oliguria and inability to void. Urinary catheters should be checked for kinking and obstruction by blood clots or debris. Patient position might also place the catheter tip above the urinary level in the bladder.[85]

Polyuria, a state of profuse urine output, usually reflects generous intraoperative fluid administration. Osmotic diuresis caused by hyperglycemia and glycosuria is another cause, particularly if glucose-containing crystalloid solutions have been infused. Polyuria might also reflect intraoperative diuretic administration. Sustained polyuria (4 to 5 mL/kg/hr) can indicate abnormal regulation of water clearance, especially if urinary losses compromise intravascular volume and systemic blood pressure. Polyuria related to diabetes insipidus occurs secondarily to intracranial surgery, pituitary ablation, head trauma, increased intracranial pressure, and inadvertent omission of preoperative vasopressin. The diagnosis is made by comparing urine and serum electrolytes and osmolarity. High-output renal failure also should be considered as a cause.[16]

TABLE 50-3 Antiemetic Drugs for Postoperative and Postdischarge Nausea and Vomiting

Drug	Usual Adult Dose	Comment
5-HT$_3$ Antagonists		
Ondansetron (Zofran)	4-8 mg IV	Effective for prevention of both nausea and vomiting; more effective for PONV than PDNV
Granisetron (Kytril)	1 mg IV or transdermal patch	Patch may be effective for PDNV
Dolasetron (Anzemet)	12.5 mg IV	Used for PONV
Palonosetron (Aloxi)	0.075 mg IV	Long duration may make it effective for PDNV
Dopamine Antagonists		
Droperidol (Inapsine)	0.625-1.25 mg IV	See text for discussion of black box warning
Metoclopramide (Reglan)	10-20 mg IV	Contraindicated in patients with gastric obstruction due to prokinetic effects
Prochloperazine (Compazine)	10 mg IV	Sedation prominent
Antihistamines		
Hydroxazine (Atarax)	12.5-25 mg IV	Sedation prominent
Promethazine (Phenergan)	12.5-25 mg IV	Sedation prominent
Diphenhydramine (Benadryl)	25 mg IV or IM	Sedation prominent
Glucocorticoid		
Dexamethasone (Decadron)	4-8 mg IV	More effective for PDNV than PONV
Anticholinergic		
Scopolamine Transdermal (Transderm-Scop)	2.5 cm^2 patch contains 1.5 mg scopolamine	Long duration may make it effective for PDNV
Neurokinin Antagonist		
Aprepitent (Emend)	40 mg PO	Long duration may make it effective for PDNV

IV, Intravenous; *IM*, intramuscular; *PO*, oral; *PONV*, postoperative nausea and vomiting; *PDNV*, postdischarge nausea and vomiting; *5-HT$_3$*, serotonin.

DISCHARGE FROM THE POSTANESTHESIA CARE UNIT

The patient leaving the PACU may be discharged to home, an ambulatory surgical unit, a surgical inpatient unit, or an intensive care unit. The choice of a discharge facility should depend on the patient's need and physical status and the availability of appropriate resources.

When possible, before discharge, each patient should be sufficiently oriented to assess his or her physical condition and be able to summon assistance. Airway reflexes and motor function must be adequate to prevent aspiration. Ventilation and oxygenation should be acceptable and demonstrate sufficient reserve to safely cover minor deterioration in unmonitored settings. To detect hypoxemia, oxygen saturation should be monitored for an appropriate period of time after discontinuation of supplemental oxygen. Before discharge, patients should be observed for a period of time after the last IV opioid or sedative is administered to assess peak effects, as well as side effects. Hemodynamic measurement and indexes of peripheral perfusion should be relatively constant. Achievement of normal body temperature (greater than 96.8° F) should occur before discharge home or to a medical floor; the intensive care unit (ICU) staff can continue an active warming process. Resolution of shivering is important. Acceptable analgesia must be achieved and vomiting appropriately controlled. Likely surgical complications must be determined (e.g., bleeding, vascular compromise, pneumothorax, complications of coexisting diseases such as coronary artery disease, diabetes, hypertension, or asthma). The results of postoperative diagnostic tests should be reviewed. The routine requirement for urination before discharge should not be part of a discharge protocol and may be necessary only for selected day-surgery patients. Likewise, the requirement of drinking clear fluids should not be a part of a discharge protocol and may be necessary only for selected patients (e.g., diabetic patients) and determined on a case-by-case basis.[5]

Outcome indicators applied to discharge criteria should be written with a patient focus—for example—"Before discharge, the patient will maintain vital signs within the preoperative range." Examples of discharge criteria are found in Box 50-10. The patient's ability to meet these criteria constitutes clearance for discharge from the PACU but does not imply readiness for discharge to home. Two clinicians, Aldrete[87] and Chung et al.,[88] have piloted scoring systems designed to evaluate the patients for outpatient discharge.

The Aldrete modified postanesthesia recovery (PAR) score is a modification of the original Aldrete score for PAR (Table 50-4). This modification of the scoring system changed assessment of "color" to assessment of "oxygen saturation." This scoring system is for use when patients are discharged from PACU phase I. A further modification of the Aldrete scoring system for outpatients' street fitness is given in Table 50-5.

BOX 50-10

Postanesthesia Care Unit Discharge Criteria

- Regular respiratory pattern
- Respiratory rate appropriate for age
- Absence of restlessness and confusion
- Vital signs within preoperative range
- Pulse oximetry indicates 95% saturation* or value equal to preoperative saturation
- Arterial blood gas values within normal limits†
- Ability to maintain patent airway
- Surgical stability of operative site or system

*Unit policies may dictate another number needed for oxygen saturation on discharge. There is no known accepted saturation level for discharge; most units require at least 92%.
†Not routinely obtained before discharge.

TABLE 50-4 Aldrete Postanesthesia Scoring System

			Admit	15 min	30 min	45 min	60 min
Activity	Able to move voluntarily on command	Four extremities	2	2	2	2	2
		Two extremities	1	1	1	1	1
		No extremities	0	0	0	0	0
Respiration	Able to breathe deeply, cough freely		2	2	2	2	2
	Dyspnea or limited breathing		1	1	1	1	1
	Apnea		0	0	0	0	0
Circulation	BP ± 20 mmHg of preanesthesia level		2	2	2	2	2
	BP ± 20-50 mmHg of preanesthesia level		1	1	1	1	1
	BP ± 50 mmHg of preanesthesia level		0	0	0	0	0
Consciousness	Fully awake		2	2	2	2	2
	Arousable on calling		1	1	1	1	1
	Not responding		0	0	0	0	0
O_2 Saturation	Able to maintain O_2 saturation greater than 90% on room air		2	2	2	2	2
	Needs O_2 inhalation to maintain O_2 saturation greater than 90%		1	1	1	1	1
	O_2 saturation less than 90% even with O_2 supplementation		0	0	0	0	0

From Marshall S, Chung F. Assessment of 'home readiness' discharge criteria and post-discharge complications. *Curr Opin Anesthesiol.* 1997; 10:445-480.
BP, Blood pressure; O_2, oxygen.

Chung et al.[88] developed the Postanesthesia Discharge Scoring system as a simple, objective tool to assess the readiness of patients to be discharged to home (Box 50-11). A score of 9 is needed for the patient to be discharged. Although studied retrospectively, the scoring system has yet to be tried as a predictive index in a widespread clinical trial. Regardless of the method used to assess readiness for discharge, the assessment should be documented in an objective manner using criteria agreed upon by the departments of anesthesia, nursing, and surgery.

Fixed PACU discharge criteria must be used with caution, because variability among patients is tremendous. Scoring systems that quantify physical status or establish thresholds for vital signs are useful for assessment but cannot replace individual evaluation.

Fast-tracking outpatients after general anesthesia has assumed increased importance in ambulatory anesthesia because of the cost-savings potential when patients are transferred directly from the OR to the less labor-intensive phase II recovery area. Given the inherent risks of complications associated with bypassing the PACU, effective and reliable fast-track criteria that allow anesthesia providers to rapidly assess a patient's postoperative alertness, physiologic stability, and comfort level immediately before transferring the patient from the OR are clearly needed.[89] An outpatient should be discharged to a responsible adult, who will accompany the patient home and able to report any postprocedure complications. In addition, outpatients should be provided with written instructions regarding postprocedure diet, medications, activities, and a phone number to call in case of emergency.[1]

Ideally, each patient should be evaluated for discharge by a qualified anesthesia provider using a consistent set of criteria that take into consideration the severity of the underlying disease, the anesthetic and recovery course, and the level of care at the destination, especially for ambulatory patients.

TABLE 50-5 Modified Postanesthesia Recovery Score for Outpatients' Street Fitness

Parameter	Description	Score
Activity	Able to move four extremities voluntarily on command	2
	Able to move two extremities voluntarily on command	1
	Able to move no extremities voluntarily on command	0
Respiration	Able to breathe deeply and cough freely	2
	Dyspnea or limited breathing	1
	Apneic	0
Circulation	BP ± 20 mmHg of preanesthetic level	2
	BP ± 21-49 mmHg of preanesthetic level	1
	BP + 50 mmHg of preanesthetic level	0
Consciousness	Fully awake	2
	Arousable on calling	1
	Not responding	0
O_2 Saturation	Able to maintain O_2 saturation greater than 92% on room air	2
	Needs O_2 inhalation to maintain O_2 saturation greater than 90%	1
	O_2 saturation less than 90% even with O_2 supplement	0
Dressing	Dry	2
	Wet but stationary	1
	Wet but growing	0
Pain	Pain free	2
	Mild pain handled by oral medications	1
	Pain requiring parenteral medications	0
Ambulation	Able to stand up and walk straight*	2
	Vertigo when erect	1
	Dizziness when supine	0
Fasting and feeding	Able to drink fluids	2
	Nauseated	1
	Nausea and vomiting	0
Urine output	Has voided	2
	Unable to void but comfortable*	1
	Unable to void and uncomfortable	0

From Aldrete JA. The postanesthesia recovery score revisited. *J Clin Anesth*. 1995;7:89-91.
*May be replaced by Romberg's test or picking up 12 clips in one hand.

SUMMARY

Postanesthesia care units are vital to the safe recovery of patients from surgery and anesthesia. Nurses provide the skillful bridge to ensuring a successful perioperative experience. They assess and monitor patients for residual anesthetic effects and surgical complications and reinstitute care for preexisting medical problems. Integrating care provided by the nurse with that of the anesthesia and surgical teams is essential in the modern surgical center.

BOX 50-11

Postanesthesia Discharge Scoring System

Vital Signs
2 = Within 20% of preoperative value
1 = 20%-40% of preoperative value
0 = Greater than 40% of preoperative value

Activity and Mental Status
2 = Oriented 3 separate times and a steady gait
1 = Oriented 3 separate times or a steady gait
0 = Neither

Pain, Nausea, Vomiting
2 = Minimal
1 = Moderate, requiring treatment
0 = Severe, requiring treatment

Surgical Bleeding
2 = Minimal
1 = Moderate
0 = Severe

Intake and Output
2 = Postoperative fluids and void
1 = Postoperative fluids or void
0 = Neither

From Chung F, et al. A post-anesthetic discharge scoring system for home-readiness after ambulatory surgery. *J Clin Anesth*. 1995; 7:500-506.

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CHAPTER 51

Pain Management

◆ *Sandra K. Bordi*

In the United States it is estimated that approximately 76 million people suffer from some type of pain, including acute, chronic, and/or postsurgical.[1] Even though advances have been instituted to help practitioners recognize and treat pain, the incidence of unrelieved pain continues to be a major concern. In 1992 the Agency for Healthcare Research and Quality (AHRQ) devised the first clinical practice guidelines (CPGs) for pain management. Subsequently, other groups including the American Pain Society (APS), American Society of Anesthesiologists (ASA), and the American Academy of Pain Management (APM) have instituted CPGs for management of acute and chronic pain. In addition to these associations, others have developed CPGs specific to patient populations (e.g., elderly and pediatrics) and to types of pain (e.g., cancer pain, postoperative pain, and chronic noncancer pain) in an effort to improve pain management. Even though there are CPGs, pain management remains inadequate. Several professional and regulatory groups have proposed standards, responsibilities, and outcome measures to improve pain management. The Joint Commission (TJC) developed pain management standards that were implemented in 2001. TJC clearly outlined the responsibilities of hospitals, home-care agencies, nursing homes, behavioral facilities, and out-patient clinics seeking accreditation (Box 51-1). The implementation of these standards is a momentous step in the improvement of pain management.

As providers of anesthesia care in the United States, certified registered nurse anesthetists (CRNAs) are integral to the research and management of acute and chronic pain. It is their professional and ethical responsibility to participate in the assessment, management, and treatment of pain based on each patient's unique needs in a holistic and multidisciplinary manner.[2] Only recently have CRNAs been recognized as experts in the area of pain management, and their knowledge and skills are essential in pursuing effective pain management modalities.

PAIN

Definition

Pain remains a very complex and multidimensional experience. It was defined by the International Association for the Study of Pain (IASP) as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage."[3] The inherent context of this definition is that pain is a physiologic, emotional, and a behavioral experience.[4] Commonly used pain terminology is listed in Box 51-2.

Classification of pain is primarily based on longevity (acute versus chronic) and/or the underlying pathophysiology (nociceptive or non-nociceptive).[5] Nociceptive pain is associated with the stimulation of specific nociceptors and can be either somatic or visceral. *Somatic pain* refers to pain that has an identifiable locus as a result of tissue damage causing the release of chemicals from injured cells that mediate pain. Somatic pain is well localized, sharp in nature, and generally hurts at the point or area of stimulus. Conversely, *visceral pain* is diffuse, can be referred to another area, and is often described as "dull," "cramping," "squeezing," or vague in nature. Visceral pain is often associated with the distention of an organ capsule or the obstruction of a hollow viscus. It is also often accompanied with autonomic reflexes such as nausea, vomiting, and diarrhea.[6] In contrast, non-nociceptive pain can be categorized as being *neuropathic* or *idiopathic*. *Neuropathic pain* is caused by damage to peripheral or central neural structures resulting in abnormal processing of painful stimuli. It is a dysfunction of the central nervous system (CNS) that allows for spontaneous excitation in chronic pain states. Neuropathic pain is often described as "burning," "tingling," or "shocklike."[7] *Idiopathic pain* or *psychogenic pain* is also associated with chronic pain states and is used to describe pain that has no apparent cause. Neither nociceptive nor neuropathic mechanisms can be identified as a cause for pain, and psychological symptoms are commonly present. Patients in chronic pain states often exhibit more than one type of pain along with a psychological component. Therefore, psychological, cultural, and environmental factors should be addressed when assessing patients with chronic pain.[6]

Anatomy and Physiology

Somatic nociceptive pain is most commonly defined in terms of four processes: transduction, transmission, perception, and modulation. *Transduction* is the transformation of a noxious stimulus (chemical, mechanical, or thermal) into an action potential.

BOX 51-1

The Joint Commission Pain Management Standards

The Joint Commission pain management standards require organizations to:

- Recognize the right of patients to appropriate assessment and management of pain
- Screen patients for pain in their initial assessment, including the nature and intensity of the pain
- Record the results of the assessment in a way that facilitates regular reassessments and follow-up
- Establish policies and procedures that support the appropriate prescription or ordering of effective pain medications
- Educate patients and their families about effective pain management
- Address patient needs for symptom management in the discharge planning process
- Ensure staff education regarding pain assessment and management

From Berry PH, Dahl JL. The new JCAHO standards: implications for pain management nurses. *Pain Manag Nurs*. 2000;1(1):3-12.

A noxious stimulus is detected by pain receptors, or nociceptors, which are free nerve endings. These peripheral nociceptors that conduct noxious stimuli to the dorsal horn of the spinal cord are categorized according to morphology (diameter, myelination, and conduction velocity). The myelinated A-delta (Aδ) primary afferent neurons conduct action potentials at velocities between 6 and 30 m/sec and elicit fast-sharp pain. They are responsible for the initial mechanical or thermal pain that is felt and alert an individual of tissue damage, thereby resulting in the reflex withdraw mechanism. The smaller nonmyelinated C fibers conduct at velocities significantly slower, between 0.5 and 2 m/sec. Because C fibers respond to mechanical, thermal, and chemical injuries, they are also known as polymodal fibers. Due to their slow conducting velocity, a delayed, slow, second pain is elicited by C fibers.[8] Slow pain is commonly described as "dull," "burning," "throbbing," and "aching."

Consequently, when peripheral tissues (skin, bone, and viscera) receive chemical, thermal, or mechanical stimuli or are traumatized by either surgery or injury, a series of biochemical events take place in peripheral pain transduction. These events include the release of chemical mediators from the inflammatory response and the release of neurotransmitters from nociceptive nerve endings (Figure 51-1). The chemical mediators and neurotransmitters released are extensive, with the more prominent substances listed below:

- *Substance P* is a peptide found and released from the peripheral afferent nociceptor C fibers and is involved with slow, chronic

BOX 51-2

Pain Terminology

Algesia: Increased sensitivity to pain.
Algogenic: Pain producing.
Allodynia: A normally nonharmful stimulus is perceived as painful.
Analgesia: The absence of pain in the presence of a normally painful stimulus.
Dysesthesia: An unpleasant painful abnormal sensation, whether evoked or spontaneous.
Hyperalgesia: A heightened response to a normally painful stimulus.
Neuralgia: Pain in the distribution of a peripheral nerve(s).
Neuropathy: An abnormal disturbance in the function of a nerve(s).
Paresthesia: An abnormal sensation, whether spontaneous or evoked.

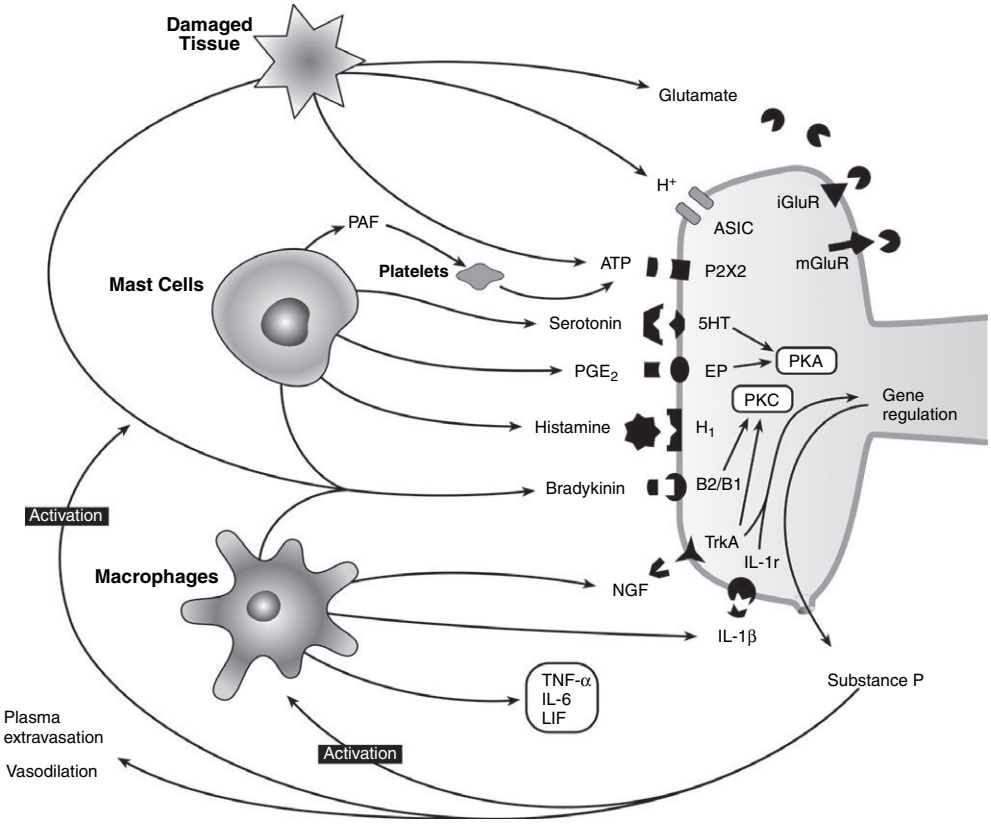

FIGURE **51-1** Inflammation and peripheral nociception. After tissue injury, mast cells, macrophages, and neutrophils are activated and/or are recruited to the area. In addition, small nociceptor nerve endings are also triggered. A variety of algogenic substances are released as a result of the inflammatory response and from the nociceptor nerve endings. These algogenic substances contribute to the pain process either directly (i.e., increasing excitability of nerves) or indirectly via second messenger (i.e., PKA, PKC) responses. *PAF*, Platelet-activating factor; *ATP*, adenosine triphosphate; *P2X2*, primary receptor family for ATP; H^+, excess free hydrogen ion; *5HT*, 5-hyroxytryptamin receptor; PGE_2, prostaglandin E_2; *EP*, prostaglandin E receptor; H_1, histamine-1 receptor; *B2/B1*, bradykinin 1 and bradykinin 2 receptor; *NGF*, nerve growth factor; *TrkA*, tyrosine kinase receptor A; *Il-1β*, interleukin-1β; *Il-1r*, interleukin 1 receptor; *PKC*, protein kinase; *PKA*, protein kinase A; *iGluR*, ionotropic glutamate receptor; *mGluR*, G protein–coupled metabotropic glutamate receptor; *TNF-α*, tumor necrosis factor-α; *IL-6*, interleukin-6; *LIF*, leukemia-inhibiting factor. (Modified from Dougherty P, et al. Neurochemistry of somatosensory and pain processing. In: Benzon HT, et al, eds. *Essentials of Pain Medicine*. 3rd ed. Philadelphia: Saunders; 2011:8-15.)

pain. It acts via the G-protein–linked neurokinin-1 receptor, resulting in vasodilation, extravasation of plasma proteins, degranulation of mast cells, and sensitization of the stimulated sensory nerve.[9]

- *Glutamate* is a major excitatory neurotransmitter released in the CNS and from the Aδ and C primary afferent nerve fibers. Its effects are instantaneous, producing initial, fast-sharp pain.[8]
- Bradykinin is a peptide released during the inflammation process and is notably algesic. It has a direct stimulating effect on peripheral nociceptors via specific bradykinin receptors (B1/B2).
- *Histamine* is an amine released from mast cell granules, basophils, and platelets via substance P. It reacts with various histamine receptors to produce edema and vasodilation.
- *Serotonin (5-hydroxytryptamine [5-HT])* is an amine stored and released from platelets after tissue injury. It reacts with multiple receptor subtypes and exhibits algesic effects on peripheral nociceptors. Like histamine, serotonin can potentiate bradykinin-induced pain.
- *Prostaglandins (PGs)*, along with *thromboxanes* and *leukotrienes*, are a metabolite of arachidonic acid. PGs, specifically, are synthesized from cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). They are associated with chronic pain; PGs sensitize peripheral nociceptors, causing hyperalgesia.
- *Cytokines* are released in response to tissue injury by a variety of immune and nonimmune cells via the inflammatory response. Cytokines including interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) can lead to the increased production of PGs, thereby exciting and sensitizing nociceptive fibers.[10]

These chemical mediators and neurotransmitters stimulate the peripheral nociceptors, causing an influx of sodium ions to enter the nerve fiber membranes (depolarization) and a subsequent efflux of potassium ions (repolarization). An action potential results, and a pain impulse is generated.

Transmission is the process by which an action potential is conducted from the periphery to the CNS. There are multiple pathways that carry noxious stimuli to the brain. The spinothalamic (anterolateral) system, which carries pain signals from the trunk and lower extremities, will be discussed here. The primary afferent neurons (Aδ and C fibers) have cell bodies located in the dorsal root ganglia of the spinal cord. Upon entering the dorsal cord, these fibers segregate and ascend or descend several spinal segments in the tract of Lissauer. After leaving the tract of Lissauer, the axons of the primary afferents enter the gray matter of the dorsal horn where they synapse with second-order neurons and terminate primarily in Rexed's laminae I, II, and V (Figure 51-2). Two types of second-order neurons exist: (1) nociceptive neurons, which receive input solely from primary afferent Aδ and C fibers and (2) wide-dynamic-range (WDR) neurons that receive input from both nociceptive (Aδ and C fibers) and non-nociceptive (A-β) primary afferents. Wide-dynamic-range neurons are therefore activated by a variety of stimulants (innocuous and noxious) (Figure 51-3).

Second-order neurons then cross the midline of the spinal cord through the anterior commissure and ascend in the anterolateral pathway of the spinothalamic tract to the thalamus. In the lateral thalamus and the intralaminar nuclei, second-order neurons synapse with third-order neurons, which then send projections to the cerebral cortex. *Perception* of pain occurs once the signal is recognized by various areas of the brain, including the amygdala, somatosensory areas of the cortex, the hypothalamus, and the anterior cingulate cortex.

Modulation of pain transmission involves altering neural afferent activity along the pain pathway; it can suppress or enhance pain signals. Suppression of pain impulses occur through local inhibitory interneurons and descending efferent pathways. The descending efferent modulatory pathways from the brain are considered the body's "analgesia system" or pain control system.[8]

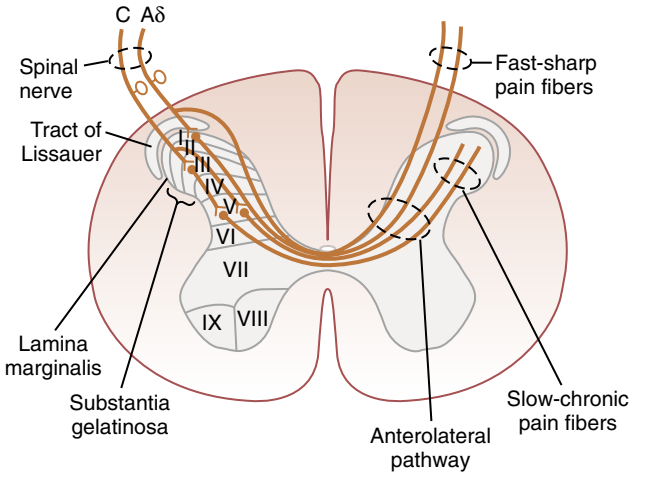

FIGURE 51-2 Transmission of primary afferents in the dorsal horn and tract of Lissauer. (From Hall JE. *Guyton and Hall Textbook of Medical Physiology.* 12th ed. Philadelphia: Saunders; 2011:585.)

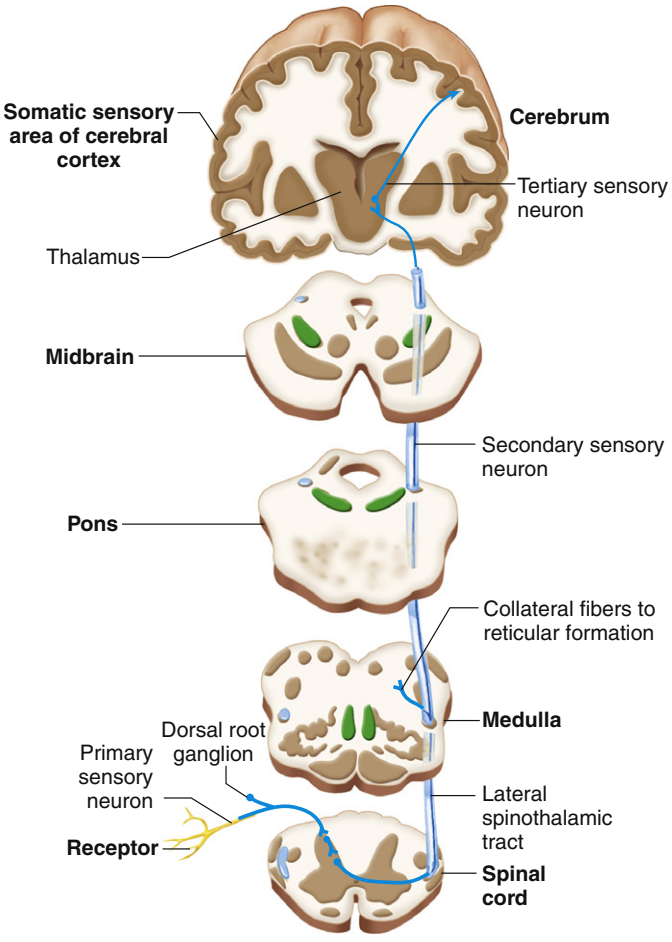

FIGURE 51-3 Ascending lateral spinothalamic tract. (From Patton KT, Thibodeau GA. *Anatomy and Physiology.* 8th ed. St. Louis: Mosby; 2013:448.)

It is proposed that the descending dorsolateral efferent pathway is activated via a noxious stimulus. Descending axons from the cerebral cortex, hypothalamus, thalamus, periaqueductal gray area (PAG), nucleus raphe magnus (NRM), and locus coeruleus (LC) via the dorsolateral funiculus (DLF) synapse with and suppress pain transmission to the brainstem and the spinal cord dorsal horn. Several neurotransmitters and their receptors play critical roles in the inhibitory modulation of pain, including the inhibitory endogenous opioids (enkephalin/dynorphin). Action potentials arrive at the substantia gelatinosa via the DLF and activate enkephalin-releasing neurons. Enkephalin then binds to the opiate receptors on presynaptic first-order or postsynaptic second-order afferent fibers, which decrease substance P release, thereby suppressing ascending pain transmission. Other inhibitory neurotransmitters released via the descending pathway include glycine, norepinephrine, serotonin, and gamma-aminobutyric acid (GABA) (Table 51-1). Pharmacotherapies for pain control are aimed at many of these neurotransmitters and their receptors.

Pain modulation is enhanced in the presence of "central sensitization." Central sensitization refers to the neural plasticity that occurs in the CNS. When tissue or neural injury exists, repetitive stimulation and activation of nerves results in changes in neurotransmitter levels and signaling in the CNS. For example, the repetitive firing of dorsal horn nociceptors causes activation of lower non-nociceptive threshold mechanoreceptors (A-β afferents) to trigger a pain response. There are also other factors involved in central sensitization, including the inflammatory response and an increase in receptive field size.[11] Central sensitization is associated with chronic pain states and is addressed in more detail later in this chapter.

Acute Pain

Acute pain is caused by noxious stimulation due to traumatic injury (chemical, thermal, or mechanical), surgery, or acute illness. Generally, the intensity of acute pain diminishes over the course of healing; however, social, cultural, and personality factors may affect this. Its duration is usually self-limited and resolves within 1 to 14 days. Acute pain is responsive to pharmacotherapy and treatment of the precipitating cause. Unfortunately, poorly controlled acute pain may lead to chronic pain states. Therefore, optimal pain management is crucial in expediting the healing process and for the prevention of chronic pain.

TABLE 51-1 Pain-Modulating Neurotransmitters

Neurotransmitters	Receptor
Excitatory Neurotransmitter	
Substance P	Neurokinin-1 (NK1), Neurokinin-2 (NK2)
Glutamate	NMDA, AMPA, kainate
Inhibitory Neurotransmitter	
Glycine	Chloride linked (GlyR)
GABA	$GABA_A$, $GABA_B$, $GABA_C$
Enkephalin	Mu, delta, kappa
Serotonin	5-HT (5-HT1-3)
Norepinephrine	$Alpha_2$ adrenergic

NMDA, N-methyl-D-aspartate; *AMPA*, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; *GlyR*, glycine receptor; *GABA*, gamma-aminobutyric acid; *5HT*, 5-hydroxytryptamine.

It is well documented that acute pain causes adverse physiologic consequences involving multiple organ systems, which can contribute to morbidity and mortality in surgical patients. Neuroendocrine responses that are triggered primarily by the sympathetic nervous system (SNS) in response to surgical stress and pain initiate these effects. Factors such as the extent of the surgical field, the number of pain receptors involved in the area, bleeding, infection, anxiety, and presence of coexisting diseases may accelerate the endocrine stress response.

The activation of the sympathetic nervous system in response to the stress of pain from surgery or trauma results in many cardiovascular responses. The increased release of catecholamines from the SNS and adrenal glands, along with cortisol, produces an increased heart rate, increased vascular resistance (peripheral, systemic, and coronary), increased myocardial contractility, and increased arterial blood pressure. These ultimately increase the myocardial demand and myocardial oxygen consumption. Additionally, in the presence of coexisting cardiovascular disease, atherosclerotic plaque from vascular walls may rupture, thereby decreasing oxygen supply further. This may lead to dysrhythmias, angina, myocardial ischemia, and myocardial infarction. Overall, the incidence of increased myocardial oxygen demand and decreased myocardial oxygen supply can have deleterious effects in those patients with coexisting cardiovascular disease. Therefore, aggressive pain management is essential in reducing the incidence of postoperative cardiac complications.[12]

The presence of pain can have significant effects on the respiratory system. These effects are most pronounced in those patients having surgery or trauma in the upper abdominal area and thorax. Inadequate pain management causes a measurable decrease in tidal volume because of limited thoracic and abdominal movement. Specifically, there are decreases in vital capacity, inspiratory capacity, and functional residual capacity (FRC), as well as a decreased physical ability to clear the airway, due to unrelieved pain. Additionally, muscle spasm below and above the site of injury caused by the noxious stimuli promotes limited movement of the respiratory muscles. Patients often voluntarily decrease the movement of the thorax and abdomen (splinting) and are reluctant to breathe deeply or cough in an attempt to limit pain, which can lead to atelectasis and pneumonia.[13,14] These pulmonary alterations may be aggravated in those patients with preexisting pulmonary dysfunction (e.g., asthma, chronic obstructive pulmonary disease) or in those with decreased FRC (e.g., morbidly obese, elderly). Consequently, those affected by postoperative respiratory compromise due to inadequate pain management also may be at risk for deep venous thrombosis and subsequent pulmonary embolism due to a decrease or delay in mobilization. See Table 51-2 for physiologic consequences of acute pain.

The physiologic effects and the consequences of inadequate pain management have been reported to have an impact in delaying postoperative stay, patient recovery, and an overall increase in healthcare costs.[15] It also negatively impacts the patient's surgical/hospitalization experience, resulting in reduced patient satisfaction.

Acute Pain Assessment

To devise a plan for intraoperative and postoperative surgical pain management, a preoperative pain assessment and discussion with the patient should be conducted. A thorough preoperative assessment should involve a physical and medical history assessment, including laboratory and diagnostic tests that are patient and surgery specific. Inquiries specific to preoperative pain also should be addressed; these are found in Box 51-3. Part of the preoperative

TABLE 51-2 Physiologic Effects of Acute Pain

Organ System	Physiologic Effect	Adverse Outcome
Cardiovascular	Increased heart rate	Dysrhythmias
	Increased PVR	Angina
	Increased ABP	Myocardial ischemia
	Increased myocardial contraction	Myocardial infarction
	Increased myocardial work	
Pulmonary	Decreased VC	Ventilation/perfusion mismatch
	Decreased TV	Atelectasis
	Decreased TLC	Pneumonia
	Muscle spasms (respiratory/abdominal)	Hypoventilation
	Decreased ability to cough/deep breathe	Hypoxia
		Hypercarbia
Gastrointestinal	Decreased gastric emptying	Nausea/vomiting
	Decreased intestinal motility	Paralytic ileus
	Increased smooth muscle sphincter tone	
Coagulation	Increased platelet aggregation	Thrombosis
	Venostasis	DVT/PE
Immunologic	Decreased immune function	Increased risk of infection
Genitourinary	Increased urinary sphincter tone	Oliguria
		Urinary retention
Psychological		Fear
		Anxiety
		Depression
		Feelings of helplessness
		Anger

Adapted from Joshi GP, Oqunnaike BO. Consequences of inadequate postoperative pain relief and chronic persistent postoperative pain. *Anesthesiol Clin North America*. 2005;23(1):21-36.
PVR, Peripheral vascular resistance; *ABP*, arterial blood pressure; *VC*, vital capacity; *TV*, tidal volume; *TLC*, total lung capacity; *DVT*, deep vein thrombosis; *PE*, pulmonary embolism.

pain assessment process also should consist of identifying those at high risk for increased postoperative acute pain. A recent study identified that the most important predictors of acute postoperative pain after elective surgery include: (1) the presence of preoperative pain, (2) patient fear regarding the outcome of his/her surgery, (3) patients who catastrophize pain, and (4) expected pain postoperatively.[16] Overall, goals for pain management should be based on patient physical/medical assessment, history, invasiveness of the surgical procedure, an individual's pain response, and prediction of identifying those who are at high risk for developing increases in acute pain postoperatively. The patient should be informed of the varying modalities for postoperative pain control, and a unique pain management plan should be implemented by both the patient and care providers. Furthermore, realistic expectations for postoperative pain control should be discussed.

BOX 51-3

Preoperative Pain Assessment

- Determine the existence of chronic pain
- Current medications (prescription and OTC)—continuous or prn for pain
- Inquiry regarding previous injuries
- Location of pain
- Quality of pain
- Intensity of pain
- Adjunctive therapies (e.g., acupuncture, TENS, injection therapy, SCS)
- Exacerbating factors
- Alleviating factors
- Limitations in movement
- Coexisting psychological diseases

OTC, Over-the-counter; *TENS*, transcutaneous electric nerve stimulation; *SCS*, spinal cord stimulator; *prn*, as needed.

As discussed earlier, adequate postoperative pain control is essential in the recovery process. Assessing the adequacy of postoperative pain control through vigilance and by using simple assessment tools is vital. Because pain is subjective, the most reliable pain assessment tool is primarily via self-report. Pain assessment scales, which are both clinically valid and used in research, are available and are based on measuring pain intensity. The common pain intensity scales include the visual analog scale (VAS), the numerical rating scale (NRS), and the Wong-Baker FACES scale. Even though these scales are available and are used in the clinical setting, they are not all-inclusive. The NRS, VAS, and Wong-Baker FACES scales assign a numerical value to an individual's pain, which is subjective and multidimensional. In addition, they do not take into consideration the patient's age or variations in cognitive level. The NRS is most often used by practitioners in assessing pain by asking the patient "What is your pain level on a scale of 1 to 10, with 10 being the worst pain you have ever experienced and 0 being pain-free?" Although this is a quick tool used to assess pain, it lacks the depth of determining the quality of pain or exacerbating factors that affect pain. Inevitably it is the provider's responsibility to investigate the patient's pain, be it surgical or nonsurgical, and intervene with a treatment modality. Key to successful acute pain control is vigilant reassessment and evaluation of the patient's response to a given treatment and changing treatment modalities, if necessary, in an effort to alleviate pain.

Preemptive Analgesia

Preemptive analgesia is a concept first postulated approximately 100 years ago. It was asserted that by administering analgesics prior to noxious stimulation, a decreased pain response would result. The premise is that peripheral and central sensitization results from noxious stimulation, thereby causing an increase in postoperative pain. Preemptive analgesia in preventing central sensitization remains controversial. For example, in an animal study by Chang et al.,[17] preincisional treatment with an *N*-methyl-D-aspartate (NMDA) antagonist was not found to be more beneficial than postincisional treatment. Likewise, Hariharan et al.[18] found in a human study that local anesthesia administered prior to incision with abdominal hysterectomy did not reduce the intensity of postoperative pain. However, in contrast, Arici et al.[19] concluded that preemptive intravenous (IV)

paracetamol provided "good quality" postoperative analgesia and a reduction in morphine administration postoperatively. Similarly, Persec et al.[20] reported that the administration of intrathecal clonidine reduced postoperative pain significantly more than did administration of intrathecal levobupivicaine.

Regardless of the controversies surrounding preemptive analgesia, a multimodal approach to acute and chronic pain management is common practice. Multimodal pain management consists of using a combination of analgesics that work on a variety of receptors with different mechanisms of action, both peripherally and centrally, resulting in additive or synergistic effects in an effort to improve pain control.

Acute Pain Analgesics

Nonsteroidal Antiinflammatory Drugs

Nonsteroidal antiinflammatory drugs (NSAIDs) are best known for their use in the management of mild to moderate postoperative pain and pain related to inflammatory conditions. They are the most common analgesic adjuvants used in multimodal analgesia remedies. When using NSAIDSs and opioids together, a synergistic effect results in analgesia along with an overall decreased dose of opioids and decreased opioid side effects. NSAIDs vary in chemical structure but all possess antiinflammatory, antipyretic, and analgesic properties. They produce their therapeutic effects by inhibiting cyclooxygenase (COX) and thereby preventing conversion of arachidonic acid to prostaglandins. Prostaglandins (primarily PGE_1 and PGE_2) are responsible for sensitizing and amplifying peripheral nociceptors to the inflammatory mediators (substance P, bradykinin, and serotonin), which are released when tissue is traumatized. Therefore, prostaglandins do not directly produce pain but instead contribute to hyperalgesia. Centrally, prostaglandins mediate pain by enhancing the release of substance P and glutamate in first-order neurons, increasing nociceptive transmission at second-order neurons, as well as inhibiting the release of descending inhibitory neurotransmitters (Figure 51-4).

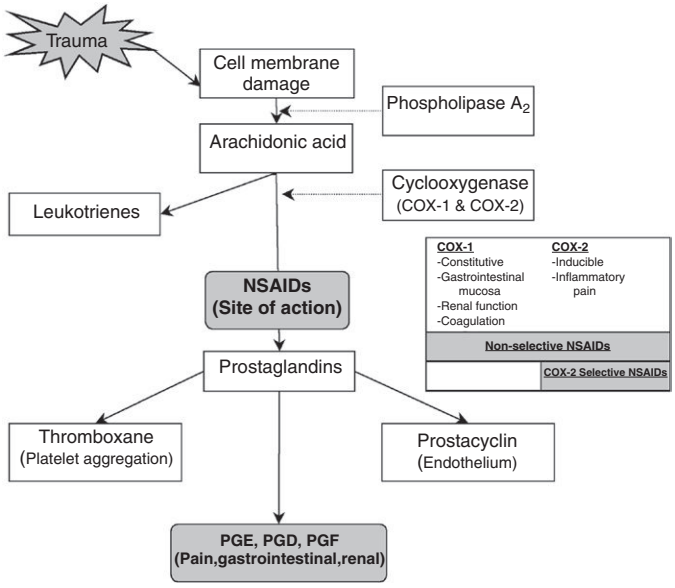

FIGURE **51-4** Nonsteroidal antiinflammatory drugs (NSAIDs) site of action and influence of prostaglandins. (From Benzon HT, et al, eds. *Essentials of Pain Medicine*. 3rd ed. Philadelphia: Saunders; 2011:131.)

COX exists in two isoforms: COX-1 and COX-2. COX-1 is constitutive, widespread throughout the body, and necessary for homeostasis. It is responsible for platelet aggregation, gastric mucosal integrity, and renal function. Conversely, COX-2 is an inducible enzyme that in the presence of inflammation releases prostaglandins, thereby mediating pain, fever, and carcinogenesis.[21] Until recently, all of the NSAIDs were nonselective in their COX inhibition. As a result, in addition to the analgesia effects from the inhibition of the COX-2 isoform, inhibition of COX-1 was responsible for the detrimental side effects of gastric irritation, renal microvasculature constriction, and platelet inhibition. Presently in the United States, celecoxib is the only COX-2–selective NSAID available. Others have been withdrawn from the market because of cardiovascular side effects. Celecoxib is available orally and is used for treating acute surgical pain, chronic pain syndromes, and cancer pain in conjunction with other analgesic approaches. It is metabolized by the liver extensively via cytochrome P450 (CYP450). A contraindication for celecoxib administration includes known hypersensitivity to sulfonamides because it contains sulfa. In addition, celecoxib should also be avoided in patients with a history of asthma or allergic reaction to aspirin or other NSAIDs, because COX-2 inhibitors can convert arachidonic acid to the precursor of leukotrienes, potentially causing bronchoconstriction and/or anaphylaxis.

Ketorolac. Ketorolac, a nonselective COX inhibiter, is also available for short-term acute postoperative pain, administered either alone or in combination with other analgesic modalities. Ketorolac can be administered orally, intravascularly, intramuscularly, and intranasally. Comparatively, the analgesic potency of ketorolac 30 mg intramuscular (IM) is equivalent to approximately 12 mg of morphine IM.[22] Because of the potential adverse effects caused by the inhibition of COX-1, ketorolac should not be administered beyond 5 days.[23] Contraindications for administering ketorolac include coagulopathies, renal failure, active peptic ulcer disease, gastrointestinal bleeding, history of asthma, hypersensitivity to NSAIDs, and surgery that involves a high risk for postoperative bleeding. In addition, controversy exists regarding bone healing and ketorolac administration. Ketorolac's inhibition of COX-1, COX-2, and prostaglandin synthesis interrupts normal prostaglandin effects on osteoblast and osteoclast functioning that promotes bone healing.[24,25] However, currently there are no recommendations regarding ketorolac administration and orthopedic procedures.

Acetaminophen. Acetaminophen reduces prostaglandin synthesis by an uncertain mechanism. It has minimal antiinflammatory effects with mainly analgesic and antipyretic properties. It is suitable for acute mild to moderate postoperative pain and fever. Oral acetaminophen is frequently combined with weak opioids (e.g., oxycodone, hydrocodone, codeine) for the treatment of moderate postoperative pain and chronic pain syndromes. Because it lacks the negative effects of typical NSAIDs (e.g., platelet inhibition, gastrointestinal irritation, renal toxicity), acetaminophen is an ideal drug for multimodal analgesia for surgical pain. Acetaminophen is metabolized primarily by the liver and is therefore contraindicated in patients with liver failure. Parenteral acetaminophen (Ofirmev) is also available for the treatment of acute mild to moderate pain and is effective in treating moderate to severe pain with adjunctive opioid analgesics.[26] Dosing for adults weighing over 50 kg is 1000 mg every 6 hours or 650 mg every 4 hours infused over 15 minutes to a maximum of 4000 mg/day. Dosing in children over 2 years of age and under 50 kg is 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours to a maximum of 75 mg/kg/day. Onset of action is approximately 10 minutes with a duration of action of 4 to 6 hours. Adverse effects of IV acetaminophen are rare when dosed accordingly, with more common side effects being nausea, vomiting, headache, and insomnia.[27]

Opioids

Opioid analgesics remain the drugs of choice for treatment of moderate to severe pain in the early postoperative period. Opioids produce analgesia by binding to and activating G-protein coupled opioid receptors (GPCRs) peripherally and in the CNS. Centrally, opioid receptors are predominantly found in the dorsal horn of the spinal cord, specifically Rexed's lamina II of the substantia gelatinosa, and supraspinally in the periaquadectal grey (PAG) area, medial thalamus, amygdala, and limbic cortex. Peripherally, they are found on afferent sensory nerve fibers as well as in the gastrointestinal tract, lungs, and joints.[28] There are several subtypes of opioid receptors, with the principal ones being mu (μ), delta (δ), and kappa (κ). When bound by opioids presynaptically, these GPCRs cause a biochemical change that decreases adenylate cyclase activity, thereby inhibiting calcium channels resulting in a decreased release of excitatory neurotransmitters such as substance P. Postsynaptically, there is an increase in outward potassium conductance with a subsequent hyperpolarization and an inhibition of excitatory neurotransmission.[29]

A thorough understanding regarding opioid pharmacodynamics and pharmacokinetics is essential when choosing a specific opioid. This is discussed in Chapter 11. Perioperatively, the more common opioids used for acute pain are fentanyl, morphine, and hydromorphone. These are predominantly administered parenterally but can be administered in a variety of routes depending upon the opioid (e.g., orally, epidurally, intrathecally, via intraarticular, and transdermally). Common side effects found with most opioids are dose dependent and include respiratory depression, pruritus, urinary retention, constipation, and nausea and vomiting.

Fentanyl. Intravenously, fentanyl's analgesic potency is approximately 80 to 100 times more than morphine. Its short onset of action (2-5 minutes) makes it an ideal opioid for treating acute pain. The duration of action of fentanyl is approximately 30 minutes to 1 hour because it is metabolized by the liver via the *N*-dealkylation into inactive metabolites and excreted by the kidneys. Fentanyl can be administered intrathecally, epidurally, and intravenously via postoperative patient-controlled analgesia (PCA). It is also available transdermally for the treatment of chronic pain. Because fentanyl is highly lipophilic, its administration intrathecally is limited due to its short duration of action, with a single dose lasting 2 to 4 hours.[30] Likewise, the duration of action for a single dose of epidural fentanyl (50-200 mcg) will be approximately 2 to 3 hours.[30,31] Intrathecal and epidural fentanyl can be given as a single dose or a continuous infusion and is discussed in Chapter 44.

Morphine. Morphine is the prototypical opioid by which all others are compared and is the most widely used for acute and chronic pain management. Metabolism of morphine is via hepatic glucuronidation, resulting in the metabolites morphine-3-glucuronide and morphine-6-glucuronide (M6G) with the latter being the active metabolite. Both metabolites are excreted via the kidneys; however, in patients with renal failure M6G may result in prolonged effects.

Morphine is commonly used to treat moderate to severe perioperative and postoperative pain. Morphine can be administered intravenously, intrathecally, epidurally, or orally. When administered IV, the onset of analgesia is approximately 20 minutes with duration of action being approximately 4 to 5 hours, depending on the dose administered. Unlike fentanyl, morphine is hydrophilic, making penetration of the blood-brain barrier and spinal cord more difficult. This results in a delayed onset of action (20-30 minutes) and a prolonged duration of action (8-24 hours) for single-dose intrathecal or epidural morphine. However, intrathecal morphine does result in a more profound analgesic effect as compared with IV or epidural administration.[32] Similar to fentanyl, morphine can be given in a single dose or continuous intrathecal or epidural infusion. Likewise, patient-controlled analgesia intravenously is also an option for morphine administration.

Hydromorphone. Hydromorphone is a derivative of morphine and is approximately 7 to 8 times more potent. Metabolism of hydromorphone is via hepatic conjugation; however, unlike morphine, it lacks the active metabolite M6G. Therefore administration in renal patients is considered safe. IV administration results in analgesia in approximately 15 minutes with a duration of action equivalent to morphine, approximately 4 to 5 hours. Hydromorphone is an ideal opioid for moderate or severe acute perioperative pain and is used for chronic pain management. Modes of administration include oral, intrathecal, epidural, intraarticulate, and intravenous PCA. When administered via single dose intrathecally or epidurally, onset of action is more rapid than morphine (approximately 15 minutes), with a duration of action of approximately 10 to 16 hours.[30] The common side effects associated with morphine administration remain similar to hydromorphone when equivalent doses are administered.[33] Hong et al.[34] reported that there were no differences between morphine and hydromorphone in efficacy of pain control or in opioid-related side effects with patients receiving intravenous PCA.

Acute Pain Analgesic Adjuncts

N-Methyl-D-Aspartate (NMDA) Antagonists

Ketamine, a noncompetitive NMDA antagonist and a phencyclidine derivative, is primarily used as an anesthesia induction agent. It is also used as part of a multimodal approach for perioperative pain control in conjunction with other medications. Ketamine prevents the activation of the NMDA receptor, which, along with the AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor, has been associated with the development of "wind-up" or central sensitization and chronic pain states. The NMDA receptor, at rest, remains closed due to a magnesium plug. Activation of the receptor involves the simultaneous binding of the excitatory neurotransmitter glutamate, which causes an influx of calcium, resulting in an increase in second messengers. The upregulation of second messengers produces a hyperexcitability of the NMDA receptors, which causes neuronal plasticity, excitability, and wind-up. In chronic neuropathic pain states such as complex regional pain syndrome type I and phantom limb pain, it is well established that ketamine is beneficial in reducing hyperalgesia and allodynia.[35] Likewise, ketamine may be helpful in reducing acute perioperative pain, and research suggests that it also exhibits antiinflammatory effects.[36]

Ketamine is rapidly acting in that an anesthetic IV dose response is seen in 30 to 40 seconds with a duration of 80 to 180 minutes. In addition to IV administration, it can be administered intramuscularly, nasally, rectally, via epidural, and intrathecally. Metabolism of ketamine is predominantly by the liver and produces norketamine.

Because ketamine exhibits both anesthetic and analgesic effects, its use has drawn more interest in the perioperative setting. Its administration at higher doses and as the sole anesthetic is less desirable because of psychomimetic adverse effects. Recently, ketamine has been used in "low doses" either as a single dose administered on induction of anesthesia and/or as a continuous infusion. There is no conclusive, consistent consensus in regard to what is considered "low-dose" ketamine. Studies report minimal adverse effects with subanesthetic doses of ketamine, as well as decreased perioperative opiate consumption. However, randomized control

trials and reviews have noted mixed results regarding efficacy of low-dose ketamine and postoperative analgesia.[37,38] Himmelseher et al.[39] suggest that dosing be made according to surgical procedure invasiveness and that dosing continue throughout the surgical procedure after the initial noxious stimulus and continue postoperatively.

Alpha$_2$ Adrenergic Agonists

Clonidine and dexmedetomidine are α_2 adrenergic agonists that are used as analgesic adjuncts for multimodal anesthesia. They exhibit their analgesic effect by interacting with the G-coupled α_2 receptors, both centrally (dorsal horn of the spinal cord) and peripherally. Activation of the α_2 receptor results in inhibition of adenyl cyclase and decreased cyclic adenosine monophosphate (cAMP) levels. It also activates postsynaptic potassium channels while inhibiting presynaptic voltage-gated calcium channels, thereby reducing neurotransmitter release. In addition, it is suspected that activation of central α_2 adrenoreceptors in the locus coeruleus are responsible for supraspinal analgesia.[40]

Clonidine, a centrally acting selective partial α_2 adrenergic receptor agonist can be administered orally, intravenously, rectally, transdermally, intrathecally, epidurally, and via an intraarticulate route. Its half-life is approximately 5 to 13 hours. Metabolism of clonidine is via the liver with the remainder of the drug being excreted unchanged in the urine. Because clonidine exerts its effects on both α_2 and α_1 receptors (220:1 α_2 to α_1), side effects such as sedation, hypotension, and bradycardia can occur. Clonidine has been reported to decrease postoperative morphine requirements when used with maintenance infusions intraoperatively. When combined with local anesthetics in peripheral nerve blocks and/or intrathecal administration, postoperative analgesia has been effective with decreased time to first supplemental analgesic request.[40]

Dexmedetomidine is a highly selective α_2 adrenergic agonist. It is approximately 7 to 10 times more selective for the α_2 receptors (1,620:1 α_2 to α_1) as compared with clonidine.[40] Like clonidine, it exhibits sedative, anxiolytic, analgesic, sympatholytic, and vagomimetic effects with little or no respiratory depression. Dexmedetomidine is most commonly administered intravenously; however, it can be administered intramuscularly, transdermally, or intranasally. It has a rapid onset of action, approximately 5 minutes, with a short duration of action, and an elimination half-life of approximately 3 hours. Metabolism of dexmedetomidine is via extensive hepatic glucuronide conjugation with the absence of active metabolites. Hepatic clearance may be decreased in the presence of liver disease. Dexmedetomidine is often used for procedural sedation in nonintubated patients, sedation for intubated and mechanically ventilated patients, as well as a general anesthesia adjunct. Similar to clonidine, dexmedetomidine decreases postoperative analgesic requirements and decreases postoperative morphine consumption.[41]

Local Anesthetics

Unlike the previous analgesics whose actions are targeted at specific receptors on primary nociceptors and in the CNS, resulting in reduced presynaptic transmitter release and decreased postsynaptic excitability, local anesthetics inhibit conduction of action potentials along a nerve fiber. Local anesthetics block sodium channels in both afferent and efferent neuronal membranes, thereby inhibiting pain transmission. They are often given as the sole anesthetic; however, for optimal postoperative analgesia, local anesthetics should be administered with adjuvant medications.

TABLE 51-3 Methods of Administering Local Anesthetics

Route	Technique	Mode of Delivery
Topical		SS
Local infiltration	Subcut, subdermal	SS
	Intraarticular	SS, C
Neuraxial	Subarachnoid	SS, C, PC
	Epidural	
	Caudal	
Peripheral nerve blocks	*Lower extremity*	SS, C, PC
	Lumbar and sacral plexus	
	Femoral	
	Sciatic	
	Popliteal	
	Ankle	
	Upper extremity	
	Brachial plexus	SS, C, PC
	Cervical plexus	SS, C
	Intercostal	SS, C, PC
	IV regional (Bier block)	SS
	Digit	SS
Systemic	IV	SS
Diagnostic/ interventional	Trigger point injection	SS
	Somatic nerve blockade	SS
	Sacroiliac injection	SS
	Facet injection	SS
	Epidural steroid injection	SS
	Selective sympathetic blockade	SS
	Intervertebral disc injection	SS
	Differential nerve blockade	SS

IV, Intravenous; *SS*, single shot; *C*, continuous; *PC*, patient-controlled.

Nerve morphology (diameter and myelination) affects the sensitivity of nerve blockade achieved. An understanding of local anesthetic properties such as potency, onset of action, and duration of action is crucial in choosing a specific local anesthetic. These are addressed in Chapter 10. Metabolism of local anesthetics is determined by the chemical class. Amide local anesthetics are metabolized primarily by the liver, whereas ester local anesthetics are metabolized via plasma cholinesterase. Conditions that alter liver function (hepatic disease) and/or decrease plasma cholinesterase levels will inevitably reduce the rate of metabolism.

Methods for administering local anesthetics are listed in Table 51-3. The most common techniques for acute pain management are local infiltration of the operative area, peripheral nerve blocks, as well as epidural and subarachnoid blocks with adjuvant medications (primarily opioids). Prior to surgical incision, local anesthetic can be injected intradermally or subcutaneously near the incisional area to decrease the inflammatory response; local anesthetic infiltration reduces up-regulation of peripheral nociceptors. Common local anesthetics used for operative area infiltration include bupivicaine or ropivacaine due to their longer duration of action.

Peripheral nerve blocks can be administered as a single injection or via a continuous catheter technique. Chapters 44 and 45

provide a thorough description of regional techniques and peripheral nerve blocks. Most peripheral nerve blocks consist of a bolus dose of local anesthetic injected to infiltrate an area, or a peripheral nerve site. These techniques are primarily used for minor surgical procedures that provide analgesia in the immediate postoperative period. Likewise, the use of continuous catheters or continuous peripheral nerve blocks (CPNBs) involves an initial bolus dose of local anesthetic followed by a continuous infusion near the surgical site and adjacent to a nerve. CPNBs are increasing in popularity; they provide prolonged analgesia in those patients who are expected to have moderate-to-severe postoperative pain lasting more than 24 hours. CPNBs are commonly used for the brachial plexus, intercostal, femoral, and sciatic nerves.

Both subarachnoid and epidural blockade (primarily epidural) have been found to be useful in the management of postoperative pain. The primary site of action of local anesthetics when injected in the subarachnoid or epidural space is the nerve roots of the spinal cord. Because neuraxial anesthesia (local anesthetic with or without opioids) provides profound analgesia, some clinicians use the epidural technique with light general anesthesia during the surgical procedure; at the end of the procedure, the epidural catheter is left in place for postoperative pain management. Medications (e.g., local anesthetics, opioids, and adjuvant medications) can then be administered as bolus injections, continuous infusion, or via a patient-controlled device. The continuous epidural technique can be used for thoracic, abdominal, and lower-extremity surgery.

Local anesthetics are used not only for acute postoperative pain management but also commonly used in the diagnosis and treatment of several chronic pain states. Examples of diagnostic and interventional uses include facet joint injection, sacroiliac injection, selective sympathetic blockade, and trigger point injection.

Patient-Controlled Analgesia

Patient-controlled analgesia (PCA) was developed in the early 1970s with the advent of microprocessor technology. This administration technique has changed the face of acute pain management and has become a standard technique for postoperative pain control. Intravenous PCA involves self-administration of predetermined doses of analgesics. This ideally results in the patient's ability to self-medicate to his/her pain needs and allows for more effective pain control while avoiding peaks (opioid side effects) and troughs (pain) in plasma concentrations that are commonly present with "as needed" IV administration. Current PCA models have different variables for administration allowing for selective dosing. These variables include: (1) an initial loading dose, (2) a demand dose or bolus dose, (3) a lockout interval, (4) a basal continuous infusion rate, and (5) 1-hour and 4-hour maximal dose limits.[42-44] The initial loading dose is administered by the programmer or postanesthesia care nurse for initial set-up in titrating the analgesic and/or for "breakthrough pain." The demand or bolus dose is the quantity of analgesia administered to the patient on activation of the PCA demand button. The length of time after a demand dose is given by the patient, during which another demand dose will not be delivered, is the lockout interval. The lockout interval prevents overdosage with continual demand, with lockout intervals between 5 and 10 minutes being optimal.[43,44] A basal or continuous infusion is the administration of analgesics at a constant given rate regardless of the patient using the demand button. Continuous infusion rates are predominantly only administered in chronic opioid-dependent patients because continuous infusion in opioid-naïve patients may result in overdose and increased risk for respiratory depression/arrest. Likewise, in chronic opioid-dependent patients, a continuous infusion may suffice their daily equivalent dose of opioid with demand doses assisting with their postoperative analgesia. However, extreme caution and vigilance should be used in monitoring these patients. A maximal dose limit of 1-hour or 4-hour intervals is proposed to be another safety mechanism against overdose. Nevertheless, this remains controversial because opponents argue that if a patient reaches his or her 1-hour or 4-hour demand dose limit, then he or she probably requires more analgesia.

TABLE 51-4 Intravenous Patient-Controlled Analgesia Regimens

Drug Concentration	Size of Bolus	Lockout Interval (min)	Continuous Infusion
Agonists			
Morphine (1 mg/mL)			
Adult	0.5-2.5 mg	5-10	—
Fentanyl (0.01 mg/mL)			
Adult	10-20 mcg	4-10	—
Hydromorphone (0.2 mg/mL)			
Adult	0.05-0.25 mg	5-10	—
Methadone (1 mg/mL)	0.5-2.5 mg	8-20	—

From Miller RD, et al. *Miller's Anesthesia*, 7th ed. Philadelphia: Churchill Livingstone; 2010.

Because PCA requires the patient to control the delivery system, candidates for PCA must be cooperative, able to understand the concept, follow the directions of use, and be able to push the demand button. In addition, education should be provided to the patient and family members regarding the PCA delivery system.

The medications most often used for PCA are morphine, hydromorphone, and fentanyl. Meperidine is not recommended because of its neurotoxic metabolite, normeperidine. The neurotoxic side effects that are not reversible with naloxone include shakiness, tremor, twitches, multifocal myoclonus, and grand mal seizures.[45,46] Other medications that can be used via IV PCA include local anesthetics, ketamine, and clonidine. Dosing guidelines for specific medications are institution specific. A sample IV PCA dosing guideline for opioid-naïve patients is found in Table 51-4.

CHRONIC PAIN

The IASP defines chronic pain as pain that has no apparent biologic value and lasts longer than 3 months in duration or beyond the normal course of healing. It is often associated with insomnia, lost work days, impaired mobility, and emotional distress (i.e., anxiety, depression, anger, and fear). Chronic pain can be classified as being malignant (related to cancer and its treatment) or nonmalignant. Nonmalignant chronic pain is the focus of this discussion, with its categorization ranging from neuropathic, inflammatory, musculoskeletal, and idiopathic or a combination thereof. Management of the chronic pain patient is complex with cultural, emotional, biologic, and social influences all needing to be addressed. Treatment is aimed at reducing pain, improving activities of daily living, and enhancing functioning. In accomplishing this, an interdisciplinary approach to chronic pain management is essential. A team consisting of a pain management specialist, a psychologist, a physical therapist, an occupational therapist, and the patient is critical for the development of a comprehensive, specialized treatment plan.

Physiology

The transition from acute to chronic pain can be initiated or maintained by peripheral and/or central mechanisms. Physiologic mechanisms of acute pain, as previously described, include changing the chemical environment within the area of the nerve fibers that results from the inflammatory process. These changes consist of the release and accumulation of algogenic substances (e.g., bradykinin, serotonin, Il-6, IL-1β, prostaglandins) along with the release of neurotransmitters (e.g., substance P, glutamate). Exposure to these substances in the periphery induces enhanced excitability of the nerves, reduces nociceptive thresholds, and renders high-threshold nerve endings responsive to normally non-noxious stimuli.[8-10] This process is termed *peripheral sensitization* and may contribute to chronic pain states. It is clinically manifested as hyperalgesia.[47]

Despite the sequelae regarding chronic inflammation and its effects on nerve excitability and alteration in stimulus threshold, changes also can occur directly to nerve endings when nerve injury is present. Nerve injury may result in the sprouting of new hyperexcitable nerve endings, which fire ectopically. If nerve sprouting is unsuccessful, a neuroma may form, causing abnormal mechanosensitivity. Regenerated and/or damaged nerves also have reduced thresholds, which render them responsive to non-noxious stimuli. Pain that is initiated or caused by changes in the peripheral or central nervous system is defined as neuropathic pain. Clinical manifestations of neuropathic pain may include "shooting," "burning," or "stinging" sensations that are accompanied by hyperalgesia and allodynia.[48]

Central mechanisms involved with chronic pain include the continuous effects of chronic inflammation with hyperexcitability and sensitization of second-order neurons in the dorsal horn. Sensitization of the WDR neurons as well as an increase in the release of excitatory neurotransmitters, specifically glutamate, results in a phenomenon termed *wind up*. Repetitive stimulation of afferent C fibers causes a longer sustained depolarization of the cell with subsequent susceptibility to afferent input and sensitizes low-threshold afferents, leading to an increased neuronal receptive field size.[9,11]

Glutamate, the primary excitatory neurotransmitter released by primary afferents in the dorsal horn, is believed to play a role in the development of wind up. It acts at several receptors sites in the dorsal horn including the metabotropic, kainite, AMPA, and the NMDA receptors, with the latter being most recognized for its role in wind up and central sensitization. The NMDA receptor is an ionotropic receptor and, at rest, remains closed because of a magnesium plug. Activation of the receptor involves simultaneous binding of glutamate, which causes an influx of calcium inside the cell and results in an increase in second messengers such as protein kinases and phospholipases.[47,48] Other excitatory neurotransmitters, such as substance P and calcitonin-gene–related peptide, bind to and activate their receptors, also triggering up-regulation of these second messengers. The up-regulation of second messengers produces hyperexcitability of the NMDA receptors, resulting in long-term neuronal plasticity, excitability, and eventually gene transcription changes, which all contribute to central sensitization and chronic pain states.[47]

Acute and Chronic Pain

Overall, many peripheral and central physiologic factors are involved in pain processing and with peripheral and central sensitization (Figure 51-5). However, there are still many deficiencies in our knowledge regarding neurotransmitters, receptors, and the pathophysiology of pain and chronic pain states. Specific chronic pain states and syndromes are extensive and beyond the scope of this chapter.

In the presence of a chronic pain state, interdisciplinary treatment includes medicinal therapy in an attempt to improve analgesia and to enhance functional ability. Because the nature of nonmalignant chronic pain syndromes may be inflammatory, neuropathic, musculoskeletal, or idiopathic, or a combination thereof, a multimodal approach to medications may be needed as part of the treatment regimen. In addition to the acute pain analgesics previously presented, other common analgesics used for the treatment of chronic pain syndromes are discussed here.

Chronic Pain Analgesics and Adjuncts

Anticonvulsants

Anticonvulsants or antiepileptics are commonly used in certain neuropathic pain syndromes when treatment is refractory to traditional analgesics. First-generation anticonvulsants, such as carbamazepine and phenytoin, have been used for many years for neuropathic pain; however, more recently the second-generation anticonvulsants gabapentin (Neurontin) and pregabalin (Lyrica) are the most widely used. Anticonvulsants inhibit neuronal excitation and stabilize nerve membranes in an effort to decrease repetitive neural ectopic firing, which is common in neuropathic pain.

Gabapentin and pregabalin are used for the management of postherpetic neuralgia, diabetic neuropathy, trigeminal neuralgia, and other neuropathic pain and chronic pain syndromes. Their mechanism of action is similar, because it is believed that both block the alpha 2 delta (α2δ) subunit of the presynaptic voltage-gated calcium channels in the CNS, thereby preventing excitatory neurotransmitter release.[49] Pregabalin and gabapentin are structural analogs of GABA, which lack affinity to the GABA receptors. Both exhibit anticonvulsant, anxiolytic, and antihyperalgesic effects.[50] When compared with gabapentin, pregabalin displays a pharmacokinetic profile that requires less dosing with fewer side effects.[49-51]

Common side effects are dose dependent and include dizziness, somnolence, peripheral edema, and weight gain.[49] Currently, pregabalin and gabapentin are available in the oral form only. Because neither drug undergoes hepatic metabolism, drug-to-drug interactions are minimal. The unchanged form of the drug is excreted by the kidneys; therefore, patients with compromised renal function may require dose modifications.[51] Pregabalin and gabapentin use is not limited to chronic pain syndromes. They are also being effectively used in multimodal techniques for acute postoperative pain management, which resulted in lower reported pain scores and lower opioid consumption.[50,52,53] Lastly, patients presenting for surgery who are routinely taking anticonvulsants as part of a chronic pain syndrome treatment regimen should continue taking their medication throughout the perioperative period because this will optimize their pain management.

Antidepressants

Several antidepressants are being used for chronic pain syndromes. Similar to anticonvulsants, they are effective in the treatment of neuropathic pain syndromes. Common antidepressants include the tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and selective norepinephrine and serotonin reuptake inhibitors (SNRIs) (Table 51-5). In the presence of central sensitization, the descending inhibitory pathway, which uses inhibitory neurotransmitters (i.e., serotonin and norepinephrine), is altered. It is believed that antidepressants may exert their analgesic effects by blocking the reuptake of serotonin and norepinephrine in the CNS, thereby increasing their availability. They may also act at other sites via (1) blocking of sodium and calcium channels, (2) decreasing PGE_2 and TNF-α, (3) blocking NMDA receptors, and (4) enhancing opioid

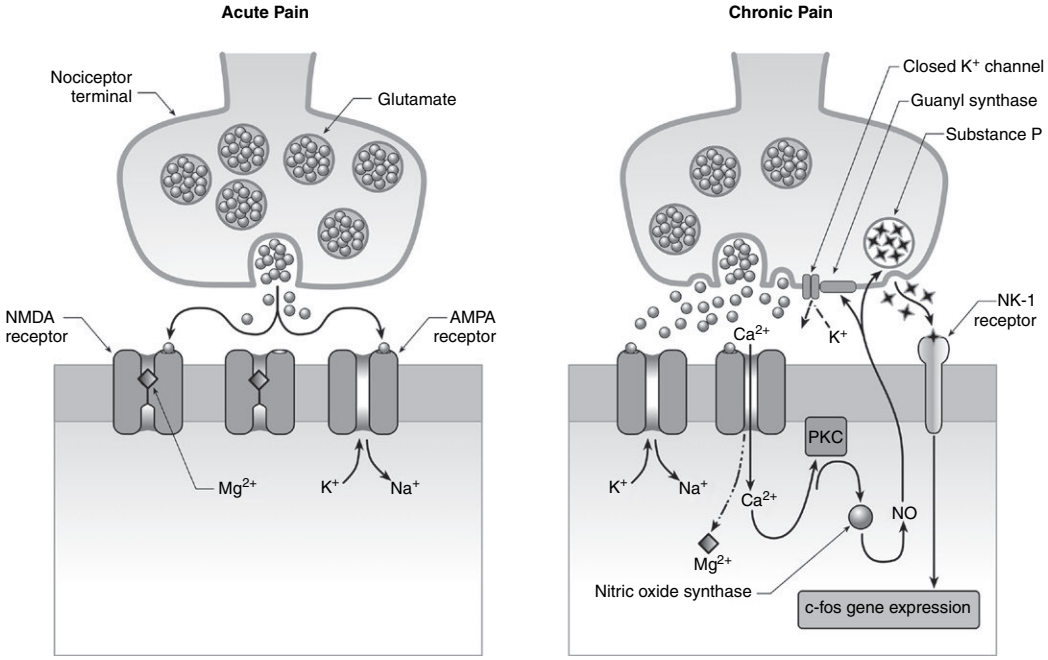

FIGURE **51-5** Comparison of acute and chronic pain. Acute pain signals trigger glutamate release, thereby activating AMP receptors and fluxing Na^+ and K^+. Typically in acute pain, the NMDA receptors remain blocked by the Mg^{2+} ion "plug." Hence, weak stimulation normally activates the AMPA receptors and not the NMDA receptors. With chronic pain, there is continuous stimulation that forces the Mg^{2+} plug out of the NMDA receptor. This allows a large amount of Ca^{2+} to flux into the cell where it reacts with second messengers (i.e., PKC and NO synthase) to produce NO. NO leaves the cell and reacts with guanyl synthase. Guanyl synthase closes the K^+ channel, which may contribute to opioid resistance. NO also stimulates the release of SP, which leads to gene expression changes, increased sensitization, and neural remodeling. *NMDA*, *N*-methyl-D-aspartate; *AMPA*, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; *PKC*, protein kinase; *NO*, nitric oxide; *NK-1*, neurokinin-1; *c-fos*, protein oncogene encoded by the FOS gene in humans.

TABLE 51-5 Common Antidepressants Used for Chronic Neuropathic Pain

Drug Class	Generic Name	Trade Name
TCAs	Amitriptyline	Elavil
	Nortriptyline	Pamelor
	Imipramine	Tofranil
SNRIs	Venlafaxine	Effexor
	Duloxetine	Cymbalta
	Milnacipran	Savella
SSRIs	Fluoxetine	Prozac
	Citalopram	Celexa

TCA, Tricyclic antidepressant; *SNRI*, selective serotonin-norepinephrine reuptake inhibitors; *SSRI*, selective serotonin reuptake inhibitors.

receptors, which may account for additional analgesic effects.[54] Analgesic dosage is much lower than the recommended antidepressive dose, and their analgesic effects may not occur until 4 to 10 days after initiating treatment.

TCAs (amitriptyline and nortriptyline) tend to have more side effects than the selective serotonin reuptake inhibitors (SSRIs) and selective serotonin-norepinephrine reuptake inhibitors (SNRIs) because they antagonize other receptors including muscarinic (e.g., dry mouth, blurred vision, and urinary retention), histaminergic (e.g., sedation, appetite stimulation with subsequent weight gain), and adrenergic (e.g., orthostatic hypotension, prolonged QT interval). They are contraindicated in patients with a history of a recent myocardial infarction, prolonged QT interval, cardiac dysrhythmias, or unstable congestive heart failure. Drug levels can be monitored to ensure unintentional overdose. The metabolism of all antidepressants is primarily hepatic. TCAs are commonly used for the treatment of postherpetic neuralgia, headaches, and fibromyalgia.

SNRIs (duloxetine, venlafaxine) are generally better tolerated than the TCAs because of the lack of affinity for the adrenergic, histaminergic, and cholinergic receptors. Therefore, they are preferred for those patients with cardiac disease. Both drugs (duloxetine and venlafaxine) have similar side effects: nausea, dry mouth, somnolence, headaches, and sexual dysfunction.[55] Likewise, the concomitant use of SNRIs with SSRIs or triptans is not recommended because this may precipitate a *serotonin syndrome*. Serotonin syndrome is an acute toxicity of serotonin manifesting as anxiety, agitation, delirium, seizures, hyperthermia, diaphoresis, tachycardia, hypertension or hypotension, hyperreflexia, myoclonus, and muscle rigidity. Symptoms vary from mild to life threatening, and diagnosis is based on patient medication history, physical examination, and exclusion of other neurologic disorders.[56,57]

SSRIs for the treatment of chronic pain are still under investigation because very few clinical trials have been done. They are primarily used for the treatment of depression, and their analgesic effects, thus far, are relatively weak.[58] Regardless of the type of antidepressant being taken for chronic pain, they should be continued throughout the perioperative period.

BOX 51-4

Systemic Effects of Steroids

Endocrine
- Adrenal-pituitary insufficiency
- Hypercortisolism
- Hyperglycemia
- Cushing's syndrome

Cardiovascular
- Hypertension
- CHF
- DVT
- Cardiomyopathy

Musculoskeletal
- Muscle weakness
- Osteopenia/osteoporosis
- Avascular necrosis of bone
- Pathologic fractures
- Truncal obesity

Dermatologic
- Skin thinning
- Alopecia
- Petechiae
- Facial flushing
- Striae
- Hirsutism

Renal
- Sodium and water retention

Gastrointestinal
- Peptic ulceration
- Gastritis
- Hyperacidity

Neurologic/Psychological
- Headache
- Vertigo
- Euphoria
- Restlessness
- Insomnia
- Mood swings
- Depression

Adapted from Baqai A, Bal R. The mechanism of action and side effects of epidural steroids. *Techniques Reg Anesth Pain Mgmt*. 2009;13(4):205-211.
CHF, Congestive heart failure; *DVT*, deep vein thrombosis.

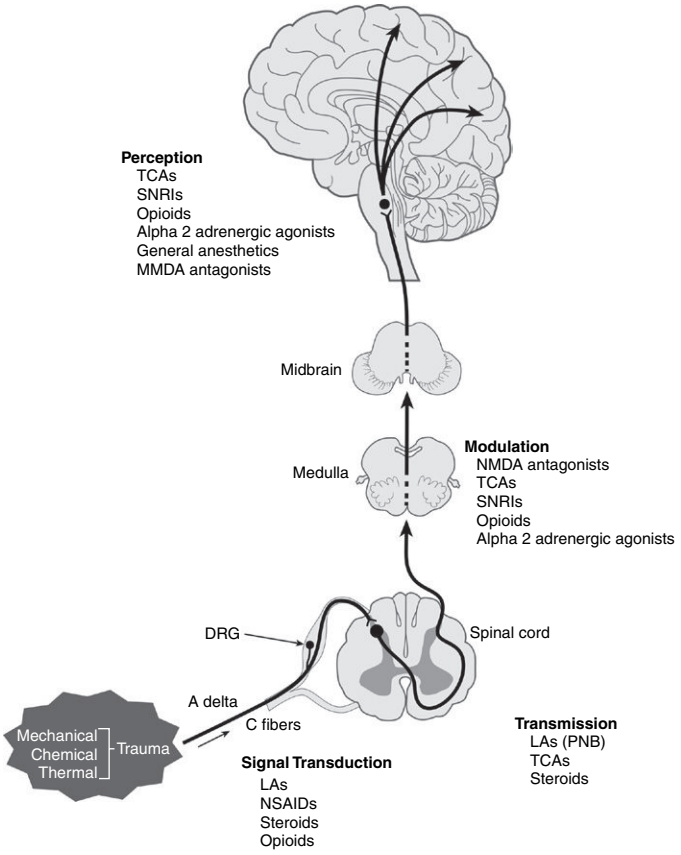

FIGURE **51-6** Pharmacotherapy and pain processing targets. The four processes of somatic nociceptive pain are signal transduction, transmission, modulation, and perception. Pharmacotherapy has an overall inhibitory effect on these processes. Modulation occurs primarily in the dorsal horn of the spinal cord, but also takes place in supraspinal structures. The endogenous descending inhibitory modulating pathway is also involved in pain inhibition, and it is not present in this illustration. *TCA*, Tricyclic antidepressant; *SNRI*, selective serotonin-norepinephrine reuptake inhibitor; *NMDA*, *N*-methyl-D-aspartate antagonist; *NSAIDs*, nonsteroidal antiinflammatory drugs; *LA*, local anesthetic; *PNB*, peripheral nerve block.

Corticosteroids

Exogenous corticosteroids (glucocorticoids) are administered in a variety of routes (e.g., orally, intravenously, epidurally, caudally, and via intraarticular) as adjunct analgesics for multiple types of acute onset and chronic pain syndromes. They exert multiple effects on the body including autoimmune, antiinflammatory, antiedema, and antiallergic. Typical disease processes and pain syndromes that are treated with corticosteroids include rheumatoid arthritis, osteoarthritis, herpetic neuralgia, chronic low back pain, and chronic neck pain. In the treatment of acute and chronic pain syndromes, corticosteroids exert their effects in several ways. They are primarily known for their antiinflammatory effect because they prevent the release of arachidonic acid by inhibiting phospholipase A2 on cell membranes. Through this mechanism, they decrease inflammatory cytokines (Il-6, IL-1, TNF-α) and prostaglandins. When corticosteroids are injected epidurally, it is also purported that corticosteroids exhibit nociceptive properties by blocking C fiber transmission. In addition, they suppress ectopic firing of nociceptors in the presence of nerve injury, which produces a direct membrane-stabilizing effect.[59]

Side effects of corticosteroids are reflective of supraphysiologic doses that usually exceed the rate of endogenous steroid production, which is approximately 20 mg per day of hydrocortisone or its equivalent.[59] Many organ systems can be affected with long-term steroid use (Box 51-4). These effects are variable among patients and are dependent upon the degree of hypothalamic-pituitary-adrenal axis (HPA) suppression, which is attributed to the type of steroid, duration of use, frequency of ingestion, route of administration, and dosage. However, when corticosteroids are administered as an intermittent injection (e.g., epidural, intraarticular, caudal) versus chronic daily use, side effects are usually mild and transient. It has been purported by Kay et al.[60] that weekly epidural steroid injections given over 3 weeks caused dramatic HPA suppression with normal cortisol levels returning within 1 month. Similarly, it has been found that a single epidural steroid injection can cause HPA suppression from 4 to 5 days of injection and lasting up to 5 weeks.[61] Currently, there is no consensus among pain management specialists on the dosing, frequency, or total number of repeated steroid injections. Regardless, in the event of a major surgical procedure after the recent administration of an epidural steroid, it may be prudent to administer a dose of exogenous steroid (Figure 51-6).

Methadone

Methadone is a synthetic opioid historically used for the treatment of opioid addiction in detoxification or treatment programs. Recently its use is increasing for the treatment of severe acute pain as well as for chronic cancer and noncancer pain management. Structurally, methadone is a racemic mixture of two enantiomers, d-isomer (S-methadone) and l-isomer (R-methadone). The d-isomer (S-methadone) is responsible for antagonizing the NMDA receptor and inhibiting serotonin and norepinephrine uptake, which possibly contributes to its benefits in the

treatment of neuropathic pain, along with the prevention of opioid tolerance and hyperalgesia.[62] The l-isomer (R-methadone) is responsible for binding to opioid receptors, thereby owing to its analgesic effects.

Methadone is a viable option for chronic pain patients who have tolerance (intolerable side effects or inadequate analgesia) to current opioids. It can be administered orally, intravenously, rectally, and subcutaneously. Due to its high degree of lipid solubility, it is well absorbed via the gastric mucosa with peak analgesic effects in 30 to 60 minutes. When given intravenously, the drug has peak effects that are seen in 15 to 20 minutes. Unlike other opioids, methadone has a long half-life of approximately 15 to 60 hours. This long half-life is ideal for maintenance programs, thereby preventing withdrawal symptoms. However, when methadone is administered for chronic pain states, it is difficult to initiate, to titrate, and to convert from another opioid, which makes dosing a challenge.[63]

Metabolism of methadone is primarily via the CYP450 enzyme, specifically CYP3A4 and CYP2B6, into inactive metabolites that are excreted in the urine.[64] Therefore, any medications that inhibit (e.g., phenytoin, carbamazepine) or induce CYP450 may dramatically alter methadone metabolism.[65]

Side effects of methadone are similar to other opioids including respiratory depression and excessive sedation; respiratory depression peak effects occur later than the analgesic peak effects. A unique side effect of methadone includes QT interval prolongation, which could lead to potentially lethal ventricular tachyarrhythmias and torsades des pointes. Patients taking methadone on a continuous basis should be carefully monitored with a cardiac evaluation. An electrocardiogram should be obtained pretreatment, after 30 days of initiating methadone, and annually thereafter. An additional electrocardiogram is recommended when methadone dosage exceeds 100 mg per day. A QT interval that exceeds 500 ms is deemed a risk factor for lethal arrhythmias, and discontinuation of methadone or a dose reduction is advisable.[66]

Due to methadone's long half-life, its use in acute pain management is limited but effective. Gottschalk et al.[67] reported improved postoperative pain control for patients undergoing complex spine surgery after a single dose of methadone injected prior to surgical incision as compared with a continuous sufentanil infusion. Those who received the preincisional methadone injection had a significant reduction in opioid requirements 48 to 72 hours after surgery.[67] In the event that methadone is chosen as an analgesic for perioperative pain management, an electrocardiogram is warranted preoperatively with identification of those at risk for prolonged QT interval. These risk factors include the concomitant use of antiarrhythmic agents, some TCAs and calcium channel blockers, the presence of hypokalemia, and a history of prolonged QT interval. Furthermore, chronic pain patients are often taking a combination of medications such as benzodiazepines and other CNS depressants, which poses an added risk for respiratory depression and sedation.[65]

Methadone's lack of active metabolites, long half-life, and low cost make it desirable for chronic nonmalignant pain management. Nonetheless, prolonged use of methadone and other opioids for the treatment of chronic pain are associated with the risks of dependence, tolerance, addiction, and in rare instances, misuse.

Dependence can be either physiologic or psychological in nature. Physiologic dependence is a pharmacologic property of opioid drugs defined by the manifestation of a "withdrawal syndrome" after abrupt discontinuation of the opioid, or after the administration of an opioid antagonist (naloxone) or a mixed agonist-antagonist. Because opioids inhibit cAMP, any abrupt discontinuation of the opioid can cause a rebound disinhibition of cAMP and subsequent withdrawal symptoms. Withdrawal symptoms include autonomic nervous system responses such as increased irritability, restlessness, tremors, chills, muscle cramps, sweating, mydriasis, abdominal pain, diarrhea, and tachycardia.[68] Physiologic dependence should always be assumed to exist after repeated administration of an opioid for more than a few days.[69,70] To prevent opioid withdrawal syndrome, opioids should always be tapered before being discontinued, and daily scheduled opioids should be continued perioperatively.

Psychological dependence is characterized by the craving for an opioid drug to achieve a psychological effect, resulting in the continual use of the drug despite harm to self or others. Psychological dependence is inappropriately referred to as "addiction." Psychological dependence is more accurately described as a component of addiction and is defined by the American Academy of Pain Medicine, the American Pain Society, and the American Society of Addiction Medicine as a "primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving."[71] Iatrogenically induced psychological dependence or addiction of opioids is rare when they are taken for medicinal reasons.[72]

Pseudoaddiction is often confused with psychological dependence because the behavior of the patients can be the same. That is, patients with both of these conditions exhibit what appears to be drug-seeking behavior. However, in the patient who is pseudoaddicted, the origin of the behavior is inadequate analgesia. When these patients receive adequate analgesia, they no longer demonstrate drug-seeking behavior.

Tolerance refers to a change in the dose-response relationship induced by repeated exposure to the drug and manifested as a need for a higher dose to maintain an analgesic effect. Tolerance may be the result of several mechanisms, such as enzyme induction due to continued opioid administration or down-regulation of opioid receptors.[73] Other mechanisms involved with tolerance continue to be debatable and include changes in drug-receptor interactions, cellular alterations, as well as long-term adaptations in gene expression.[74,75] The development of tolerance to an opioid is a normal physiologic response. When tolerance to an opioid occurs, opioid rotation is suggested. Opioid rotation involves switching from one opioid to another in an effort to improve analgesia and decrease side effects.

Opioid-induced hyperalgesia (OIH) is a phenomenon that occurs with chronic opioid therapy, which attributes worsening pain to high, escalating doses of opioids. Complaints of pain in locations different from the original pain area, whole-body hyperesthesia, allodynia, agitation, multifocal myoclonus jerks, and seizures are manifestations of OIH.[76] OIH is often improved with reducing or discontinuing the opioid. The exact mechanism of action of OIH is not fully understood. However, there are many proposed theories. For instance, central activation of NMDA receptors via glutamate may play a role in OIH, as well as a shifting of the pain modulation system from a descending inhibitory pathway to a facilitating pronociceptive pathway.[77,78] It also has been suggested that prostaglandins stimulate glutamate release, which may contribute to the development of OIH.[79] Diagnosing OIH is difficult because it resembles opioid tolerance. Once diagnosed, treatment strategies consist of weaning the patient from high-dose opioids and starting non-opioid analgesics (e.g., NMDA receptor antagonists, NSAIDs, COX-2 inhibitors).[76,78]

Chronic Opioid Therapy and Perioperative Pain Management

Chronic opioid therapy (COT) for the treatment of chronic nonmalignant pain is escalating in the United States. It is inevitable that COT patients, along with patients who are on drug maintenance programs for opioid addiction, will require elective or emergent surgery. This patient population presents many challenges for the anesthesia provider in regard to perioperative analgesia. A recent observational study found that patients using COT are at risk for higher than normal levels of postoperative pain and slower pain resolution than those not on COT for chronic pain or without preexisting chronic pain.[80] Thus it is imperative to collaborate with the patient and the surgical team to develop a unique and realistic perioperative pain management plan. As with treating patients in acute pain, a multimodal approach to pain management should be implemented.

Preoperative

Preoperatively, preferably prior to the day of the surgical procedure, an investigation regarding the types of medications, dosages, and duration of therapy is helpful in determining the extent and severity of the chronic pain syndrome. Inquiries specific to preoperative pain and the patient's chronic pain state should be addressed; these are shown in Box 51-3. If the patient is on an opioid maintenance program for addiction, methadone dosage should be verified by the prescribing physician/clinic. Chronic opiate therapy, including methadone, should be continued throughout the perioperative period because this will provide uninterrupted dosing for the patient's baseline opioid requirement and avoid withdrawal. If the patient has not taken his/her daily scheduled opioid, an equivalent dose of opioid should be administered preoperatively. In the event the patient has a transdermal fentanyl patch, it should remain on throughout the perioperative period unless a collaborative decision has been made based on the invasiveness of the surgical procedure to remove it. If the patch is removed, a continuous IV infusion of fentanyl should be initiated and maintained perioperatively. Alternatively, equipotent morphine also can be administered. Likewise, if a patient has an implanted intrathecal or epidural opioid infusion system, it should continue perioperatively.[81] Other medications taken for chronic pain (e.g., antidepressants, anticonvulsants, α_2 agonists) should be continued on the day of surgery.

The preoperative assessment is the ideal setting in which to establish a positive rapport with the patient, especially in the presence of a chronic pain state or a maintenance program. Chronic opiate therapy patients can be highly anxious, fearful, or depressed, and reassurance that their pain will be aggressively treated is paramount. Furthermore, realistic expectations regarding pain control should be discussed. Administering a benzodiazepine, along with initiating multimodal analgesia with adjuvant analgesics, is optimal and should be started within 1 to 2 hours prior to surgery.[82] This is also the time to discuss options for regional anesthesia/analgesia techniques. These techniques would be of great benefit for intraoperative and postoperative analgesia in the COT patient.

Intraoperative

There are no data supporting a specific opioid for pain control intraoperatively for COT patients, nor have any specific dosing guidelines been established. The specific opioid selected is an anesthesia provider preference with patient coexisting diseases and surgical procedure dictating one versus another. The intraoperative opioid selected should provide adequate baseline opioid requirements as well as render intraoperative and postoperative analgesia. Intraoperative opioids may need to be increased 30% to 100% as compared with the opioid-naïve patient because of receptor down-regulation and/or tolerance. Titration of opioids to heart rate and blood pressure response, in addition to pupil size, may be useful for estimating adequate analgesia with general anesthesia. Respiratory rate and depth also may be monitored in the spontaneously breathing awake or anesthetized patient to estimate adequate analgesia. In the event that a specific opioid is not efficacious, opioid rotation is recommended.[83] Cross tolerance among opioids may be incomplete. Hence, a specific opioid will not produce a similar degree of tolerance as a different opioid within the same class. Opioid antagonists and agonist-antagonists should be avoided because these will precipitate an acute withdrawal syndrome.

Nonopioid analgesic adjuncts (ketamine, clonidine, and dexmedetomidine) also should be a part of the multimodal approach to perioperative pain management. These will aid with analgesia and produce opioid-sparing effects. In a recent randomized control study, COT patients with chronic back pain undergoing back surgery were administered ketamine 0.5 mg/kg IV on induction. A continuous ketamine infusion of 10 mcg/kg/min was initiated after induction and discontinued upon wound closure. Unlike the placebo group who received saline, the COT group required less morphine 48 hours postoperatively.[84]

Lastly, it is recommended that regional anesthesia with local anesthetics and opioids be a part of the anesthetic plan whenever possible in COT patients; this will reduce opioid requirements and provide analgesia. If regional anesthesia is used, intrathecal, and/or epidural opioid administration is not adequate for baseline opioid therapy. Equipotent IV opioids should be given as the baseline therapy for the prevention of withdrawal.[85] Another option for perioperative analgesia includes peripheral nerve blocks with a continuous catheter infusion of local anesthetic.

Postoperative

If the patient is not a candidate for regional anesthesia/CPNB or did not benefit from it, then intravenous PCA should be considered. Setting appropriate parameters for the PCA in the COT patient can be very challenging. A basal continuous infusion is suggested to replace the daily dose of opioid with demand doses varying among individuals.[56,86] When COT patients are able to resume oral intake, dosing is variable among individuals with gradual weaning to their presurgical therapy regimen. Consultation with a pain specialist regarding PCA dosing and opioid conversion for various routes of administration for COT patients is highly recommended. Other recommendations for perioperative pain management for the patient on COT are found in Table 51-6.

SUMMARY

Pain physiology and treatment are continuously being researched. It is essential that nurse anesthetists are knowledgeable and current with the advances in pain assessment, management, and treatment modalities. CRNAs are in a unique position to initiate and participate in the treatment of pain across the life span and for a variety of disease states in a holistic manner. Including patients in their pain treatment plan empowers them to adhere to treatment modalities and to manage their own pain. As educators, CRNAs have the opportunity to share their knowledge regarding effective pain management in an effort to improve the health and well-being of patients.

TABLE 51-6 Recommendations for Perioperative Management of the Chronic Opioid Therapy Patient

Preoperative	Intraoperative	Postoperative
Pain assessment	Continue baseline opioid (oral, transdermal, IV, intrathecal pump)	Multimodal analgesic techniques
Precise opioid use (dose/type)—continue DOS	Increases in intraoperative opioids due to tolerance—titrate or continuous infusion	Maintain baseline opioid
Adjuvant medications for CP—continue DOS	Consider opioid rotation	Titrate opioids aggressively to achieve adequate pain control
Reassurance and address fears/anxiety	Multimodal approach	PCA—primary or supplementary for epidural/regional
Multi-modal pain plan—consider NSAIDs, acetaminophen, 1-2 hrs prior to surgery, anxiolytics	Consider regional, LA wound infiltration, PNB, CPNB, epidural/SAB	Continue applicable regional techniques
Consult with addiction specialist/clinic if indicated—continue methadone maintenance	Consider adjuvants—ketorolac, ketamine, clonidine, dexmedetomidine	Continue ketamine or low-dose ketamine infusion, if started in the OR
Plan for postoperative analgesia	Anticipate increases in inhalation agent	Monitor for respiratory depression
	Avoid opioid antagonists and mixed agonists	Continued assessment of analgesia
		Implement nontraditional comfort measures

CP, Chronic pain; *DOS*, day of surgery; *PCA*, patient-controlled analgesia; *LA*, local anesthetic; *PNB*, peripheral nerve block; *CPNB*, continuous peripheral nerve block; *SAB*, subarachnoid blockade; *IV*, intravenous; *NSAIDs*, nonsteroidal antiinflammatory drugs.

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52 CHAPTER Anesthesia for Therapeutic and Diagnostic Procedures

◆ *Adree N. Williams*

Considering the evolving patient population and dynamic needs of a healthcare system under redesign, it should come as no surprise that the world of anesthesia, including the setting, is also under reconstruction. Although most anesthetics were traditionally administered in the operating room, it is no longer unusual for services to be provided outside the operating suite in a variety of locations that are far from the traditional setting. Estimates today indicate that up to 55% of the procedures that require anesthesia services are taking place outside the conventional operating room.[1] These include diagnostic, interventional, and traditional surgery involving cardiology, vascular, emergency department, gastroenterology, gynecology, hematology, oncology, thoracic, neurologic and neurosurgical, plastic, ophthalmology, orthopedic, psychiatric, radiologic, and other diagnostic and dental procedures.[2] Patients treated in these new settings deserve the same safe, vigilant attention, anesthetic administration, and recovery care as those patients treated in the operating suite. The key for the anesthesia provider is to make sure the therapeutic and diagnostic environment where anesthesia is to be performed is as familiar, as well equipped, and as safe as it is in the operating room.

Although certain therapeutic and diagnostic procedures are sometimes performed without anesthesia, the patient's condition or the requirements of the test or procedure may necessitate administration of an anesthetic. Anesthesia could range from local anesthetic infiltration and regional anesthesia techniques to monitored anesthesia care involving enteral minimal sedation, parenteral moderate sedation/analgesia, deep sedation/analgesia, or general anesthesia. Patients can range in age from pediatric to geriatric. In remote locations, patients who require anesthesia could be confused or disoriented, uncooperative, unwilling or unable to understand the requirements of the procedure, claustrophobic, anxious, or mentally disabled. As medical technology rapidly progresses, more patients will be seen outside the operating room for therapeutic and diagnostic procedures. Older and medically higher-risk patients are being treated more often in this environment.[1,3-5] Of the patients treated in these settings, 20% are over the age of 70 and 69% have ASA classifications of 3 to 5.[1,3,4] The therapeutic or diagnostic procedure might require the patient to lie still for an extended length of time or cause moments of painful, visual, and audio stimulation alternating with long periods of no stimulation, which makes anesthesia delivery challenging for the anesthetist. Some reasons why these procedures present a special challenge to the anesthesia team are noted in Box 52-1.

Given the rapid advances in medical knowledge and technology, coupled with a strong societal impetus to reduce healthcare costs, more therapeutic and diagnostic procedures will be performed in remote locations.[1,3]

ADMINISTRATION OF ANESTHESIA IN REMOTE LOCATIONS

Special Considerations

The operating room provides an ideal environment for the administration of anesthesia and the performance of surgical procedures because of its familiarity for medical staff and the rapid availability of needed anesthesia equipment, medications, supplies, and well-trained adjunct personnel. The anesthesia setting in a remote location must possess the same level of safety and high standards. Many considerations and plans must be made before a patient can safely receive anesthesia for a therapeutic or diagnostic procedure in a remote location. Box 52-2 provides a comprehensive checklist of the requisites that will facilitate planning and gathering needed equipment, supplies, and medications.

A policy must be developed that outlines the organization of emergency services for either in-hospital or office-based facilities. Office-based facilities should have a plan for regular emergency training of personnel, interoffice communication during an emergency, communication with emergency medical personnel, and transportation to the nearest hospital emergency department.

An anesthesia machine and portable anesthesia cart with the listed equipment, supplies, and medications should be dedicated strictly for use in remote locations. This can save preparation time whenever a procedure is required in a remote location. It also increases patient safety and decreases the risk of a mishap resulting from lack of necessary equipment and materials.

As part of the planning process before patient treatment, it is important to familiarize oneself with the personnel and the work area in the remote environment. The workplace allotted for anesthesia care may be small, crowded, and different from the usual operating room setting. Pre-planning is important to make this *different* location *familiar* to the anesthetist and safe for the patient to receive the anesthetic and therapeutic or diagnostic procedure. No remote location should ever limit the ability to manage these anesthetic procedures or prevent equipment, medications, supplies, positive-pressure ventilation, resuscitation, and suction from being readily available.

The Anesthesia Patient Safety Foundation is a good resource for seeking information regarding new anesthesia-related developments, new anesthesia products, and discussion of safety issues.

The American Association of Nurse Anesthetists (AANA),[6] the American Society of Anesthesiologists (ASA),[7,8] and The Joint Commission[9-13] have established written standards and professional commentary to provide for the basic rights and safety of patients, along with the safety of anesthesia providers and ancillary personnel. As technology advances, these standards are adapted and new recommendations are made.

Licensed registered nurses who are not qualified anesthesia providers have become involved in the monitoring of patients and the administration of medications for procedural sedations involving therapeutic and diagnostic procedures, as well as for certain surgical procedures.

The AANA and the ASA separately and together have issued statements in regard to criteria (Box 52-3) that must be met by non-anesthesia providers to protect the safety and well-being of the patient.[14,15]

BOX **52-1**

Unique Challenges of Anesthesia Administration Outside Operating Rooms

- Working with individuals who do not understand the nuances of anesthetic management and may not appreciate the fine line between a stable and uneventful case and a potentially dangerous or lethal one
- Less efficient or effective scheduling, resulting in inefficient or hurried patient preparation
- Equipment that is less well maintained than in the operating room
- Greater variation in physical set-ups and anesthesia and monitoring equipment, resulting in the clinician's decreased familiarity with the environment and the equipment
- Greater variability in the time needed to obtain patient records, which can cause delays in collecting adequate information about patient history and the procedures to be performed
- Inadequate monitoring of stock items, which therefore may be missing or in short supply
- Nursing and support personnel who do not follow rigorous preprocedure check-in processes
- Working with individuals whom the anesthesia provider has not met before or does not know well
- Being positioned away from the patient or in a different room for long periods during the procedure
- Being at a distance from the core areas where anesthesia personnel congregate, so less local support is available when problems arise, there are fewer opportunities to discuss questions or concerns, and there are fewer opportunities to collaborate if problems appear

Modified from Frankel A. Patient safety: anesthesia in remote locations. *Anesthesiol Clin*. 2009;27(1):127-139.

Standards for the Delivery of Anesthesia in a Remote Location

A. Perform a complete preanesthesia assessment.

The patient, parent(s), or legal guardian(s) must be thoroughly and unhurriedly interviewed before the performance of an anesthetic procedure. The preanesthesia assessment should be performed in consideration of the patient's right to privacy and confidentiality and which safeguards their dignity and respects aspects of their psychological, cultural, and spiritual values. During this assessment, information is obtained regarding the patient's medical history (prior allergy must be assessed), anesthesia history (noting any prior complications and responses to prior anesthetic experiences), surgical history, and medication history (including tobacco, alcohol, and any substance abuse). A complete physical assessment of the patient is made, along with inspection of the head, neck, mouth, and airway. The anesthetist's head and neck assessment can be especially beneficial to the patient's well-being, because common oral conditions and suspicious head/neck, skin, and oral pathologic lesions can be detected and referred for further evaluation by a dentist or a physician. Early referral for diagnosis and treatment of any disease contributes to patient cure and recovery to wellness, as well as reduced morbidity and mortality.[16] Lung and heart sounds are auscultated. Review is made of objective diagnostic data such as patient laboratory values, radiographs, and electrocardiogram (ECG). Important findings are noted in the patient's anesthesia record. A physical status classification is then assigned the patient.

Box 52-4 outlines specific patient conditions that alert the anesthetist to a need for special attention and care for anesthetics provided for therapeutic and diagnostic procedures.

B. Obtain informed consent for the planned anesthetic intervention from the patient or legal guardian.

The anesthesia provider should discuss the course of the anesthetic care and enumerate the following in understandable terms appropriate for the patient or guardian:

- How the anesthetic procedure will be performed
- Possible risks of the anesthetic procedure
- Pertinent possible reactions or complications the patient might expect while receiving a typical anesthetic, along with informing the patient or guardian that the anesthetist has permission to make changes or adjustments as deemed necessary in his or her professional judgment
- Possible options to the type of anesthetic to be received by the patient
- The ability for the patient/parent(s)/guardian(s) to have any concerns addressed and questions answered

At times, anesthesia for therapeutic and diagnostic procedures will require only minimal, moderate, or deep sedation, which by definition may not include patient amnesia. Only general anesthesia ensures amnesia as a standard of care. Therefore, discussion of what the patient can reasonably expect should take place at this time.[17,18] It is far easier to discuss these points with the patient before the anesthetic procedure than to explain these points after the fact.

C. Formulate a patient-specific plan for anesthesia care.

The art and science of anesthesia mandate that the safest and least invasive anesthetic technique be administered to the patient to simplify delivery of the anesthetic and to avoid complications for the patient while in the remote location.

D. Implement and adjust the anesthesia care plan based on the patient's physiologic response.

Immediately before implementation of anesthesia, reassess the patient (e.g., vital signs, airway status, and response to preprocedure medications given), and document a reassessment note in the anesthesia record. The Joint Commission defines "immediately" as the moments just before the sedation is administered. Also, make sure all anesthesia equipment, supplies, and medications are checked and immediately available in case the patient needs a change in the anesthetic plan.

E. Properly prepare, dispense, and label all medications to be used for the patient.

All medications drawn up prior to the case must be labeled with the drug name, strength (concentration), amount (if not apparent from the container), and expiration date (if not used within 24 hours). Medications drawn up and used immediately for the procedure do not require labeling.

F. Adhere to appropriate safety precautions, as established with the institution, to minimize the risks of fire, explosion, electrical shock, and equipment malfunction.

This standard is important for the patient, the anesthesia provider, and ancillary personnel for the prevention of accidents and injury. It is also important from a medicolegal standpoint. The anesthesia provider should also be an integral part of the team involved with protocols for preventing wrong site, wrong procedure, and wrong person surgery, also known as the *Universal Protocol* established by The Joint Commission.[19-23] Safety must be a consideration for scheduling obligations of anesthesia personnel because anesthesia for therapeutic and diagnostic procedures is often more involved and complex when compared with anesthesia delivered in the operating room.

G. Monitor and document the patient's physiologic condition as appropriate for the type of anesthesia and specific patient needs.[6,7]

BOX **52-2**

Requisites for Administration of Anesthesia in Remote Locations

Utilities

- Adequate workspace
- Adequate overhead lighting
- Adequate number of and current-carrying capacity of electrical outlets
- Electrical service with either isolated electric power or ground fault circuit interrupters
- Uncluttered floor space
- Two-way communication devices—telephone, intercom, Internet availability (instant messaging), personal digital assistant (PDA) device, two-way radios. Consider devices with power independent of the electrical service.
- Backup power
- Suitable area for postprocedure recovery (All building codes, fire codes, safety codes, and facility standards must be met.)

Equipment

- Local infiltration, intravenous sedation, regional and general anesthesia
- Patient chair, cart, or operating surface that can be quickly placed into Trendelenburg position
- Regularly serviced and functioning equipment
- Patient monitors
- Pulse oximeter
- Electrocardiograph
- Blood pressure monitor with a selection of adequate-sized cuffs
- Capnograph
- Anesthesia awareness/level of consciousness/anesthesia-depth monitor
- Body temperature monitor
- Oxygen supplies
- Minimum of two oxygen sources must be available with regulators attached (compressed oxygen should be the equivalent of an E cylinder)
- Positive-pressure ventilation sources, including a self-inflating resuscitator bag capable of delivering at least 90% oxygen and a mouth-to-mask unit
- Defibrillator—manual biphasic or automatic external defibrillator (AED) (charged, ready, and easily accessible)
- Suction source or a suction machine (electric-powered suction, battery-powered suction, or foot pump suction devices are available), tubing, suction catheters, and Yankauer suctions
- Lockable anesthesia cart to permit organization of supplies, including endotracheal equipment, laryngeal mask airways, dental laryngeal mask airways, tube of water-soluble lubricating jelly, Combitubes, an assortment of various-sized disposable facemasks, nasal cannulas, Connell airways, disposable facemasks with oxygen tubing, oral and nasal airways, syringes (1-mL tuberculin syringe, 3 mL, 5 mL, 10 mL, 20 mL, 60 mL), needles, intravenous catheters, tourniquet, intravenous fluids and tubing, alcohol pads, adhesive tape, sterile intravenous site covers, disposable gloves, stethoscopes, precordial stethoscope with monaural earpiece and extension tubing, precordial stethoscope adhesive disks, and appropriate anesthetic medications
- Battery-powered flashlight for the illumination of the patient, the anesthesia machines, and the monitors along with spare batteries
- Syringe pump, wall plug/transformer, and spare batteries
- Warm blankets, electric blanket (check with hospital policy before using an electric blanket), or forced-air warming devices with the appropriate blanket; towels, or hat to cover the patient's head to preserve body warmth
- Blankets, towels, or foam for padding for protection of skin integrity, bony prominences, and body extremities
- Emergency medications to include, at a minimum: adenosine, aminophylline, amiodarone, atropine, dextrose 50%, diphenhydramine, ephedrine, epinephrine, flumazenil, hydrocortisone, lidocaine, naloxone, nitroglycerin, phenylephrine, succinylcholine, verapamil, and a bronchial dilator inhaler such as albuterol or nebulized epinephrine (such as Primatene mist)
- Preoperative anesthesia evaluation forms
- Anesthesia consent form
- Anesthesia charts, clipboard, black ink pens, indelible ink pens

Additional Requirements for General Anesthesia

- Oxygen fail-safe system
- Oxygen analyzer
- Waste gas exhaust scavenging system
- End-tidal carbon dioxide ($ETCO_2$) analyzer, extra $ETCO_2$ filter, and extension sample tubing
- Vaporizers—calibration and exclusion system
- Respiratory monitoring apparatus (for the anesthesia circuit reservoir bag)
- Alarm system
- Anesthetic medications (Note that some anesthetic medications must be kept refrigerated until ready for use. To have fresh and active medications, check with the drug manufacturer's package insert or the bottle label.)
- In addition to the emergency medications listed above, consider the following:
  - Premedication drugs—midazolam, pentobarbital, ketamine, nitrous oxide, diazepam, chloral hydrate
  - Induction drugs—propofol, etomidate, ketamine
  - Maintenance drugs—bottles of sevoflurane, isoflurane, desflurane, propofol, ketamine, dexmedetomidine
  - Narcotics—midazolam, diazepam, fentanyl, alfentanil, sufentanil, remifentanil
  - Muscle relaxants—succinylcholine, rocuronium, cisatracurium, atracurium, vecuronium
  - Muscle relaxant reversal agents—edrophonium, neostigmine, atropine, glycopyrrolate
  - Cardiovascular drugs—labetalol, esmolol, verapamil, hydralazine
  - Narcotic reversal drugs—naloxone
  - Antiemetic drugs—ondansetron, dolasetron, granisetron, metoclopramide, droperidol*
- Emergency cart and equipment
- Basic airway equipment (adult and pediatric)
- Nasal and oral airways
  - Facemask (appropriate for patient)
  - Laryngoscope handle assortment with spare batteries
  - Assortment of laryngoscope blades and spare light bulbs, endotracheal tubes (adult and pediatric), laryngeal mask airways (LMAs), and dental LMAs
- Combitube
- Self-inflating resuscitator bag (Ambu bag)
- Difficult airway equipment
- Laryngeal mask airway
- Light wand
- Emergency cricothyrotomy kit
- Defibrillator—manual biphasic defibrillator or automatic external defibrillator (AED)
- Supplemental oxygen and nitrous oxide tanks with attached and functional regulators; allow for safe transportation and storage of tanks

BOX 52-2–cont'd

Requisites for Administration of Anesthesia in Remote Locations

- Emergency medications
- Cardiopulmonary resuscitation (CPR) compression board
- Suction equipment (suction catheter, Yankauer type)
- Malignant hyperthermia emergency drugs, equipment, and the phone number for the Malignant Hyperthermia Association of the United States (MHAUS) for live help during the treatment of malignant hyperthermia on-site (United States and Canada: 1-800-MH HYPER or 1-800-644-9737. Outside the United States and Canada: 001-1-315-464-7079). More information is available at the Malignant Hyperthermia Association of the United States website at: http://www.mhaus.org.

*Be aware of droperidol use in patients with prolonged QT syndrome.

BOX 52-3

Criteria for the Management and Monitoring of Patients Undergoing Sedation Delivered for Therapeutic or Diagnostic Procedures by Non-Anesthesia Providers

- Guidelines for patient monitoring, drug administration, and protocols are available for dealing with potential complications or emergency situations, developed in accordance with accepted standards of anesthesia practice.
- A qualified anesthesia provider or attending physician selects and orders the agents to achieve sedation and analgesia.
- Registered nurses who are not qualified anesthesia providers should not administer agents classified as anesthetics, including but not limited to ketamine, propofol, etomidate, nitrous oxide, and muscle relaxants. (A computer-assisted personalized sedation device [CAPS] is being developed to enable a non-qualified anesthesia provider [physician-nurse team] to safely and effectively administer propofol for colonoscopy or esophagogastroduodenoscopy [EGD] procedures.)
- The registered nurse managing and monitoring the patient receiving an analgesia sedation shall have no other responsibilities during the procedure.
- Venous access shall be maintained for all patients having sedation and analgesia.
- Supplemental oxygen shall be available for any patient receiving sedation and analgesia and, when appropriate, in the postprocedure period.
- Documentation and monitoring of physiologic measurements including but not limited to blood pressure, respiratory rate, oxygen saturation, cardiac rate and rhythm, and level of consciousness should be recorded at least every 5 minutes.
- An emergency cart must be immediately accessible to every location where analgesia sedation is administered. This cart must include emergency resuscitative drugs, airway and ventilatory adjunct equipment, defibrillator, and a source for administration of 100% oxygen. A positive-pressure breathing device, oxygen, suction, and appropriate airways must be placed in each room where analgesia sedation is administered.
- Back-up personnel who are experts in airway management, emergency intubations, and advanced cardiopulmonary resuscitation must be available.
- A qualified professional capable of managing complications is present in the facility and remains in the facility until the patient is stable.
- A qualified professional authorized under institutional guidelines to discharge the patient remains in the facility to discharge the patient in accordance with established criteria of the facility.

- *Monitor ventilation continuously*. Ventilation may be monitored in the patient undergoing mild, moderate, or deep sedation with a precordial stethoscope or by direct auscultation of the patient's ventilatory effort. Verify intubation of the trachea by auscultation, chest excursion, and confirmation of carbon dioxide in the expired gas. In cases of moderate or deep sedation, the ASA has set forth new guidelines mandating the measurement of end-tidal carbon dioxide unless the patient, procedure, or equipment interfere or preclude monitoring. Continuously monitor end-tidal carbon dioxide ($ETCO_2$) during controlled, assisted, or spontaneous ventilation, including any anesthesia or sedation technique requiring artificial airway support. Use spirometry and ventilatory pressure monitors as indicated.[13]
- *Monitor oxygenation continuously* by clinical observation, pulse oximetry, cerebral oximetry, and, if indicated, arterial blood gas analysis.
- *Monitor cardiovascular status continuously* via electrocardiography and heart sounds. Record blood pressure and heart rate at least every 5 minutes.
- *Consider the use of a monitor of anesthesia awareness/level of consciousness/depth of sedation* via electroencephalographic processing for procedures intended to produce loss of consciousness.[24] It is recommended that consciousness monitoring be used when available; however, the research remains inconclusive regarding the effectiveness of this evolving technology.[25,26]
- *Monitor body temperature continuously* in all patients when clinically significant changes in body temperature are intended, anticipated, or suspected. Maintenance of normothermia must be an integral part of the anesthetic plan to preserve essential body functions (Box 52-5) and to prevent complications leading to patient morbidity and mortality.[27,28] Temperature monitoring is a standard of care when delivering general anesthesia to the patient and optional while performing mild, moderate, or deep sedation.
- *Monitor neuromuscular function and status* prior to the procedure and recovery when neuromuscular blocking agents are administered.
- *Monitor and assess patient positioning and protective measures* at frequent intervals. Periodic assessment of eye protection, skin, bony prominences, and extremities is necessary.
- *Perform a complete anesthesia equipment safety check daily and document in the patient's medical record*. An abbreviated check of all equipment is acceptable before each subsequent anesthetic is administered.

Patient indications for the necessity of anesthesia in remote locations are listed in Box 52-6.

BOX **52-4**

Specific Patient Conditions That Warrant Anesthesia-Care Vigilance

- Mental impairment with no possibility of cooperation
- Severe gastroesophageal reflux; delayed gastric emptying; aspiration risk
- Gastroparesis secondary to diabetes mellitus
- Orthopnea; obstructive sleep apnea
- Decreased level of consciousness; depression of airway protection reflexes
- Increased intracranial pressure
- Known difficult intubation; assessed oral, dental, craniofacial, cervical, or thoracic abnormalities that could preclude airway access and maintenance
- Respiratory tract infection; unexplained fever
- Morbid obesity
- Therapeutic or diagnostic procedures that impede access to the airway
- Therapeutic or diagnostic procedures that are complex, lengthy, painful, or invasive
- Positioning that is complex, atypical, painful; prone position
- Patient suffering acute trauma
- Patients at extremes of age
- Prematurity
- Physical status 3 or 4

BOX **52-5**

Reasons for Maintaining Normothermia for Therapeutic and Diagnostic Procedures

- To decrease sympathetic activity related to vasoconstriction while hypothermic
- To decrease cardiac morbidity and cardiac demand during recovery from hypothermia
- To minimize patient morbidity and discomfort related to being cold and shivering
- To maintain the normal pharmacokinetics of administered medications (Hypothermia decreases the normal metabolism of medications.)
- To decrease anesthesia recovery time (Hypothermia impairs the rapid recovery from anesthesia.)
- To maintain bodily metabolic functions (The enzymes involved in body metabolic chemical reactions function ideally at normothermia.)
- To maintain normal blood coagulation and to decrease blood loss. (The coagulation cascade is impaired or delayed during hypothermia.)
- To decrease the incidence of wound infection
- To decrease the incidence of complications that may require hospitalization

H. Precautions shall be taken to minimize the risk of infection to the patient, the operator, and ancillary personnel.

Clean equipment and fresh medications and supplies (to include personal protective equipment and supplies) should be used to ensure safety.

I. There shall be complete, accurate, and time-oriented documentation of pertinent information on the patient's anesthesia record.

Document baseline patient vital signs before the anesthetic procedure and the therapeutic or diagnostic procedure has begun.

BOX **52-6**

Patient Indications for the Necessity of Anesthesia in Remote Locations

Central Nervous System

- Presenile dementia
- Drug-induced mental disorders
- Major depressive disorders or schizophrenia
- Hysteria, unspecified (includes fear of pain)
- Phobic disorders, unspecified (claustrophobia)
- Transient cerebral ischemia
- Cerebrovascular disease, other and ill-defined

Cardiovascular

- Hypertensive heart disease, malignant, benign, unspecified
- Ischemic heart disease, acute or subacute forms
- Old myocardial infarction
- Coronary atherosclerosis, bundle branch block, other and unspecified cardiac dysrhythmias
- History of atrial or ventricular fibrillation or flutter

Pulmonary

- Bronchitis, acute, chronic, or unspecified
- Chronic airway obstruction
- Radiation-induced pulmonary disease, acute or chronic

Other

- Acquired hypothyroidism
- Electrolyte imbalance
- Morbid obesity
- Adverse effects not classified elsewhere
- Opioid, barbiturate, cocaine, cannabis, amphetamine, or unspecified drug dependence
- Combative patient
- Patient with low pain thresholds or experiencing severe pain
- Chronic liver disease or cirrhosis
- Gastrointestinal (GI) tract hemorrhage, unspecified

Pediatric

- Procedure is lengthy or painful
- The child is uncooperative or seems uncomfortable
- The operative or diagnostic area of interest lies close to critical anatomic structures
- The child is completely covered, which impedes quick access to the airway
- If an air embolus may be avoided by using an endotracheal tube or laryngeal mask airway

Modified from Bader AM, Pothier MM. Out-of-operating room procedures: preprocedure assessment. *Anesthesiol Clin*. 2009;27(1): 121-126; Cutter TW. Radiologists and anesthesiologists. *Anesthesiol Clin*. 2009;27(1):95-106.

Documentation must be made of all vital signs: heart rate, blood pressure, pulse oximeter readings, patient temperature, and the presence of $ETCO_2$. Also, documentation that includes names and quantities must be made of all fluids and drugs administered. A narrative must be written concerning the technique(s) of anesthesia used and any unusual events that occurred during the anesthetic period. An anesthesia form approved by the AANA is available on their website.

J. After the anesthetic treatment for therapeutic or diagnostic procedures, transfer the responsibility for care of the patient to other qualified personnel in a manner that ensures continuity of care and patient safety.

Anesthesia care does not end with the completion of the therapeutic or diagnostic procedure. The patient may receive postanesthesia

care at the site of the therapeutic or diagnostic procedure. Those sites that preclude postanesthesia recovery at that particular location must be safely transported to a separate area for postanesthesia care. From there patient care can be transferred to another qualified healthcare provider along with a full verbal report. To whom the report was given must be documented as well. The transported patient must be accompanied by a person capable of initiating basic life support (CPR), and that person must have immediate access to portable anesthesia monitors, equipment, and supplies, especially if transport will require some time and/or distance. Recovery from anesthesia can be divided into three phases. Phase I recovery encompasses the recovery from sedation, during which assessment is made of adequate patient oxygenation and respirations, cardiovascular function, neuromuscular function, mental status, body temperature, pain, postoperative nausea and vomiting (PONV), fluid status, urine output, the ability to void, and any bleeding or drainage, which must be noted and continually assessed. Treatments may be administered as necessary for any adverse signs or symptoms elicited by the patient. Phase II recovery encompasses the adequate resumption of psychomotor functions, such as the ability to communicate, ambulate, and consume fluids. Finally, before discharge from this area, a responsible individual must be present to escort the patient home and be available to observe and assist the patient for the next 24 hours. In phase III recovery, the patient regains full preanesthetic psychological and physical recovery.[29] It is important to remember that phase III may occur several hours or days later, depending on the anesthetic technique and patient variables, but with newer anesthetics, recovery time has dramatically decreased. Postanesthesia recovery and discharge guidelines are discussed in Chapter 50.

K. Reimbursement.

Third-party payers of anesthesia services may require documentation of the necessity for anesthetic services for therapeutic and diagnostic procedures. Box 52-6 lists some patient indications that can require the need for anesthesia in remote locations.

L. Conclusion.

The standards listed in this section describe the minimum requirements for treatment and monitoring of any patient who requires anesthesia care. The standards must be followed wherever and whenever anesthesia is given. Adherence to standards is considered essential in a malpractice case, and an anesthetic incident will be judged according to those standards.[30] The omission of any monitoring standard should be documented and the reason for such omission stated on the patient's anesthesia record. Any anesthetic procedure, including those performed in a remote location, should not begin until the anesthetist feels sufficiently comfortable, safe, and well prepared to deliver the anesthetic treatment required for the patient.

Guidelines for Sedation

Therapeutic and diagnostic procedures can be performed with various types of sedation. Sedation is possible with enteral, parenteral (intravenous), and inhaled medications. It is important to remember that the depth of sedation in a patient is a continuum of progressive changes in cognition, respirations, and protective reflexes.[31] Sedation does not have strict boundaries. The patient may quickly progress from one level of sedation/anesthesia to another; therefore, it is essential that the competent anesthesia provider is able to rescue patients in each level, as well as have quick access to vital equipment, supplies, and trained and qualified ancillary personnel who are familiar with anesthesia delivery, emergencies, and monitoring.[3,31-33]

Box 52-7 lists ancillary personnel requirements the anesthetist should consider during the planning stages of anesthesia for therapeutic and diagnostic procedures.

BOX 52-7

Considerations and Requirements of Ancillary Personnel for Areas of Anesthesia Delivery for Therapeutic or Diagnostic Procedures in Remote Locations

- Training in basic life support
- Awareness of and training in emergency protocols
- Familiarity with anesthesia responsibilities; to serve as an assistant
- Assist with patient positioning and comfort
- Training in postprocedure observation and recovery

Modified from Robbertze R, et al. Closed claims review of anesthesia for procedures outside the operating room. *Curr Opin Anaesthesiol.* 2006;19:436-442; Metzner J, et al. The risk and safety of anesthesia at remote locations: the US closed claims analysis. *Curr Opin Anaesthesiol.* 2009;22(4):502-508; Frankel A. Patient safety: anesthesia in remote locations. *Anesthesiol Clin.* 2009;27(1):127-139.

The Joint Commission and the ASA publish definitions for the four levels of sedation and anesthesia in their *Comprehensive Accreditation Manual for Hospitals: The Official Handbook (CAMH)*.[31] Box 52-8 lists definitions of the four levels of sedation and anesthesia as described by The Joint Commission and the ASA. Figure 52-1 illustrates the continuum of sedation described by the two aforementioned groups. From these definitions, standards are provided to practitioners for the administration of safe and high-quality care to patients.[32]

Accepted standards for moderate sedation/analgesia and deep sedation/analgesia state the following[11,31,32,34]:

1. The process from minimal sedation (anxiolysis) to general anesthesia is a continuum, and individuals vary in their responses to medications.
2. Qualified individuals with appropriate credentials (e.g., nurses, certified registered nurse anesthetists [CRNAs], anesthesiologists, dentists) who are trained in professional standards and techniques do the following:
   a. May administer pharmacologic agents to achieve a desired level of sedation.
   b. Must monitor patients carefully to maintain the patient's vital functions at the desired level of sedation. Appropriate equipment must be available for monitoring heart rate via ECG, respiratory rate and adequacy of pulmonary ventilation, oxygenation via pulse oximetry, and blood pressure measurement at regular intervals (at least every 5 minutes).
   c. Must be competent to evaluate the patient before performing the moderate sedation/analgesia and deep sedation/analgesia.
   d. Must be competent to support the patient's psychological functions and physical comfort.
   e. Must be competent in the administration of sedatives, analgesics, hypnotics, and other medications to produce and maintain moderate sedation/analgesia and deep sedation/analgesia.
   f. Must be competent to rescue the patient who unavoidably or unintentionally moves into a deeper than desired level of sedation and analgesia. In the case of the CRNA, competency is mandatory for all levels of the sedation continuum. This includes competency in management of a compromised airway, the provision of oxygen, and the initiation of emergency rescue procedures such as basic life support (BLS), advanced cardiac life support (ACLS), or pediatric

BOX **52-8**

The Continuum of Depth of Sedation: The Four Levels of Sedation and Anesthesia

Minimal Sedation (Formerly Known as Anxiolysis)
A drug-induced state during which patients respond normally to verbal commands. Although cognitive function and coordination may be impaired, ventilatory and cardiovascular functions are unaffected.

Moderate Sedation/Analgesia (Formerly Known as Conscious Sedation)
A drug-induced depression of consciousness during which patients respond purposefully to verbal commands, either alone or accompanied by light tactile stimulation. No interventions are required to maintain a patent airway, and spontaneous ventilation is adequate. Cardiovascular function is usually maintained. (NOTE: Reflexive withdrawal from a painful stimulus is not considered a purposeful response.)

Deep Sedation/Analgesia
A drug-induced depression of consciousness during which patients cannot be easily aroused but respond purposefully after repeated or painful stimulation. The ability to independently maintain ventilatory function may be impaired. Patients may require assistance in maintaining a patent airway, and spontaneous ventilation may be inadequate. Cardiovascular function is usually maintained.

Anesthesia (General Anesthesia)
Consists of general anesthesia and spinal or major regional anesthesia. It does not include local anesthesia. General anesthesia is a drug-induced loss of consciousness during which patients are not arousable, even by painful stimulation. The ability to independently maintain ventilatory function is often impaired. Patients often require assistance in maintaining a patent airway, and positive-pressure ventilation may be required because of depressed spontaneous ventilation or drug-induced depression of neuromuscular function. Cardiovascular function may be impaired.

Modified from The Joint Commission. *Comprehensive Accreditation Manual for Hospitals: The Official Handbook (CAMH)* (refreshed core). Chicago: The Joint Commission; 2009; American Society of Anesthesiologists: *Continuum of Depth of Sedation: Definition of General Anesthesia, and Levels of Sedation/Analgesia*. Accessed September 19, 2012, at the ASA website http://www.asahq.org/for-members/standards-guidelines-and-statements.aspx.

advanced life support (PALS). In addition, for patients undergoing deep sedation/analgesia, one must also have competency to manage an unstable cardiovascular system.

g. Must be competent to assess and treat problems the patient may attain related to the therapeutic or diagnostic procedure he or she is having performed.
h. Must properly document the patient's response to care.
i. Must supervise recovery of the patient after the sedation in a postsedation area or a postanesthesia recovery area.
j. Must discharge the patient. This may be done in consultation with qualified personnel and/or the physician, surgeon, or dentist.

3. Adequate numbers of qualified and competent personnel must be present during the performance of moderate sedation/analgesia, deep sedation/analgesia, and general anesthesia to serve as a skilled second pair of hands if necessary. This should include not only qualified anesthesia providers as described earlier but also nurses, assistants, technicians, and other office staff to meet the needs of the patient.[31]

The Pediatric Patient

The pediatric population can pose complex challenges for the delivery of anesthesia (Box 52-9). Pediatric patient behavior and degree of cooperation can range from very helpful to extremely anxious. Fortunately, several common anesthetic medications can help patients with slight to high levels of anxiety. Pediatric sedation and anesthesia increases the quality of care the patient receives by greatly reducing anxiety and by eliminating movement when necessary for therapeutic or diagnostic procedures.

First and foremost in the practice of nurse anesthesia are patient safety and guardianship of patient welfare. Important lessons can be learned from the literature regarding anesthesia in pediatric patients. Children under the age of 5 years seem to be at the greatest risk for adverse events, even with no underlying disease. Adverse events have occurred more commonly with the use of multiple drugs, especially sedative medications.[35-39] The problems encountered most often are respiratory events: respiratory depression, respiratory obstruction, and apnea.[36-38]

Adverse events can be reduced by proper adherence to patient selection and a comprehensive preoperative assessment, proper dosage of medications to minimize unexpected responses, proper monitoring, skilled administration of anesthesia, and proper recovery time. The anesthesia provider must plan to minimize the possibility of adverse reactions.[36-39] General patient selection criteria to help minimize the possibility of adverse events are seen with patients 6 months of age and older and applied during the preoperative assessment. It is during this time that the temperament of the child can be assessed.[40] Consideration must be made for the type of procedure to be performed, past medical history, past sedation/anesthesia history, current medication therapy, allergies, and respiratory or airway difficulties.[35,37,40] Questions regarding the degree of patient stimulation expected throughout the procedure, amount of anticipated blood loss, ability to maintain normothermia, and ability to have close proximity in which to monitor the patient, are all questions the anesthesia provider is responsible for addressing. It is found that adverse reactions are reduced with procedures that last less than 1 hour.[39] Clear communication with the technician and the medical practitioner is essential to clarify the requirements for the patient to be safe and properly anesthetized for the procedure.

The pediatric patient and the parent or legal guardian must be properly prepared for the planned therapeutic or diagnostic procedure. Clear explanation of the entire anesthetic process to the parent or guardian is based on the developed treatment plan and is offered in age-appropriate terms for the pediatric patient.[35,40] "Inform before you perform."

Fasting times are constantly being reevaluated in clinical anesthesia and must be stringently adhered to. Fasting guidelines are discussed in Chapters 19 and 48. Premedication with oral, intranasal, intramuscular, or rectal sedatives may be necessary. Common pediatric premedications and doses are chosen as appropriate.[40-44]

It is essential to have qualified personnel to assist in the safe care of pediatric patients receiving anesthesia in remote locations for therapeutic or diagnostic procedures. An extra pair of trained hands enhances the ability for the patient to receive safer care throughout the entire procedure.

Knowledge of the most common causes of adverse pediatric anesthesia events can help the anesthetist plan for and avoid these events (Box 52-10).[36,37,39] Most anesthesia adverse events are caused when multiple anesthetic agents are used. Adverse

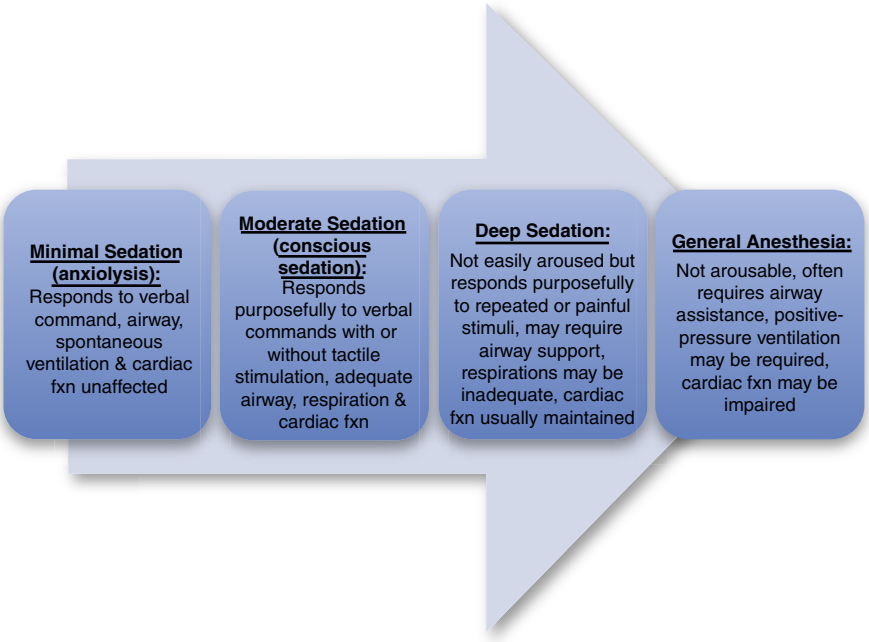

FIGURE **52-1** Depth of sedation continuum.

BOX 52-9

Goals of Pediatric Anesthesia

- Foremost, to provide safety and welfare to the patient
- To minimize physical discomfort/pain or to provide more profound analgesia when necessary to the patient
- To minimize negative psychological consequences of the therapeutic or diagnostic procedure for both the pediatric patient and the parent(s)/guardian(s). This can be accomplished by the provision of proper preprocedure discussions along with sedative medications, analgesics, and amnestic agents for the patient
- To ideally obtain patient cooperation and safely control uncooperative or endangering behavior
- To obtain immobility of the patient to achieve therapeutic or diagnostic procedure goals
- To provide the patient a safe discharge to the guardian and to home
- To minimize or eliminate patient complications from applied therapeutic or diagnostic procedures and administered anesthetic medications

Modified from Cravero JP, et al. The incidence and nature of adverse events during pediatric sedation/anesthesia with propofol for procedures outside the operating room: a report from the Pediatric Sedation Research Consortium. *Anesth Analg*. 2009;108:795-804.

BOX 52-10

Most Common Causes of Pediatric Anesthesia Adverse Events for Therapeutic or Diagnostic Procedures

- Drug errors
- Nitrous oxide in combination with any other sedative medication
- Inability to rescue the patient from an adverse anesthetic event
- Unmet monitoring standards—especially respiration, oxygenation
- Respiratory depression/hypoventilation/apnea
- Airway obstruction
- Bradycardia secondary to hypoxia
- Laryngospasm/stridor
- Vomiting, aspiration, diarrhea
- Hypotension
- Inadequate sedation/paradoxical excitation (sustained irritability or combativeness)
- Prolonged sedation after the procedure

events are not dependent on the class of the drug (e.g., opioids, benzodiazepines, barbiturates, antihistamines, local anesthesia, intravenous anesthesia, inhaled anesthesia) or the route of administration (e.g., oral, rectal, nasal, intramuscular, intravenous, local infiltration, inhalation).[37,38,45,46]

The Geriatric Patient

As a result of a number of factors, including better nutrition, more physical activity, less tobacco and alcohol use, and improved medical care and medical technologies, more Americans are living longer. In 2008 the U.S. Census Bureau released population projections stating that the population of people within the United States currently over the age of 65 is 14.8% and will reach 20% by 2025 and 24.6% by 2050, with continued increased life expectancy.[47] The increasing elderly population is placing, and will continue to place, many demands on the public healthcare system. Medical technology is advancing, and therefore more procedures requiring anesthesia will be performed in elderly patients. It is estimated that 20% to 40% of anesthesia cases may be performed outside of the traditional operating room and that the elderly prefer ambulatory settings, with trends pointing toward more invasive therapeutic or diagnostic procedures.[48] Perioperative complications can increase with age. Special considerations related to the physiology of aging are necessary if anesthetic treatment is to be performed safely.[48,49]

The elderly have a greater prevalence of comorbidities such as atherosclerosis, infections, autoimmune diseases, chronic disorders, and cancer. The immune system gradually and slowly diminishes in function with age. Therefore, the ability to heal and fight foreign bacteria, viruses, and malignant cells diminishes. There are no fewer T cells in a person at an older age than at a younger age, but T-cell function is decreased in the elderly. Many of the body's cells begin to diminish in function or to function abnormally. Cells also may have increasing difficulty in membrane transfer of nutrients and waste.[49]

The normal aging process results in an increase in the ratio of adipose tissue to aqueous body tissues.[49-50] This means more lipid-soluble anesthetic drug is stored. Basal metabolic rate and liver and kidney function all decrease with age. This results in a decrease in the rate of metabolism and excretion of anesthetic drugs. Nervous system function generally produces decreases in the perception of sight, hearing, touch, smell, taste, pain, and temperature sensations. Cerebral atrophy occurs with aging, resulting in an overall loss of neurons in the neocortex.[50] This suggests increased sensitivity to anesthetic medications. The elderly are at an increased risk for perioperative delirium and postoperative cognitive dysfunction.[48] Therefore, the dosage requirements for anesthetic drugs usually are decreased. The geriatric patient's level of activity is one indicator of cardiovascular function and this generally decreases with age; this decrease in activity usually correlates with limited physiologic reserves. Patients may be restricted in their activity because of arthritis or other debilitation. Circulation time is decreased. Skeletal muscle size is decreased with decreases in physical activity, which decreases total oxygen consumption and blood-flow needs to the muscles, resulting in decreased cardiac output.[50] The ability of the cardiovascular system to respond to the effects of anesthetic drugs, fluid administration, and the stresses of therapeutic and diagnostic procedures can cause decreased cardiac function, resulting in hemodynamic instability and reduced circulation to vital organs.[48-50] Tissue oxygenation can decrease because of changes in ventilation ability and lung tissue. Lung compliance is decreased, resulting in ventilation-perfusion mismatch. Aging itself brings on the increasing inability to respond to hypoxia and hypercapnia, especially while experiencing the effects of anesthesia. Therefore, the anesthetist must always ensure and constantly monitor the supply of adequate amounts of oxygen to the elderly patient and be ready to offer needed respiratory support. The ability to thermoregulate is also decreased with age.[48] Body metabolism, enzyme function, and the coagulation cascade best function at 37° C. Changes in mental status or even delirium can occur more frequently in geriatric patients. All of these factors must be taken into consideration when one provides anesthesia to all patients, but especially to geriatric patients.

Significant variability exists in each of these vital functions among patients. Geriatric patients who are more physically fit have a decreased mortality, reduced incidence of cardiovascular disease, lower blood pressure, reduced blood cholesterol, and most important, better bodily reserves when they become surgically challenged or sick.[49] A thorough and comprehensive preanesthetic assessment is necessary, from which a plan of treatment can be deduced.[48]

To prevent confusion, delirium, or cognitive impairment in the elderly, agents with short half-lives and durations are ideal.[51,52] Carefully consider the use of drugs that are synergistic or antagonistic in their effects. Such drugs as propofol, midazolam, fentanyl, alfentanil, remifentanil, and local anesthetics are ideal because doses are calculated and titrated according to the patient's responses. Most literature reports no difference of outcome in the elderly as a result of anesthetic choice when either a regional anesthetic or general anesthesia is used.[48]

Several electroencephalographic (EEG) processing monitors are available that help in assessment of patient responses to anesthetic medications. These devices monitor anesthesia awareness/level of consciousness/depth of sedation, and response to anesthetic medications, which allows for more precise titration of anesthetic medications according to the patient's needs. Care must be taken to preserve body warmth and ensure the continual delivery of adequate warmth when necessary. Ensure the protection of the eyes, skin, and the extremities while moving the patient and during the procedure by skin padding of bony prominences.[40] Consideration must also be given to the preprocedure, and postoperative care of the elderly patient in regard to possible malnutrition, depression, immobility, cognitive dysfunction, pulmonary difficulty, dehydration, acute pain, and chronic pain.[48] Finally, consider verbal and written postoperative instructions to both the elderly patient and caregivers/significant others who will accompany the patient and be present to both monitor and care for the elderly patient after a therapeutic or diagnostic procedure.[51]

A new formulations of propofol is available for use in anesthesia for therapeutic and diagnostic procedures (see Chapter 9 for a complete discussion). Fospropofol (Lusedra) is a water-soluble prodrug that is enzymatically converted to propofol. The formulation contains no lipids, egg, or preservative products and therefore has a decreased likelihood of allergic reactions or bacterial growth. Pain on injection is also decreased since it is not a lipid formulation. Because of its need to be converted to propofol, Fospropofol has a delayed onset and slightly prolonged duration when compared with propofol.[52] Some studies suggest that it is an ideal sedative choice for the geriatric patient with multiple comorbidities due partly to its lower rate of apnea and respiratory depression.[52-54]

ANESTHESIA FOR SPECIFIC PROCEDURES IN REMOTE LOCATIONS

Cardiology Procedures

Automatic Implantable Cardiac Defibrillator and Cardiac Pacemaker

Procedure Overviews. It is estimated that between 170,000 and 462,000 people within the United States experience sudden cardiac death each year, and of those, 50% to 70% do not survive the event.[55] Patients who experience sudden cardiac death are usually around 60 years of age, and their most common underlying rhythm is pulseless ventricular tachycardia (VT) or ventricular fibrillation (VF).[55,56]

Defibrillation is the application of a flow of electric current through the appropriate chambers of the heart to completely depolarize the entire myocardium to restore a suitable heart rhythm to sustain life.[57-59] If enough stores of high-energy adenosine triphosphate molecules remain and are available within the myocardium, automaticity can resume. Fibrillating myocardium rapidly consumes high-energy phosphate molecules.[50,59] It has been proven that early defibrillation, along with cardiopulmonary resuscitation, can result in high long-term survival rates. The automatic implantable cardiac defibrillator (AICD) is designed to bypass the delay patients experienced before receiving defibrillation. The AICD is composed of two basic parts: a pulse generator and a lead electrode for detection of dysrhythmias, delivery of a defibrillating shock, cardiac pacing, telemetry, and provision of diagnostic data. The pulse generator is a hermetically sealed titanium can that contains a computer microprocessor, resistors, transformers, capacitors, and a battery. The battery is designed to deliver 120 shocks and usually lasts for 3 to 6 years. The computer

is programmed with algorithms to detect VT and VF. If VF occurs, an electric shock is administered within 10 to 15 seconds of detection (much of the time delay results from the charging of the capacitor). VT is treated with overdrive pacing called *antitachycardia pacing* (ATP). ATP is an extremely successful procedure. AICD implantation has been a crucial technique for prevention of sudden cardiac death.[60]

A cardiac pacemaker is used to treat bradycardia, atrioventricular block, sinus nodal dysfunction, and other dysrhythmias. The pacemaker is used concurrently with other therapies for management of dysrhythmia and hemodynamics. The pacemaker consists of a pulse generator containing a computer and a battery that is designed to last 6 to 10 years. Attached to the pulse generator is a lead, which delivers the current used to depolarize the myocardium, and an anode, which completes the electrical circuit. Two different types of pacemaker leads are available. A unipolar pacemaker lead uses one lead as the cathode and the pulse generator as the anode. Unipolar leads are less likely to fail. A bipolar pacemaker uses two separate leads that are close together, the advantage of which is a sharper signal with less noise. The leads are inserted under fluoroscopic guidance via the cephalic vein or the subclavian vein into the cardiac chamber, usually the right ventricle in the case of an AICD and the right atrium and right ventricle for a cardiac pacemaker. The leads are then tunneled and connected to the pulse generator, which is then inserted into a subcutaneous pocket in the patient's pectoral region or into a subpectoral muscle pocket.[60] Figure 52-2 shows a postoperative radiograph of a pacemaker pulse generator, computer, and battery inserted into a patient. Figure 52-3 shows a postoperative radiograph of a unipolar pacemaker lead inserted into the right ventricle of a patient. Research and continual improvements allow more people to receive better and more reliable AICD and cardiac pacemaker therapy.

Anesthetic Considerations. The AICD or cardiac pacemaker procedure may be performed in the operating room, in a special cardiac procedure room, or in the cardiac catheterization suite by a cardiologist or other physician.[61] Routine monitors are attached to the patient, with special attention paid to a properly functioning five-lead ECG. The ECG monitor screen must be available to the anesthesia team, the operating physician, and the AICD or pacemaker manufacturer's technical service representative, who is always present during insertion. The procedures are usually adequately performed with local anesthetic and moderate sedation/analgesia or deep sedation/analgesia, although some clinicians prefer a general anesthetic.

AICD insertion requires purposeful triggering of VF in an attempt to test thresholds and functioning of the AICD.[62] A range of anesthesia techniques from mild sedation with local anesthesia infiltrate to general anesthesia may be required depending upon factors such as surgeon preference, procedural length, number of thresholds tests, and patient physical and mental status. As in all anesthetic procedures, endotracheal intubation may be required to secure the airway in case a cardiac emergency arises.

After insertion of the cardiac pacemaker and before wound closure, the device is threshold tested by the pacemaker manufacturer's technical service representative to ensure adequate contact between the leads and the myocardium.[60,61] After wound closure and dressing application, all computer-function programming of either the AICD or the cardiac pacemaker can then be performed with a pacemaker programmer that connects to a portable wand. The wand is placed within close proximity to the implanted pulse generator by the manufacturer's technical service representative, which allows a telemetric connection to properly program or interrogate the AICD or cardiac pacemaker.

Postanesthesia Care. When the procedure is completed, the patient is transported to the recovery room with oxygen and observed for any hemodynamic or cardiovascular ECG changes.

AICDs are generally well tolerated by patients. Some patients display anxiety or depression because of the possibility of sudden cardiac death, device failure, inappropriate shocks, and recalls of certain devices.[61] Shocks from the AICD are described as a sudden, heavy blow to the chest. Medical technology is ever improving, and the demand for AICDs and cardiac pacemakers increases annually.

Cardioversion

Procedure Overview. Cardioversion is the discharge of electrical energy, synchronized to the R wave of the QRS complex of the electrocardiogram, to convert hemodynamically unstable supraventricular rhythms such as atrial flutter or atrial fibrillation

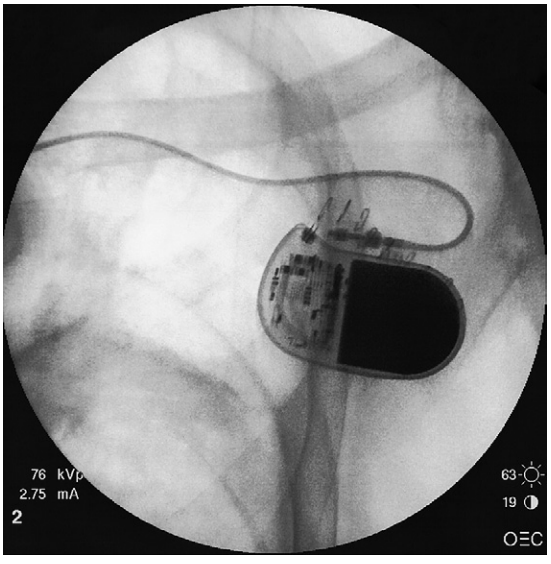

FIGURE **52-2** Radiograph of a pacemaker pulse generator, computer, and battery inserted into a patient.

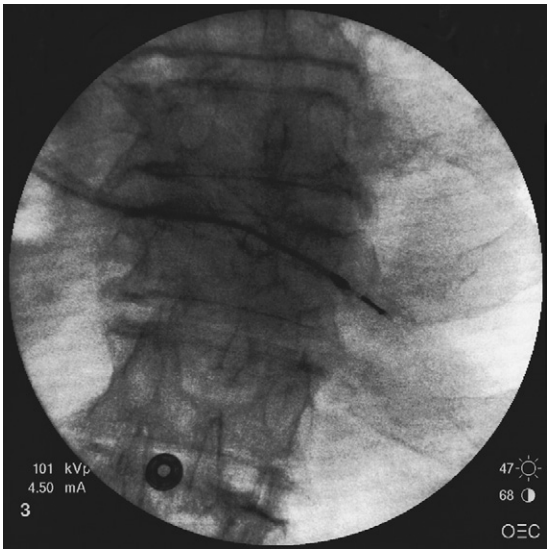

FIGURE **52-3** Radiograph of a unipolar pacemaker lead inserted into the right ventricle of a patient.

or hemodynamically stable VT. These rhythms can be life threatening if left untreated. Atrial flutter and atrial fibrillation are associated with the development of congestive heart failure and with the formation of thromboemboli, which can lead to stroke. Cardioversion is usually a scheduled and planned procedure unless the patient's condition warrants otherwise. Patient optimization may not be possible if there is urgency for cardioversion as a result of hemodynamic instability. Much less electrical energy is required to synchronously cardiovert a patient when compared with asynchronous defibrillation.[58] Defibrillation is an unplanned and usually emergent application of unsynchronized electrical energy. Cardioversion is believed to be therapeutic because it closes an excitable gap in the myocardium, which causes currents to reenter and excite the electrical system of the heart.[61]

Anesthetic Considerations. Because cardioversion is usually a nonemergent and planned procedure, patient conditions usually can be optimized. Proper nothing-by-mouth (*nil per os* [NPO]) status must be observed unless the cardioversion is deemed urgent or emergent. Standard monitors are applied, with special attention paid to the ECG. A monitor of anesthesia awareness/level of consciousness/depth of sedation via electroencephalographic processing can be used to assess consciousness during cardioversion.[63-64] Intravenous access is necessary. The energy required for cardioversion is measured in joules (watt-seconds). The cardiologist or physician uses a cardioverter-manual monophasic or biphasic defibrillator for the procedure. The optimal shock dose for cardioversion of atrial flutter and other supraventricular tachycardias is 50 to 100 J.[57-59,65] The operator applies cardioversion-defibrillator paddles with conduction gel or defibrillator pads to the patient's skin. One paddle or pad is placed parasternally over the second and third intercostal space. The other paddle or patch is placed over the area of the apex of the heart.[56-59] The cardioverter-defibrillator is set to the synchronized (sync) mode. Visible synchronization marks are placed by the cardioverter atop the tallest R waves of the ECG. Energy shocks are delivered initially at 50 to 100 J and are titrated progressively, up to 360 J as necessary, after observation of the effectiveness of the synchronized shock.[58-59,65]

Midazolam may be administered as both a sedative and amnestic agent before cardioversion. The patient is then assisted in breathing oxygen via facemask and Ambu bag with high-flow oxygen. Because of the intense and brief pain of cardioversion, an ultra–short-acting general anesthetic such as propofol or etomidate is administered.[63-64] After the loss of eyelash reflex occurs, an "all-clear" signal is given by the operator. Positive-pressure respirations are temporarily suspended, with care taken not to touch any part of the patient or the patient's bed. Then the synchronized shock or shocks are administered.[64,65] Muscle relaxation is not necessary. As always, an assortment of oral airways, nasal airways, laryngeal mask airways (LMAs), endotracheal tubes, and laryngoscopes with blades and suction should be readily available in case complications occur. If cardioversion is required in a patient who has not fasted, general anesthesia with tracheal intubation is necessary to prevent aspiration of gastric contents.[64]

Postanesthesia Care. It is hoped that the patient's heart is now beating in a desirable cardiac rhythm and that the patient's blood pressure is stable. Spontaneous respirations return, along with swallowing and coughing reflexes. The patient is observed for any reactions to the anesthetic, and care is turned over to the nurse accompanying the patient.

Radiofrequency Catheter Ablation

Procedure Overview. Radiofrequency catheter ablation (RFCA) uses a catheter with an electrode at its tip, which is guided under fluoroscopy to an area of heart muscle that has demonstrated accessory electrical conductive pathways.[66-68] RFCA has all but replaced arrhythmia surgery and is now considered the foremost therapy for the treatment of many arrhythmias in pediatric and adult patients.[66-67] Supraventricular tachycardia is the most common tachyarrhythmia in children, and symptomatic supraventricular tachydysrhythmias are most often treated by RFCA.[66] Accessory electrical conductive pathways are distributed unevenly along the right and left atrioventricular valve annuli.[66] Left-sided accessory pathways are most common, but both right- and left-sided accessory electrical pathways can be accessed and ablated.[66-67] Other treatments possible with RFCA are modification of the sinus node or AV node, ablation of atrial flutter and atrial tachycardia, and ablation of focal atrial fibrillation and VT foci.[66-68] Patients must undergo electrophysiologic studies to determine the origin and pathway of the arrhythmia, as well as the mechanism of action, before RFCA can be chosen as a therapy.

Cryoablation is now being used prior to RFCA, or in place of RFCA. Liquid nitrous oxide is circulated through the catheter tip to cause temperatures at the tip of −22° C to −75° C. At a higher temperature (−22° C or lower), tissue can be temporarily "ice mapped," which is a trial to see whether this nonpermanent freezing of the tissue will successfully eliminate the dysrhythmia. If the ice mapping is successful, then the probe is further cooled, causing permanent destruction of the arrhythmogenic tissue. Cryoablation causes less discomfort and has been found to be safer to use in cases of dysrhythmias in the area of the atrioventricular (AV) node, where iatrogenic complete AV heart block can be caused. Iatrogenic AV block is relatively common and may require placement of a transvenous pacemaker.[69-70]

RFCA is an extremely safe and successful procedure, with success rates of 95% overall. Many patients no longer need their antiarrhythmic medications soon after therapy.[65-66]

RFCA is now being used as treatment for liver metastases from colorectal cancer. RFCA is providing a new treatment option for those patients with high risks for surgery but who would be at a lesser risk for the less-invasive RFCA.

Anesthetic Considerations. Electrophysiologic studies conducted before RFCA are time-consuming procedures that may require moderate sedation in adults or general anesthesia in children. RFCA can be performed in the operating room, in a special cardiac procedure room, or in the cardiac catheterization suite by a cardiologist. The electrode catheter is guided via the femoral artery and vein to the area of the accessory electrical pathway or an area of arrhythmogenic focus.[66,69] The internal jugular vein also may be used. The electrode is then energized with radiofrequency energy, and cells within the path of the electrode are obliterated. The procedure can produce brief periods (less than 1 to 2 minutes) of mild to moderate retrosternal, angina-like pain.[69]

RFCA is a short procedure. Patients must remain perfectly still, except for respiratory movement, during the procedure.[68-69,71] Many adults can be anesthetized with moderate sedation/analgesia along with local anesthetic applied by the operator.[71] Children may be best treated with general endotracheal anesthesia using either an LMA or an endotracheal tube to secure the airway. If general endotracheal anesthesia is used, the patient may be held apneic for a short period of time while the catheter is accurately directed and the ablation procedure performed.[69] Full monitors and an intravenous catheter are necessary. Total intravenous anesthesia (TIVA) using propofol as the key medication has been used. TIVA with propofol and ondansetron has a much lower rate of nausea (postoperative nausea and vomiting [PONV]) than does use of an inhaled anesthetic and an antiemetic. Careful attention must be paid to the ECG, because

the patient must stop taking any antiarrhythmic drugs before the electrophysiologic study and RFCA are performed.[66-69,71]

Possible thermal injury to the esophagus is a concern during RFCA of the left atrium resulting in esophageal ulcerations or an atrioesophageal fistula, which is an extremely rare but often fatal complication of RFCA. Insertion and use of an esophageal temperature probe during general anesthesia is essential, as is the position of the probe. The probe should be inserted so that it is alongside the esophageal tissues with no space in between. Constant monitoring and communication with the procedural team is a necessity for prevention, identification, and treatment of complication.[72-74]

Postanesthesia Care. Patients must be monitored during recovery from administered anesthetics after RFCA. Patients also must be observed for possible RFCA procedural complications such as bleeding, ECG changes, cerebrovascular accidents, cardiac tamponade, or damage to the aortic valve.[66-69]

Percutaneous Coronary Intervention

Procedure Overview. Percutaneous coronary intervention (PCI) encompasses a wide variety of procedures performed in the cardiac catheter laboratory (CCL). PCI is being performed on adults and is now more commonplace on younger and sicker patients. The CCL is generally located remotely from the operating rooms and the blood bank. It consists of a large procedural area with a small control room. PCI procedures use x-radiation/fluoroscopy doses "as low as reasonably achievable" (the ALARA principle), as well as the use of intravenous radiocontrast media. The heart is commonly accessed via the femoral artery (although the brachial or radial artery can be used). The right heart and pulmonary circulation are commonly accessed via the femoral vein.[75-76]

Anesthetic Considerations. PCI necessitates access to major blood vessels and the heart itself. Box 52-11 lists possible PCI complications that affect the safety of the anesthetic and may require interventions from the anesthetist. Consideration for rapid access to competent anesthesia help has to be prepared well in advance of PCI anesthesia. Anesthesia techniques can range from intravenous moderate sedation/analgesia or deep sedation/analgesia to general anesthesia, aided with local anesthetic infiltration at the insertion site and alongside the major vein (usually the femoral vein) used for insertion of the PCI armamentaria.[75-76]

Postanesthesia Care. Care of the patient undergoing PCI usually does not end with completion of the PCI procedure. Arrangements can be made for observation and ongoing care of the patient in a telemetry environment or in the intensive care unit, depending on the criticality of the patient. Immediate postanesthesia concerns are continuing dysrhythmias, hypothermia, current fluid status, changes in fluid status, PONV, hemodynamic status related to hemorrhage, and analgesia.[76]

BOX 52-11

PCI Complications That May Affect the Delivered Anesthetic and Require Anesthetist Intervention

- Supraventricular dysrhythmias
- Ventricular dysrhythmias
- Severe and rapid hemorrhage
- Pain
- Anaphylaxis related to administration of intravenous contrast media
- Vasovagal response
- Cardiac arrest
- Thromboembolic events
- Hypotension/hypertension
- Respiratory instability

Adapted from Shook DC, Savage RM. Anesthesia in the cardiac catheterization laboratory and electrophysiology laboratory. *Anesthesiol Clin.* 2009;27:47-56.
PCI, Percutaneous coronary intervention.

Gastroenterology Procedures

Colonoscopy, EGD, and ERCP

Procedure Overview. Endoscopy came into popular use in the early 1960s with the invention of a snare for collecting intestinal polyps for biopsy. Endoscopy for gastrointestinal procedures is the use of a flexible fiberoptic endoscope that transmits brilliant, coherent, high-resolution, magnified, direct visual images to the operator. The operator can then examine, biopsy, dilate, or cauterize portions of the gastrointestinal tract. The endoscopist may pass accessory devices down the endoscope such as biopsy forceps, dilation devices, cytology brushes, measuring devices, needles for injection, Doppler probes, ultrasound probes, and probes to measure electrical activity and pH. Even foreign bodies may be removed with the aid of a snare passed through an endoscope. Endoscopes are available in different diameters for use in pediatric to adult patients.[77]

An upper endoscopy, such as an esophagogastroduodenoscopy (EGD), is an accurate way for the operator to evaluate the mucosa of the esophagus, stomach, and duodenum. A colonoscopy allows total diagnostic visualization of the mucosa of the tortuous colon from the anus to the cecum. Endoscopic retrograde cholangiopancreatography (ERCP) is used for the diagnosis of obstructive, neoplastic, or inflammatory pancreatobiliary structures. The use of ERCP is decreasing because of the availability of less-invasive and noninvasive techniques. Box 52-12 provides a brief list of indications for colonoscopy, EGD, and ERCP.[77] Use of endoscopic ultrasound (EUS) has been growing since its inception in the 1980s and continues to broaden possibilities for the patient and practitioner. Once used solely for diagnostic and cancer staging purposes of the pancreas, periluminal structures, and biliary tract, it is now being used for therapeutic modalities such as cyst drainage and celiac plexus neurolysis for pain, and for fine-needle injection of therapeutic medication.[78-79]

Endoscopy for gastrointestinal procedures may be performed by a gastroenterologist, general surgeon, family practitioner, or proctologist. The endoscope is passed into the gastrointestinal tract with the aid of lubricant. The endoscope has controls to change the direction of the flexible tip, allow flushing with water, application of suction, or insufflation of air or carbon dioxide within the portion of the gastrointestinal tract being observed.[77]

Anesthetic Considerations. Because of the expectations of patients, endoscopically caused discomfort, and the desirability for no patient movement, some degree of sedation and, in some cases, general anesthesia is used. A proper preanesthetic assessment of the patient must be performed, focusing on the areas of age, ability to cooperate, level of anxiety, mental disability, allergies, fluid status, laboratory electrolyte values, cardiac history, hypertension, bleeding history, clotting status, respiratory status, obesity, drug and alcohol abuse, gastroesophageal reflux, and pregnancy.[13,32]

Endoscopy has been safely performed in pregnant patients.[77] Consideration should be given to any anesthetic drugs administered to the parturient, because transfer can occur through the placenta to the fetus. Rarely, elective procedures should be reconsidered and performed only after consultation with the patient's physician or obstetrician. Urgent endoscopic procedures must be performed. None of the common sedative drugs such as propofol or

the opioid fentanyl have been demonstrated to cause teratogenic changes in the fetus. Benzodiazepines are typically avoided in the parturient, especially in the first trimester, due to reported teratogenic effects on the fetus. Midazolam also has been shown to cross the placenta and cause neonatal central nervous system (CNS) depression.[80] Studies of the obstetric effect of anesthetic drugs are limited because of the infrequent requirements for surgery during pregnancy and the ethical difficulties associated with performing controlled trials.

Patients must adhere to proper NPO guidelines. Bacteremia is possible as a result of endoscopic procedures. Necessary medications may be given, such as cardiac medications, antihypertensives, and antibiotics.[77] Preemptive analgesia with gargled flavored viscous lidocaine may help reduce the patient's gag reflux, making an endoscopy of the upper gastrointestinal tract more feasible.[81] Moderate sedation/analgesia is usually accomplished with the short-acting sedatives midazolam or propofol and analgesics such as remifentanil, alfentanil, or fentanyl. Deep sedation can be achieved with titration of propofol until effective along with an analgesic medication.[81-84] Upper endoscopy may necessitate the use of any antisialagogue such as glycopyrrolate.[82-83]

Colonoscopy requires thorough cleansing of the lumen of the colon of fecal material. The colon may be partly prepared with a cleansing enema. Full preparation of the colon is accomplished commonly with orally administered balanced electrolyte solutions in a volume of up to 4 L. Other types of solutions are also available.[77] Patients often find this preparation the most distressing portion of the procedure. The bowel preparation can lead to abdominal cramping, diarrhea, weakness, and nausea. Patients who arrive for the procedure require reassessment and the insertion of an intravenous catheter with intravenous fluid, usually lactated Ringer's solution or normal saline. Conventional monitors, including pulse oximeter, noninvasive blood pressure monitor, and ECG, are attached. The patient is supplied with oxygen through a disposable nasal cannula or disposable facemask, ideally with end-tidal carbon dioxide monitoring as discussed previously. Patients are usually asked to assume a left lateral decubitus position and are able to remain on the transport stretcher for the procedure duration. It is optimal for the body to be flexed, the head and back bent downward toward the knees and for the patient's legs to be bent toward the abdomen to optimize visualization of the gastrointestinal tract. Patient anxiety, distention because of insufflation, and acute discomfort during the maneuvering of the endoscope usually necessitates the administration of deep sedation or a general anesthetic in some cases. The depth of sedation required may be titrated with the use of an available monitor of anesthesia awareness/level of consciousness/depth of sedation via electroencephalographic processing.[85-86] Strong vagal nerve stimulation can occur as a result of distention of the colon. This may cause hypotension, bradydysrhythmias, and ECG changes.[77,85-86]

EGD and EUS requires a patient assessment with special emphasis on any cardiac history, hypertension, bleeding disorders, nausea (PONV), dysphagia, and gastroesophageal reflux. The patient must be NPO according to guidelines. Occasionally, patients require moderate sedation or deep sedation because topical anesthesia and even hypnosis have been found less effective.[81-84] An intravenous catheter is inserted, with fluids such as lactated Ringer's or normal saline attached. The patient is connected to standard monitors. Oxygen can be supplied through a disposable nasal cannula or a disposable facemask preferably with end-tidal carbon dioxide monitoring. EGD is generally performed with the patient positioned supine or in a left lateral decubitus position. After the patient is adequately sedated, the operator inserts a hollow oral airway gently into the patient's mouth, and the endoscope is advanced through this airway, allowing direct visualization of the larynx, hypopharynx, esophagus, and stomach, and through the pylorus into the duodenal bulb.[77,84]

ERCP requires thorough assessment of the patient, including a review of laboratory values of a complete blood count, serum liver chemistries, and amylase or lipase levels to evaluate liver function, and clotting studies. Patients also must be evaluated for anticoagulant medications, bleeding history, and prosthetic heart valves.[77,87] Allergies must be evaluated, especially those to iodinated contrast media.[88] Patients who require ERCP are usually more ill than patients seen routinely for colonoscopy or EGD.

BOX 52-12

Indications for Colonoscopy, Esophagogastroduodenoscopy, and Endoscopic Retrograde Cholangiopancreatography, with Anesthetic Implications

Colonoscopy
- Gastrointestinal bleeding and occult bleeding
- Evaluation of an abnormality on barium enema
- Polypectomy
- Unexplained iron deficiency anemia
- Significant diarrhea
- Chronic inflammatory bowel disease
- Malignancy
- Dilation of stenotic lesions
- Foreign body removal

Esophagogastroduodenoscopy
- Persistent and recurrent dyspepsia (heartburn)
- Persistent nausea or vomiting (PONV)
- Dysphagia (difficulty swallowing)
- Chest pain with a negative cardiac evaluation
- Iron deficiency anemia
- Suspected small bowel malabsorption
- Malignancy
- Stomach or esophageal ulcer
- Control of bleeding
- Ligation or sclerosis of varices
- Dilation of strictures
- Percutaneous gastrostomy
- Polypectomy
- Removal of foreign body

Endoscopic Retrograde Cholangiopancreatography (ERCP)
- Suspected biliary ductal disorder
- Suspected pancreatic ductal disorder
- Biliary drainage
- Pancreatic drainage
- Biopsy
- Bile or pancreatic juice collection
- Mapping of the pancreatic duct before intended surgery
- Manometry of the sphincter of Oddi or other ductal mapping

Data from Waye JD, et al. Colonoscopy and flexible sigmoidoscopy. In: Yamada T, ed. *Textbook of Gastroenterology*. 5th ed. Oxford: Wiley Blackwell; 2009:2917-2932; Yusuf TE. Endoscopic retrograde cholangiopancreatography, endoscopic sphincterotomy and stone removal, and endoscopic biliary and pancreatic drainage. In Yamada T, ed. *Textbook of Gastroenterology*. 5th ed. Oxford: Wiley Blackwell; 2009:2933-2957; Stockland AH, Baron TH. Endoscopic and radiologic treatment of biliary disease. In: Feldman M, et al, eds. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*. 9th ed. vol. 1. Philadelphia: Saunders; 2010:1185-1200.

The patient must be NPO according to guidelines. Intravenous access is obtained and fluid is administered. Standard monitors are applied, and oxygen is supplied to the patient via a disposable facemask or nasal cannula, or as appropriate for anesthesia plan. The procedure requires that the patient be in a prone, semi-prone, or slightly left lateral decubitus position. Deep sedation or general anesthesia are usually required.[87-90]

Pediatric endoscopy has been performed with patients under deep intravenous sedation with agents such as propofol, midazolam, and alfentanil (when the patient will allow placement of the intravenous catheter) and under general endotracheal anesthesia.[83] Propofol has been found to provide anterograde amnesia during the procedure with no provided retrograde amnesia.[82-83] The use of a eutectic mixture of local anesthetics lidocaine and prilocaine (EMLA cream) facilitates the placement of the IV catheter. EMLA must be applied to undamaged skin, under an occlusive dressing for a period of 45 to 60 minutes, before the IV catheter is inserted.[83] When general anesthesia is administered, a sturdily secured endotracheal tube should be considered because of relative inaccessibility to the airway, as in the patient position required for pediatric colonoscopy or for EGD in which the oral cavity will be shared with the operator.[83]

These procedures can cause bowel rupture or duct rupture. One must be ready with immediate airway and hemodynamic support as necessary, along with monitored emergency transport to the operating room for surgical intervention.[77]

Postanesthesia Care. Postprocedure morbidity differs with each of the described procedures. All patients must be monitored in a postanesthesia care area until they have recovered from the sedation or general anesthetic.

Colonoscopy patients have intestinal distention, which is relieved with encouragement to pass flatus. Rectal bleeding, nausea, hypotension, and vomiting also may be seen. Administration of a bolus of intravenous fluids along with an intravenous antiemetic agent.[91-92]

EGD morbidity relates to bleeding, nausea, vomiting, aspiration, dysphagia, and hypotension. Treatments such as those used for colonoscopy may be indicated.[91-92]

ERCP morbidity relates to possible reactions to iodinated contrast media. Patient reactions can be mild (such as nausea, vomiting, pruritus, diaphoresis, flushing, or mild urticaria), moderate (such as faintness, severe vomiting, profound urticaria, mild bronchospasm, mild hypotension, mild tachycardia, or bradycardia), or severe (hypotensive shock, angioedema, respiratory arrest, cardiac arrest, convulsions, or death).[91] Postprocedure bleeding, nausea, and vomiting (PONV) are possible and can be treated as described previously.

Gynecology Procedures

Assisted Reproductive Technologies

Procedure Overview. *Assisted reproductive technologies* (ARTs) refers to all techniques used to retrieve and fertilize the human oocyte. In vitro fertilization (IVF) is the most common technique used to artificially fertilize the human oocyte. Research by reproductive endocrinologists has advanced technology since the first "test-tube baby" was born in 1978 and continues to result in new and more effective techniques. The Centers for Disease Control and Prevention (CDC) reports that approximately 12% of women over childbearing age within the United States have used some form of fertility aid in an attempt to become pregnant. In 2009, 146,244 cycles of ART resulted in 45,870 live births and 60,190 infants, and the numbers of ART procedures continues to grow.[94] The procedure, which takes approximately 20 to 30 minutes to complete, is generally performed by a gynecologist who has had an advanced training fellowship in reproductive endocrinology and infertility.

The procedure is performed by initially stimulating maturation of the follicle with a gonadotropin-releasing hormone agonist, which induces pituitary-gland suppression and creates quiescent ovaries to prevent the production of a single dominant follicle. Follicle-stimulating hormone (FSH) and human menopausal gonadotropin are then administered, which induces 10 to 15 ovarian follicles. The patient is then given human chorionic gonadotropin (hCG), which induces the follicle to mature and move into the follicular fluid. The oocyte is retrieved transvaginally, transabdominally, or via laparoscopy with an ultrasonically guided probe 34 to 36 hours after hCG administration. All visible follicles are collected, washed, incubated for 4 to 6 hours in a culture medium, and examined microscopically. Most follicles contain only one oocyte.[93-94] Fertilization occurs in the IVF laboratory. The oocyte is identified and has minimal exposure to ambient room temperature, room air, and especially any chemical odors. Sperm are washed and centrifuged. Fresh media is added next to the centrifuged sperm, and those sperm that swim to the media, which can number 50,000, are placed with the oocyte. Male factor infertility, which affects 37% of couples seeking ART procedures, requires direct intracytoplasmic injection of sperm; 16 to 20 hours later, the fertilized oocytes are examined for evidence of fertilization. Within 3 to 5 days after fertilization is verified, the embryo (which has developed into 8 to 10 cells) is transferred into either the fallopian tube or (more commonly) the uterus. Timing must be coordinated with proper maturation of the uterine endometrium.[93-95] ART is found to increase the risk of multiple gestations. Also, it has been reported that atypical implantations of the fertilized ovum or zygote, such as abdominal, cervical, ovarian, or tubal pregnancy, occur more frequently with ART.[95] Common ART techniques are listed in Table 52-1. IVF was first performed over 30 years ago and is accepted now because of increased success rates, 31.4% in 2009. The CDC estimates that according to their research, over 1% of all live births within the Unites States today occur as a result of ART.[94]

Patients are assessed for antibodies to human immunodeficiency virus types 1 and 2 (HIV-1, HIV-2) and human T-cell lymphotropic virus type 1 (HTLV-1), hepatitis B antigen, and antibodies to hepatitis B and C. Patients are also tested for chlamydia, syphilis, gonorrhea, and cytomegalovirus. Smokers require twice as many attempts at successful IVF than nonsmokers, so smoking is actively discouraged.[93-95]

Anesthetic Considerations. IVF is generally performed on patients who are ASA class 1 or 2 in their third or fourth decade of life. Although IVF is a relatively simple procedure for the reproductive endocrinologist to perform, especially outside the operating room, IVF is an uncomfortable procedure and requires that patients do not move while the probe is guided for retrieval and later reimplantation. The vaginal wall must be pierced for the desired ovary to be accessed. Also, major blood vessels are present in the proximity of the ovaries, and their injury could lead to complications.[96]

Anesthesia requirements vary with the individual needs of the patient and the reproductive endocrinologist.[93,96] Multiple ART procedures may need to be performed until one of them is successful, so safe yet inexpensive anesthetic techniques are desirable.[94-95] Minimal sedation, moderate sedation/analgesia, regional intrathecal anesthesia, paracervical block, or general anesthesia can be administered to assist in making the procedure as comfortable and successful as possible.[93,95-96] Moderate sedation with analgesia is usually sufficient for most patients. None of the anesthetic techniques cause differences in reproductive outcome.[93,95-96]

TABLE 52-1 Common Assisted Reproductive Technology Techniques

Procedure	Description
In vitro fertilization (IVF)	Oocytes are removed, fertilization occurs in the laboratory, and the embryo is placed transcervically into the uterus or into the distal portion of the fallopian tube(s).
Gamete intrafallopian transfer (GIFT)	Oocytes and sperm are transferred into one or both fallopian tubes for fertilization. *Advantage:* Oocyte retrieval and gamete transfer occur with a single procedure. *Disadvantages:* Requires at least one patent fallopian tube and laparoscopic surgery. Fertilization cannot be confirmed.
Zygote intrafallopian transfer (ZIFT)	Fertilized embryos are placed into the fallopian tube. *Advantages:* Fertilization is confirmed. Laparoscopic surgery can be avoided if fertilization has not occurred. The embryos can be transferred at an appropriate developmental stage. *Disadvantage:* Requires a two-stage procedure, with added risks and costs. Requires at least one patent fallopian tube.
Tubal embryo transfer (TET)	Cleaving embryos are placed into the fallopian tube.
Peritoneal oocyte and sperm transfer (POST)	Oocytes and sperm are placed into the pelvic cavity.

Modified from Speroff L, et al. *Clinical Gynecologic Endocrinology and Infertility*. 6th ed. Baltimore: Lippincott Williams & Wilkins; 1999:1133-1148; Tsen LC. Anesthesia for assisted reproductive technologies. *Int Anesthesiol Clin*. 2007;45:99-113.

Anesthetic medications generally considered safe for use in anesthesia for ART are listed in Box 52-13. Anesthetists should consider using safe anesthetic techniques with quick onset and a short duration. It should be noted that propofol, lidocaine, and alfentanil have been shown to accumulate in the follicular fluid. Although no deleterious effects of any anesthetics have been identified, this area continues to be studied.[96-97] No data from human trials have ever condemned the use of local anesthetic agents for oocyte retrieval. Morphine has been shown to adversely affect fertilization of sea urchin eggs in vitro by allowing more than one sperm to enter the oocyte in 30% of cases, so it is not used because of the existence of safe alternatives such as fentanyl, alfentanil, remifentanil, and meperidine. Midazolam, when titrated in small doses to provide mild to moderate sedation and anxiolysis, has been shown to be safe, with no accumulation in follicular fluid or being a teratogen. Ketamine (0.75 mg/kg) with midazolam (0.06 mg/kg) used as moderate sedation/analgesia is safe as an alternative to general anesthesia with isoflurane. The literature has suggested the use of caution if the anesthetist desires to select a potent inhaled agent (especially sevoflurane and desflurane) because of possible negative effects to ART outcomes.[97] Nonsteroidal antiinflammatory agents such as ibuprofen, indomethacin, ketoprofen, ketorolac, meloxicam, naproxen, or oxaprozin are avoided owing to inhibition of prostaglandin synthesis and possible effects on embryo implantation.[96-97] Droperidol and metoclopramide have been shown to induce rapid hyperprolactinemia and should be avoided. Low plasma prolactin levels are associated with higher incidences of pregnancy.[97] Box 52-14 lists common anesthetic agents that could cause problems with ART.[96-97] The necessity for any medication given to the patient should be carefully considered, and the anesthetic technique should be kept simple and basic.

BOX 52-13 Anesthetic Medications Used for Assisted Reproductive Technologies

Intrathecal
- Bupivacaine
- Lidocaine
- Fentanyl
- Morphine

Paracervical Block
- Bupivacaine
- Lidocaine
- Mepivacaine

Intravenous Sedation or Total Intravenous Anesthesia
- Fentanyl
- Alfentanil
- Remifentanil
- Meperidine
- Ketamine
- Midazolam
- Propofol

Inhalation Agents
- Nitrous oxide

BOX 52-14 Common Anesthetic Agents That Could Cause Problems with Assisted Reproductive Technologies

- Morphine
- Sevoflurane
- Desflurane
- NSAIDs—ibuprofen, indomethacin, ketoprofen, ketorolac, meloxicam, naproxen, oxaprozin
- Droperidol
- Metoclopramide
- Postanesthesia care: As in all cases of anesthetic administration, the patient is assessed in a postanesthetic recovery area. Vital signs and pulse oximetry are assessed and must be stable. If intrathecal anesthesia was used, the patient must have a recovery of sensorium, be able to ambulate, and be able to void. All patients must be free of nausea.

NSAIDs, Nonsteroidal antiinflammatory drugs.

Office-Based Surgery

General Dental Procedures

Procedure Overview. Anesthesia for dental procedures and dental surgery can present many challenges. The demand for dental care and visits from patients are increasing. Dentistry has changed from a role of therapeutic treatment of dental disease to a role of prevention. The old mainstay was that 50% of the population never visited a dentist. This group used dentistry only for treatment of extreme pain or in an emergency. Latest demographic statistics show that this has changed for the better. Overall, rates vary drastically across the U.S. population, with approximately 44.5% of the population visiting a dentist at least once annually. More women see dentists annually than men, and as employment status, income, and educational levels increase, so do the number of annual visits to the dentist. Also, children ages 6 or younger and adults ages 65 or older are seeing dentists more frequently than in the past.[98] These numbers are expected to increase drastically

as with the United States government Healthy People Initiative adding oral health to the objectives for the current and coming years.[99]

Dental procedures may be performed in an operating room, a specially equipped hospital suite, an ambulatory surgical center, or a dental office operatory (dental surgical area).[100] Anesthesia may be required for dental procedures in the following areas of dentistry[101]:

- *Pediatric dentistry*—an age-defined specialty that provides primary and comprehensive preventive and therapeutic oral health care for infants and children through adolescence, including those with special healthcare needs.
- *Oral and maxillofacial surgery*—the specialty that includes the diagnosis, surgical, and adjunctive treatment of diseases, injuries, and defects involving both the functional and esthetic aspects of the hard and soft tissues of the oral and maxillofacial region.
- *Periodontics*—the specialty that encompasses the prevention, diagnosis, and treatment of diseases of the supporting and surrounding tissues of the teeth, or their substitutes, and the maintenance of the health, function, and esthetics of these structures and tissues.
- *Endodontics*—the specialty that is concerned with the etiology, diagnosis, prevention, and treatment of diseases and injuries of the pulp and associated periradicular (concerning the root of the tooth) conditions.
- *Prosthodontics*—the dental specialty involved with the diagnosis, treatment planning, rehabilitation, and maintenance of oral functions, comfort, appearance, and patient health associated with clinical conditions of missing or deficient teeth and/or oral and maxillofacial tissues along with biocompatible substitutes.
- *General dentistry*—encompasses the etiology, diagnosis, and treatment of conditions of oral, head, and neck tissues; the general dentist may perform procedures that encompass any or all of the dental specialty areas, depending on the training, abilities, and experiences of the general dentist.
- *Dental hygienist*—a licensed oral health professional trained to treat patients by the removal of dental plaque and calculus (tartar) above or below the gingiva.[100-101]

Anesthetic Considerations. Important considerations that must be part of the anesthesia treatment plan for the dental setting are outlined in Box 52-15. The patient may require minimal sedation, moderate sedation/analgesia, deep sedation/analgesia, or general anesthesia for dental surgery. The anesthesia required depends on the patient-related factors of fear, anxiety, age, medical condition, level of cooperation and behavior, gagging, ineffective local anesthesia in the past, mental impairment, and physical disability. A thorough, documented patient assessment along with appropriate laboratory studies and possible physician consultation regarding patient clearance for physically and/or psychologically stressful dental surgery are necessary.[102-104] In pediatric dentistry, a comprehensive and personalized discussion with the parent or guardian (with or without the patient present) of what the anesthetic procedure will entail, coupled with an opportunity for the parent or patient to engage in dialogue and ask questions, can alleviate the stress of the upcoming procedures for all parties.[102]

The dental operatory must be of adequate size for both access and egress of both the patient and personnel. Proper considerations and advanced planning must be made to accommodate patients according to the Americans with Disabilities Act.[105-106] Also, the anesthetist must have full and rapid access to both the patient and all required equipment and supplies. Full monitors are necessary.

BOX 52-15

Considerations Related to Anesthesia in the Dental Setting

- Anesthesia may be administered in an unfamiliar area. Carefully plan, equip, and set up the operatory so that it is as familiar and comfortable as in an operating room.
- The established airway will be shared with the dental surgeon.
- The potential exists for heavy bleeding because of the vast blood supply to the head and neck region.
- There could be the use of small instruments, burs (dental drill bits), files, implants, and filling materials in the mouth, with the potential of falling into the oropharynx or being aspirated.
- Patients may be receiving dental prosthetic devices such as crowns, bridges, or full or partial dentures, which can also affect the airway.
- There exists the possibility of intense pain, transmitted primarily by the maxillary and mandibular divisions of the trigeminal nerve.
- Patients usually display a high level of anxiety, and adequate time must be incorporated into the schedule to allow for safe anesthetic treatment.

Consider the use of the antisialagogue glycopyrrolate, because dental surgery can stimulate the flow of saliva. Excess salivation can lead to coughing, choking, laryngospasm, or aspiration in the sedated patient. Delivery of anesthesia in the dental operatory should be as familiar as if it were in an operating room. Postoperative problems in dentistry generally are minimal but can involve pain, swelling, bleeding, PONV, the vasovagal response, airway problems, hypoxemia, or hypothermia, as a result of anesthetic procedures other than local anesthesia administered. Hypothermia can be addressed by the use of an electric blanket; forced-air warming may or may not be feasible for the dental operatory.

General dentists and board-certified dental specialists are also trained to administer intraoral local anesthesia, which is a cardiac depressant and may cause either CNS depression or excitation. Local anesthesia for dentistry is commonly administered with an aspirating syringe/needle system. Local anesthetic is available in 1.8-mL glass capsules, both with and without epinephrine, or levonordefrin (Neo-Cobefrin) as a vasoconstrictor.

Dental specialists and specially trained general dentists can be licensed by state dental boards to administer the continuum of anesthesia, from minimal sedation to general anesthesia while performing the dental surgery. The dental literature reports good long-standing success rates and safety, but caution is necessary.[107-109]

Each dental specialty has particular anesthetic considerations, which are discussed in the following sections.

Pediatric Dentistry. Pediatric dental patients can require the continuum of anesthesia from enteral minimal sedation to parenteral moderate sedation/analgesia, deep sedation/analgesia, or general anesthesia if the patient is behaviorally uncooperative, immature, frightened, or mentally disabled or because of the necessity to perform all necessary dental surgery in one session. Pediatric dentists may have a patient immobilization device available, commonly called a *papoose board*, to safely restrain the patient until anxiolytic anesthesia can be administered. Anesthetic choices such as oral or intravenous ketamine; a mixture of oral chloral hydrate, meperidine, and hydroxyzine; intravenous diazepam; midazolam; and propofol have been used with success.[107,109-110] Premedication with orally administered midazolam

dissolved in a small amount of the liquid forms of acetaminophen, ibuprofen, aspirin, or low-sugar clear juice is commonly used. For the liquid forms of acetaminophen, ibuprofen, or aspirin, the anesthesia provider should refer to the package insert for the proper dosing based on the patient's weight. Intranasal or rectal midazolam can be used alone or given before general endotracheal anesthesia and has proved as effective as nitrous oxide for sedation.[107,109-110] After an inhaled mask or intravenous induction, endotracheal intubation via either the oral or nasal route can be performed to allow the pediatric dentist full access to the mouth. Pediatric dentists typically are and should be very cognizant of the importance of sharing the airway during surgery. Typical pediatric dental procedures include restorative dentistry, such as fillings of amalgam or composite, and placement of stainless steel crowns for posterior teeth, polycarbonate crowns, composite crowns, or stainless steel crowns with porcelain for anterior teeth, pulpotomies, tooth extractions, and space maintainers. Successful treatments can be provided along with stress reduction for the patient, parents or guardians, and for the healthcare providers with appropriate airway maintenance under deep sedation or general anesthesia.[107-110]

Oral and Maxillofacial Surgery. Procedures performed within the specialty of oral and maxillofacial surgery (OMS) are among the most invasive in dentistry. Oral surgeons perform uncovering of teeth for orthodontic treatment; extraction of impacted, severely carious, and multiple teeth; insertion of dental implants, treatment of infections of the head and neck; surgical remodeling of maxillary and mandibular alveolar bone; facial cosmetics; and removal of soft-tissue or bony tumors, as well as many other procedures. These procedures can produce both severe pain and heavy bleeding. Many OMS procedures are performed within the office setting. Oral and maxillofacial surgeons receive 6 years of postdoctoral training and become licensed by the state dental board to perform the continuum from minimal sedation to anesthesia (general anesthesia) care. Patients can have challenging physical and mental conditions; therefore, a thorough preanesthetic assessment is necessary.[111] The patient's airway is shared with the oral surgeon; therefore, nasal intubation may be necessary. It may be possible to perform some oral surgical procedures while carefully working around an unsecured tube or with a standard or reinforced LMA. Local anesthesia in combination with intravenous sedation (propofol, midazolam), inhalation sedation (nitrous oxide), inhaled potent endotracheal anesthetics, and total intravenous general anesthesia are techniques available for office-based OMS.[103,111] Remifentanil has become a useful adjunct with the techniques listed to counteract the intense stimulation of OMS.[112] An anesthesia awareness/level of consciousness/depth of sedation monitor is also useful for careful anesthetic titration.[110]

Periodontics. Periodontal procedures can involve painful stimulation. Periodontists generally work in a particular quadrant of the patient's mouth and administer local anesthetic for the particular area of surgery. Periodontal treatment involves surgery of the teeth, gingiva, connective tissue, periodontal ligament, and alveolar bone, as well as insertion and maintenance of dental implants. Local anesthetics are administered with a normal epinephrine 1:100,000 concentration, unless contraindicated, along with greater than normal epinephrine concentrations (1:50,000) injected directly into the gingiva because of its local anesthetic ability and for hemostasis. Periodontal surgery can involve lengthy procedures with moderate amounts of hemorrhage, and can be well managed with minimal sedation (both enteral or with inhalation sedation) or moderate sedation/analgesia.[103,111] Use of standard monitoring is necessary. Midazolam with a propofol infusion helps achieve the goals of safety and comfort for periodontal surgical patients.[103]

Endodontics. Anesthesia for endodontic procedures is similar to that described for periodontal surgery. Local anesthesia provides adequate comfort, but in the presence of patient anxiety related to the length of endodontic procedures, minimal sedation (both enteral or with inhalation sedation) or moderate sedation/analgesia can make the procedure tolerable and less anxiety producing for the patient. A dental dam is usually applied around the tooth and held in place with a special clamp to prevent aspiration of dental burs and endodontic files.

General Dentistry and Prosthodontics. General dentistry can encompass all procedures from all of the dental specialties, depending on the interest and training of the general dentist. Anesthesia can be delivered along the continuum of care to ensure safety for the patient and to fill the requirements of the particular dental procedure.[100,103-104]

Dental Hygiene. Dental hygienists are also involved with providing dental care to patients who may require anesthesia along the continuum from minimal sedation/analgesia to deep sedation/analgesia with combinations of inhalation nitrous oxide/oxygen, local anesthesia, and intravenous medications. Thorough treatment can generate tooth or gingival sensitivity and pain. Even in the absence of pain, special populations such as pediatrics, the mentally handicapped, and those with severe anxiety disorders may require some degree of anesthesia for even routine dental care. Procedures range from routine hygiene to deep scaling and root planing of teeth with heavy dental accretions.

Postanesthesia Care. Patients should be allowed to recover in a quiet, monitored environment. Intravenous access allows the titration of additional analgesia or antiemetics as necessary. Fortunately, patient morbidity from general anesthesia for dental procedures is low.[113] Patients who receive inhaled sedation are less stressed postoperatively than those who receive general anesthesia, but TIVA procedures with proper airway maintenance and supplemental oxygen also prove to be a great success.[102,104,113]

Invasive dental procedures can be another source of distress in children, which can lead to crying, nausea, vomiting (PONV), and bleeding postoperatively. The addition of the potent opioid morphine, ketorolac, or both greatly aids patient comfort in the postsurgical anesthesia recovery area. The use of oral minimal to moderate sedation in pediatric patients ages 2 to 34 months has been found to have no effect on behavior when the individual requires treatment later.[102,109] Adolescents who have undergone sedation for childhood dental therapy are found to possess a high level of anxiety regarding dentistry, when compared with adolescents without that history.[109-110]

Psychiatric Procedures

Electroconvulsive Therapy

Electroconvulsive therapy (ECT) is the intentional inducement of a generalized seizure of the CNS for an adequate duration of time to treat patients with certain severe neuropsychiatric disorders.[114] The American Psychiatric Association continues to support ECT as a safe and evidence-based medical treatment when administered by trained, qualified personnel.[115] ECT in general, however, continues to be a topic of controversy. Research studies differ in the effectiveness of ECT. Most studies agree that the short-term effects of ECT are substantial; however, they argue the long-term benefits.[116-119]Antidepressant medication administration, along with ECT, is well tolerated by patients, and both therapies can be beneficial. Most patients receive three treatments per week and can undergo a total of 6 to 12 treatments overall.[114,118] When

clinical improvement is seen, it typically occurs within the first three to five treatments, and positive response to treatment is seen in 50% to 90% of patients, even those who had been treatment resistant.[116,119] Death from ECT itself is possible but is rare. ECT is also used in certain patients who experience mania, catatonia, vegetative dysregulation, inanition, suicidal drive, and schizophrenia with affective disorders, and has begun to be used for patients with Parkinson's disease.[114,116-119]

ECT is one of the most controversial and invasive treatments in medicine. The first documented use of ECT was in 1938. Early ECT was performed without anesthesia, with the occurrence of many adverse effects such as bitten tongues, broken bones, and broken teeth. Treatment involves placement of electrodes with a conducting gel, either right-sided unilaterally or bitemporally bilaterally. An alternating current of electricity is passed through the electrodes.[114] Theories for the mechanism of ECT are related to profound changes in brain chemistry, such as enhancement of dopaminergic, serotonergic, and adrenergic neurotransmission. Another theory postulates the release of hypothalamic or pituitary hormones, which have antidepressant effects. Finally, ECT produces anticonvulsant effects that raise the seizure threshold and decrease seizure duration, exerting a positive effect on the brain.[114]

Anesthetic Considerations. Anesthesia for ECT involves the administration of an ultra-brief general anesthetic to provide lack of consciousness to the patient for the procedure (Table 52-2).

A thorough preanesthetic assessment must be performed, with consideration given to the possible critical physiologic hemodynamic responses generated by the induced seizure activity. Box 52-16 lists possible physiologic effects as a result of ECT.

Few absolute and relative contraindications to ECT exist (Box 52-17).[114,120,121]

Patients may have results of laboratory studies, a pharmacologic regimen, and ECG readily available because of their psychiatric hospitalization. Informed consent is obtained whenever possible from the patient or legal guardian. An intravenous catheter is inserted in a peripheral vein. The patient is monitored with a pulse oximeter, ECG, noninvasive blood pressure monitor, temperature-monitoring device, and peripheral nerve stimulator. Use of $ETCO_2$ monitoring has been suggested because hypercarbia and hypoxia shorten seizure duration. Suction, oxygen, a positive-pressure Ambu bag and facemask, and rubber bite protectors must be present, as well as necessary airway and cardiovascular resuscitation equipment, medications, and supplies. ECT is usually performed in a dedicated psychiatric suite or special treatment room.[121-122]

The patient is preoxygenated before induction. Anticholinergics may be administered as an antisialagogue or to prevent asystole.[122-124] The induction agent is administered intravenously. Either propofol or etomidate may be used without compromise of the therapy.[125-128] Ketamine also has been used, although an enhanced hemodynamic response and increased intracranial pressure are possible after using ketamine.[121,123] After loss of consciousness, positive-pressure ventilation is applied to the patient via the breathing bag and a facemask and is continued until after treatment is completed and spontaneous respirations resume. To assess the duration of the induced convulsion, the psychiatrist usually applies a tourniquet (or manual blood pressure cuff inflated to slightly greater than the systolic blood pressure) above a lower extremity so that the muscle relaxant cannot reach the skeletal muscle in the extremity. A rubber bite block is gently placed in the patient's mouth to prevent biting of the teeth, lips, and tongue, and an ultra–short-acting muscle relaxant is administered. Succinylcholine is typically the muscle relaxant of choice for electroconvulsive therapy because of its rapid onset, short duration, and independent reversibility.[121-123] Nondepolarizing agents can be used; however, induction dosage is typically adjusted to create a shorter duration of neuromuscular blockade.[123,129] A nerve stimulator must be used,

TABLE 52-2 Anesthetic Medications Used for Electroconvulsive Therapy

Drug	Dose
Anticholinergics	
Atropine	0.4-1 mg IV or IM
Glycopyrrolate	0.005 mg/kg IV or IM
Anesthetics	
Alfentanil	0.2-0.3 mcg/kg IV
Etomidate	0.1-0.3 mg/kg IV
Ketamine	0.5-1 mg/kg IV
Propofol	0.75-1.5 mg/kg IV
Muscle Relaxants ***Depolarizing***	
Succinylcholine	0.5-1 mg/kg IV (onset 30-60 seconds)
Nondepolarizing	
Cisatracurium	0.15-0.25 mg/kg IV (onset 1-2 min)
Atracurium	0.3-0.4 mg/kg IV (onset 6 min)
Rocuronium	0.3-0.9 mg/kg IV (onset 1-2 min)

Modified from White PF. *Perioperative Drug Manual*. 2nd ed. Philadelphia: Saunders; 2005; Wagner KJ, et al. Guide to anaesthetic selection for electroconvulsive therapy. *CNS Drugs*. 2005;19:745-758; Mirzakhani H, et al. Neuromuscular blocking agents for electroconvulsive therapy: a systemic review. *Acta Anaesthesiol Scand*. 2012;56:3-6.
IM, Intramuscular; *IV*, intravenous.

BOX 52-16

Possible Physiologic Effects of Electroconvulsive Therapy

Cardiovascular

Parasympathetic Response During Tonic Phase of Seizure

- Decreased heart rate
- Hypotension
- Bradydysrhythmias

Sympathetic Response During Clonic Phase of Seizure

- Tachycardia
- Hypertension
- Tachydysrhythmias

Cerebral

- Increased cerebral blood flow (increases of 100% to 400% above baseline are possible)
- Increased intracranial pressure

Other

- Increased intraocular pressure
- Increased intragastric pressure

Adapted from Lee M. Anesthesia for electroconvulsive therapy. In: Atlee JL, ed. *Complications in Anesthesia*. 2nd ed. Philadelphia: Saunders; 2007:903-905; Reti IM, et al. Safety considerations for outpatient electroconvulsive therapy. *J Psychiatr Pract*. 2012;18(2):130-136.

and appropriate neuromuscular blockade reversal agents should be administered if necessary. The electrodes are applied, the proper waveform and current level are selected, and the electroconvulsive seizure is induced. The seizure lasts from 30 to 90 seconds; the motor seizure is shorter than the seizure duration as seen on an electroencephalogram (EEG). Use of an anesthesia awareness/level of consciousness/depth of sedation monitor correlates with the EEG, and it can be a useful tool for the anesthetist and the psychiatrist.[122] The level of sedation displayed by this monitor correlates with the proper point to induce seizure, the duration of seizure, and the potential for awareness during the ECT procedure.[121-122] At the end of the seizure, spontaneous respirations resume, the patient is transferred to a recovery area, and vital signs are continually monitored until the patient is determined to be stable and able to be safely discharged.[114,120-122] Certain anesthetic medications and techniques such as hyperventilation can affect seizure duration (Box 52-18).

Adult patients about to undergo ECT should follow fasting guidelines of at least 6 hours for solids and 2 hours for liquids. Necessary bronchodilators may be taken. Oral medications, such as antihypertensives, cardiac medications, anticoagulants, and thyroid medications, may be taken with a sip of water up to 1 hour before the procedure.[120-122] Rapid-sequence induction of general anesthesia with applied cricoid pressure and endotracheal intubation can be performed. One must take into consideration the total number of ECT treatments to be received, weighed against the necessity for repeated intubations and the fact that most patients, even obese patients, have rarely been found to aspirate as a result of ECT.[120] The CRNA may perform a rapid-sequence induction and apply cricoid pressure until the protective reflexes return and the danger of aspiration is eliminated, rather than intubating the patient.

Postanesthesia Care. The intentional creation of CNS convulsions has profound effects on the patient's physiology. Patients usually experience temporary cognitive and memory impairment after ECT.

BOX **52-17**

Absolute and Relative Contraindications to Electroconvulsive Therapy

Absolute Contraindications to ECT

- Pheochromocytoma
- Recent myocardial infarction (less than 4-6 weeks ago)
- Recent cerebrovascular accident (3 months ago or less)
- Recent intracranial surgery (3 months ago or less)
- Intracranial mass lesion
- Unstable cervical spine

Relative Contraindications to ECT

- Angina
- Congestive heart failure
- Cardiac rhythm management device (pacemaker, automatic internal cardiac defibrillator [AICD])
- Severe pulmonary disease
- Major bone fracture
- Glaucoma
- Retinal detachment
- Thrombophlebitis
- Pregnancy

Modified from Lee M. Anesthesia for electroconvulsive therapy. In: Atlee JL. *Complications in Anesthesia*. 2nd ed. Philadelphia: Saunders; 2007:903-905; Reti IM, et al. Safety considerations for outpatient electroconvulsive therapy. *J Psychiatr Pract*. 2012;18(2):130-136.
ECT, Electroconvulsive therapy.

The first type of impairment that may be seen is postictal confusion, in which the patient is transiently restless, confused, and agitated immediately after the convulsive episode and for approximately 30 minutes. The agitation can be difficult to manage for the recovery nurse. Some patients require physical restraint or sedation with a benzodiazepine or an antipsychotic medication such as haloperidol. One theory postulates that the anxiety is a result of increased plasma lactate levels possibly caused by inadequate neuromuscular blockade and that increasing the dose of muscle relaxant is necessary with next treatment.[122,129]

A second type of cognitive impairment that may be seen later is anterograde memory dysfunction, in which the patient may rapidly forget new information. The patient may not remember things that he or she does or is told in the days after ECT. Anterograde amnesia usually subsides within days or a few weeks. However, it can be frightening to the patient. A third cognitive dysfunction is retrograde memory dysfunction, which is the forgetting of memories from several weeks to several months before the ECT treatment. No evidence suggests that ECT causes any brain damage, nor does it impair the long-term ability for the patient to learn and retain new information. The cognitive effects described vary depending on the frequency and the number of ECT treatments the patient has received. The quantities of energy used to elicit the convulsions and the placement of the electrodes are also

BOX **52-18**

Effects of Common Medications and Conditions on Seizure Duration

Medications That Can Prolong Seizure Duration

- Alfentanil with propofol
- Aminophylline
- Caffeine
- Clozapine
- Etomidate
- Ketamine (a proconvulsant)

Conditions That Can Prolong Seizure Duration

- Hyperventilation/hypocapnia

Medications That Can Shorten Seizure Duration

- Diltiazem
- Diazepam
- Fentanyl
- Lidocaine
- Lorazepam
- Midazolam
- Propofol
- Sevoflurane

Medications with No Apparent Effect on Seizure Duration

- Clonidine
- Dexmedetomidine
- Esmolol (may possibly shorten seizure duration)
- Labetalol (may possibly shorten seizure duration)
- Nicardipine
- Nifedipine
- Nitroglycerin
- Nitroprusside

Modified from Stensrud PE. Anesthesia at remote locations. In: Miller RD, et al. *Miller's Anesthesia*. 7th ed. Philadelphia: Churchill Livingstone; 2010:2477-2479; Wagner KJ, et al. Guide to anaesthetic selection for electroconvulsive therapy. *CNS Drugs*. 2005;19:745-758.

factors. Even the type of anesthetic drugs used is believed to be involved.[114]

Cardiovascular stimulation also occurs with ECT. The sympathetic and parasympathetic nervous systems are stimulated sequentially. Therefore, the patient may experience an increase in heart rate and blood pressure, followed by a period of bradycardia or even asystole. This can lead to increases in myocardial oxygen demand, arrhythmias, and transient ischemic changes in susceptible individuals. Transient cardiac changes can be managed before ECT with anticholinergics, intravenous local anesthetics such as lidocaine, or intravenous narcotics such as remifentanil.[114,121-122,130,131] Changes after ECT can be managed with β-blockers such as esmolol or labetalol, calcium channel blockers, or other antihypertensives.[131]

Finally, patients also may experience headache, muscle aches, or nausea. Symptoms of headache or muscle ache respond well to acetaminophen, aspirin, or nonsteroidal antiinflammatory agents such as intravenous or intramuscular ketorolac or oral ibuprofen.[120-122] Nausea can be caused by the stress and anxiety before the ECT treatment, the anesthetic agents used, the seizure itself, or air in the stomach from assisted ventilation. Nausea can be treated with agents such as ondansetron, dolasetron, granisetron, or metoclopramide.[120-122]

New Therapies for Major Depressive Disorders

Two new therapies for severe major depressive disorders are now available, which often require anesthetic treatment: repetitive transcranial magnetic stimulation (rTMS) and vagus nerve stimulation (VNS).[132,133] Neuroanatomic studies have suggested that patients with major depressive disorder (MDD) have dysfunction within the frontal cortical-subcortical-brainstem neural network, specifically the dorsolateral prefrontal cortices (DLPFC). ECT and antidepressant medications do not act in these discrete areas of the brain, but new therapies stimulating these focal areas of the brain are now approved and in use in the United States.

Repetitive Transcranial Magnetic Stimulation and Magnetic Seizure Therapy. Repetitive transcranial magnetic stimulation (rTMS) uses electric current passing through an electromagnetic coil that has been placed on the scalp. The coil delivers brief, rapidly changing magnetic field pulses to specific areas of the brain. These bursts of pulses are called a "train" of stimuli. Multiple trains of rTMS may be delivered in one session. The scalp and skull are transparent to magnetic fields, an advantage over ECT, in which the scalp and skull are resistors to the electrical stimulation. To produce antidepressant effects, a convulsion must be initiated by trains of rTMS, because subconvulsive trains of rTMS are ineffective.[132,134-136]

Convulsive magnetic energy levels are determined by the use of motor threshold (MT). MT is the point at which a single pulse of magnetic energy begins to elicit an electromyographic response, that is, a twitch, usually of the abductor pollicis brevis muscle of the thumb or first dorsal interosseous muscle of the index finger.[132,134] Treatment with rTMS is safe and well tolerated, with reduced cognitive side effects when compared with ECT. Patients are found to recover much more rapidly from rTMS or MST therapy as compared with ECT.[136,137]

Magnetic seizure therapy (MST) uses a higher-intensity, more frequent, and longer-duration magnetic seizure-inducing dose when compared with the magnetic dose required for rTMS. MST can stimulate tonic-clonic seizures in more localized and focal regions of the prefrontal cerebral cortex when compared with ECT, as well as generalized tonic-clonic seizures that resemble ECT.[135-137] MST does not produce the rigid bilateral masseter muscle contractions noted during ECT but can produce elevations in blood pressure and heart rate similar to ECT.[137]

After rTMS some patients experience mild headache, disorientation and inattention (although patients become reoriented much more quickly than with ECT), retrograde amnesia, some anterograde amnesia, transient auditory threshold increases due to the high-frequency clicking sound heard during coil discharge (which can be alleviated with the use of foam earplugs), and (rarely) generalized seizure.[134,135] A single TMS treatment may be all that is necessary for treating certain severe MDD nonpsychotic patients along with their medications, although rTMS may be necessary.[132]

The literature describes anesthesia requirements for rTMS or MST from none needed to ultra-brief general anesthesia as for ECT.[132,134-137] A patent and secure intravenous catheter is established, and full monitors are applied. Glycopyrrolate 0.004 mcg/kg is administered as an antisialagogue along with ketorolac, 0.4 mg/kg, 2 to 3 minutes prior to induction of ultra-brief general anesthesia. Etomidate 0.15 to 0.2 mg/kg can be used for induction, as well as propofol, 1 to 2.5 mg/kg. Succinylcholine, 0.5 to 1 mg/kg, can be used as the muscle relaxant after isolation of a lower extremity for observation of seizure duration. Use the smallest amount of muscle relaxant necessary to enable recovery from paralysis prior to the return of consciousness. The anesthetist can then manually hyperventilate the patient's lungs with a facemask to an ET_{CO_2} value of 30 to 34 torr. At this point, the magnetic stimulus may be applied.[135,137]

Vagus Nerve Stimulation. VNS requires surgical implantation of a programmable battery-powered electrical stimulator that connects with the patient's left vagus nerve (cranial nerve X). The stimulator is usually implanted in the patient's chest with minimal sedation, moderate sedation/analgesia, deep sedation/analgesia, or under general anesthesia. Because of the delicacy of the surgery and its proximity to vital structures, no extraneous patient movement is permitted. Although originally approved for treatment-resistant epilepsy, the VNS is now approved for major depressive episodes that have not responded to four antidepressant medication trials.[133,138,139]

Radiologic and Diagnostic Procedures

Medical science has been able to use the sciences of physics, chemistry, and computers to produce remarkably accurate images of the internal structure and function of the body to aid medical diagnosis. Energy is transmitted to the patient and interacts with patient tissues. This energy is then detected, processed, and displayed on a computer console, which allows images to be selected for further investigation and diagnosis. Some medical images are created in real time and allow observation of flow or changes in tissue resulting from treatment.

Procedure Overviews

Computed Tomography. Computed tomography (CT) uses x-rays generated from a rotating anode x-ray generator. The patient is placed supine on a flat, wooden, wheeled platform and moved inside the scanning gantry. X-rays are then projected through the patient at different angles, penetrating tissues differently according to the atomic numbers of the atoms within the tissue. Dense tissue such as bone attenuates (reduces the energy of) the x-ray beam more than less dense tissue such as muscle, yielding high-resolution images of the scanned tissue. The patient images are then detected, and the computer acquires the image data. Finally, an image analyzer projects the analyzed data in the form of a tomogram or body section slice onto an operator console and a

physician-viewing console. CT is excellent for imaging bone. The diagnostic quality of a CT scan is enhanced with the injection of intravenous contrast media (ICM). Contrast media containing iodine may be administered to the patient enterally or parenterally to further attenuate the x-ray beam to enhance the images for CT vascular or gastrointestinal studies.[140,141]

Magnetic Resonance Imaging. Magnetic resonance imaging (MRI) uses the dipole moment (i.e., the ability of the atomic nucleus to behave as a magnet) of the hydrogen atom. The patient is placed supine within the scanning gantry or bore of the magnet. The magnet used for MRI can be a permanent magnet or a powerful superconducting electromagnet cooled with liquid helium to 4° Kelvin. Magnetic strength is measured in teslas (T); 1 T is equivalent to 10,000 gauss or oersted. MRI magnets can generate field strengths of 0.15 to 4 T, although MRI magnetic field strength generally ranges from 0.15 to 2 T. The quality of the MRI image is directly related to the strength of the magnetic field.[140,142] The spin of the electron in hydrogen will align the hydrogen atoms parallel to this powerful magnetic field. The patient's water-containing tissues are then excited with variable radiofrequency pulses. After the proton in hydrogen receives this radiofrequency energy, it emits radiofrequency energy with three-dimensional–appearing spatial information. MRI technology now allows its use within the operating room with an open-bore, portable, 0.12-T, low-intensity magnet to assist the neurosurgeon with diagnostic decisions.[140,143] Contrast media are also used in MRI studies to enhance the patient's tissues and allow the scan to provide further diagnostic information. MRI contrast is most commonly gadopentetate dimeglumine, which contains the element gadolinium bound as a chelated structure and administered primarily parenterally but rarely enterally.[140,143,144]

The FDA classifies the MRI as a class II device. Class II devices require special labeling, mandatory performance standards, and post-market surveillance by the FDA. The electromagnetic energy greatly drops off just outside the margins of the bore of the electromagnet. This is called the *fringe field*. There are no known reports of harmful physiologic effects from magnetic fields.[140,141]

Because of the potential of danger of the powerful electromagnetic attraction of ferromagnetic objects to both the patient and healthcare personnel, the American College of Radiology divides the MRI suite into four zones:

- Zone 1 has public access and no supervision, such as the hallway outside the MRI suite.
- Zone 2 has public access and limited supervision, such as the entrance into the MRI suite.
- Zone 3 has limited access and explicit supervision, such as immediately outside the MRI scanner room where MRI controls may be located.
- Zone 4 is the MRI scanner room itself and has strict and controlled access that is under constant supervision.[145]

Interventional Radiology (Vascular and Nonvascular) and Radiotherapy or Radiosurgery. Interventional radiology (IR) involves minimally invasive procedures and therapies performed by radiologists, especially in patients at high medical risk.[121,146-147] Major IR therapies include angiography, the embolization of blood vessels such as arteriovenous malformations or for epistaxis, the delivery of chemical or physical vascular occlusive devices, the removal of thrombi, ablation of aneurysms, and angioplasty of blood vessels with stent placement.[121,146-148] Box 52-19 lists indications for endovascular embolization procedures. See Chapter 25 for a discussion of interventional vascular surgery and Chapter 28 for interventional neuroradiology procedures.

BOX 52-19

Indications for Endovascular Embolization

- Arteriovenous malformation
- Arteriovenous fistula
- Intracranial aneurysm
- Recurrent epistaxis
- Hemoptysis
- Traumatic solid organ hemorrhage
- Preoperative major organ tumor embolization for blood loss reduction
- Gastrointestinal hemorrhage
- Uterine leiomyoma (fibroid)
- Uterine hemorrhage
- Pelvic fracture hemorrhage
- Postoperative hemorrhage after prosthetic hip or knee replacement
- Varicocele

From Higgins GA. Embolization procedures. In Atlee JL. *Complications in Anesthesia*. 2nd ed. Philadelphia: Saunders; 2007:912-914.

Radiation is a treatment itself for both benign tumors (e.g., low-grade astrocytoma, meningioma, pituitary adenoma, craniopharyngioma, schwannoma, pineocytoma, chemodectoma, low-grade papillary neoplasms) and aggressive tumors (e.g., germinoma, primitive neuroectodermal tumor, chordoma, intermediate-grade pineal tumor, immature teratoma, undifferentiated sarcoma, anaplastic oligoastrocytoma, and metastatic tumors). Radiation surgery is the delivery of a single massive dose of radiation to the target tissue. Radiation therapy is the delivery of smaller doses of radiation over several sessions.[149]

Gamma radiation is used for radiotherapy and radiosurgery. The gamma radiation is introduced to the patient by the use of either a GammaKnife or a CyberKnife. Each uses beams of gamma rays obtained from the radioactive decay of cobalt 60 or from a linear accelerator. The CyberKnife is used by first obtaining stereotactic three-dimensional images, which then allow computer-controlled robot arm guidance of the CyberKnife. The CyberKnife therapy delivers a sequence of many hundreds of gamma beams to the cancerous tumor from many different directions. GammaKnife therapy delivers gamma radiation to the cancerous tumor simultaneously in a single dose.[148,149]

Interventional Neuroradiology. Interventional neuroradiology (INR) is the diagnosis and treatment of CNS diseases endovascularly to deliver therapeutic medications or devices. INR was first used in the early 1980s, when digital subtraction angiography was developed. Digital subtraction angiography first uses an original angiograph of the blood vessels to be studied. Then a contrast medium is injected into the same blood vessels, and opaque structures such as bone and tissues can be digitally subtracted or removed from the angiographic image, leaving a clear picture of the blood vessels.[150]

Improvements in vascular access techniques, new thin and flexible catheters and guidewires, and the development of innovative coils and therapeutic medications have made new treatments possible. Conditions that once required extensive surgery, with accompanying patient morbidity and mortality, can now be performed less invasively.[146,150] Some major procedures performed with INR are mechanical or chemical removal of emboli or thrombi that cause stroke, the physical occlusion of malformed vascular structures such as arteriovenous malformations with chemicals or flow-directed balloons, dilation of stenotic blood

BOX **52-20**

Some Indications for Radiologic and Diagnostic Procedures

Computed Tomography
- Assessment of the airway with neck or thoracic tumors
- Assessment of bony trauma, especially the spine
- Assessment of head trauma
- Assessment of increased intracranial pressure
- Assessment of neoplasms
- Imaging of brain tumors
- Imaging of intracerebral hemorrhage

Magnetic Resonance Imaging
- Central nervous system imaging
- Imaging of the blood-brain barrier
- Kidney imaging
- Liver imaging
- Urinary bladder imaging

Interventional Radiology (Vascular and Nonvascular), Radiotherapy, and Radiosurgery
- Angiography
- Catheterization of ducts, and vascular lesions for drainage of cysts or hemangiomas (e.g., liver hydatid cyst, renal cyst, soft-tissue hemangiomas)
- Catheterization of tumors for delivery of chemotherapy directly to tumors (e.g., liver tumors)
- Embolization or embolectomy or thrombofragmentation of vascular lesions and tumors (pulmonary thrombi or emboli)
- Radiosurgery
- Stereotactic radiosurgery
- Radiotherapy
- Transluminal dilation, angioplasty, and stent insertion for vascular stenosis, biliary stenosis, or tracheal malacia

Interventional Neuroradiology
- Angioplasty and stent placement for an atherosclerotic lesion
- Angioplasty or endovascular ablation of cerebral vasospasm from aneurysmal subarachnoid hematoma
- Balloon angioplasty of cerebral vasospasm
- Brain arteriovenous malformation embolization
- Carotid artery stenting
- Carotid cavernous fistula and vertebral fistula treatment
- Carotid test occlusion
- Dural arteriovenous malformation embolization
- Embolization of highly vascularized intracranial tumors
- Glomus tumor treatment
- Intracranial aneurysm ablation
- Juvenile nasopharyngeal angiofibroma treatment
- Meningioma treatment
- Sclerotherapy of venous angiomas
- Spinal cord lesion embolization
- Therapeutic carotid occlusion
- Thrombolysis of acute thromboembolic stroke
- Trigeminal nerve rhizotomy or glycerol injection
- Vein of Galen malformation treatment
- Vertebroplasty for back pain/vertebral body fractures

vessels, and embolization (blocking blood flow) of cerebral vascular aneurysms using catheter-deployed coils.[146,150,151]

Box 52-20 lists some current uses for each of the previously mentioned radiologic and diagnostic procedures. As technology advances, more uses will be seen.

Anesthetic Considerations

Computed Tomography. CT scans require that the patient remain as motionless as possible for several minutes to an hour. Patient motion can produce artifacts in the diagnostic images to be read by the radiologist. Patients must lie on a flat, lightly padded wheeled platform, which is rolled into the short-bore scanning gantry of the CT scanner. Although the majority of patients are able to cooperate and tolerate CT, others may not be able because of extremes in age, concurrent medical conditions, or mental disability. The CT scan is neither physically invasive nor painful. Patients enter the CT scanner without precautions for ferromagnetic objects as for an MRI scan. CT is more rapidly performed than an MRI scan, especially if a spiral CT scanner is used.

The patient may require anesthesia anywhere along the continuum from minimal sedation to general anesthesia. Use of ferromagnetic anesthesia equipment and supplies around the CT scanner is not a concern. A standard anesthesia machine, laryngoscope and blades, and intravenous infusion pumps can be used as if in the operating room. An LMA is an appropriate alternative choice as a minimally invasive and secure airway in the patient without contraindications to its use. An LMA is contraindicated in patients with gastroesophageal reflux disease or a full stomach. Attention must be paid to securing the airway, and the anesthesia breathing circuit, the leads for the ECG, the noninvasive blood pressure cuff, the intravenous line, and the pulse oximeter must extend into the scanning gantry. The anesthetist must allow for extra lengths of anesthesia circuitry and electrical monitoring leads because of patient movement that will occur during intermittent repositioning of the mechanized table that positions the patient within the scanning gantry.[121,141]

Sedation can be performed with a variety of agents, including midazolam, pentobarbital, diazepam, or propofol. General anesthesia can be performed with TIVA, such as with intravenous propofol, or with potent inhaled agents.

All personnel must be aware of the use of ionizing radiation during the CT scan and should take precautions to be shielded from any exposure to the radiation. Radiation exposure is cumulative over a lifetime, and every precaution must be made to protect oneself from any unnecessary doses of radiation, which can cause genetic mutation and may lead to cancer. Protection can be accomplished with the use of a lead-glass barrier, a lead apron, a lead thyroid collar, and lead-glass safety glasses. Radiation dose badges are available that attach to clothing. The badge monitors the dose of radiation received and is evaluated monthly.[141] Federal technical information and guidelines for working in conjunction with radiation is available from the U.S. Environmental Protection Agency.[152]

ICM can cause an unexpected allergic reaction in some patients, varying from itching with hives to severe, life-threatening anaphylactoid and anaphylactic reactions.[144,153] Adverse reactions to ICM are more likely to develop in patients with asthma, a history of allergy or in patients with multiple morbidities. These reactions can be divided into renal or general, and subdivided into acute and delayed. Fatal reactions are rare. Contrast-media–induced renal impairment can be reduced with the use of low-osmolality contrast media and extracellular volume expansion.[154] ICM also can cause local tissue sloughing and necrosis if the ICM extravasates from the vein into the surrounding tissue.[153,154] Clinicians should be familiar with treatment protocols to minimize patient morbidity (Box 52-21).

ICM is typically a water-soluble, iodine-containing solution of two available types: media that can dissociate into ions in solution and media that will remain in a neutral state in solution. ICM is also formulated as high-osmolar contrast media (HOCM), which

BOX **52-21**

Considerations and Treatment Protocols for Preventing Intravenous Contrast Medium Extravasation

Considerations

- Use intravenous catheters (as opposed to metal needles or butterfly needles).
- Avoid use of the same vein if the first attempt at intravenous catheterization was missed.
- Ensure the intravenous catheter is patent and is free flowing.

Treatments

- Attempt to aspirate as much ICM as possible.
- Elevate the affected limb.
- Apply ice packs for 20 to 60 minutes until swelling resolves.
- A heating pad may be necessary in place of ice for swelling.
- Observe the patient for possible tissue damage related to continual contact with ice or heat.
- Observe the patient for 2 to 4 hours before discharge; consider medical/surgical consultation if necessary.
- Follow up with patient assessing for residual pain, increased or decreased temperature, hardness, change in sensation, redness, or blistering.

Modified from American College of Radiology. Extravasation of contrast media. In: *Manual on Contrast Media*. vol. 7. 2010. Accessed December 1, 2011, at American College of Radiology website http://www.acr.org/SecondaryMainMenuCategories/quality_Safety/contrast_manual/Extravasation.aspx.; Doughtery L. Extravasation: prevention, recognition and management. *Nursing Standard*. 2010;24:48-55.
ICM, Intravenous contrast medium.

contain few dissolved particles and iodine atoms, and low-osmolar contrast media (LOCM), which contain greater numbers of dissolved particles with iodine. An HOCM solution causes fluid shift from the cell to the vein with the ICM, whereas an LOCM solution is closely iso-osmolar, inducing less fluid shift from the cell. Nonionized LOCM is a more costly contrast medium for the patient. Some advocate that it should be the only contrast medium used for CT with dye studies.[144,153,154]

Reactions are possible with either type of ICM solution, although fewer reactions occur with LOCM.[153-154] Some reactions may present anywhere from a half hour to a week after the administration of the ICM. Reactions to ICM are theorized to be caused by the ICM molecule's serving as an antigen and affixing itself to either mast cells or basophils. This causes release of mediators such as histamine and tryptase, which can inhibit coagulation, dilate blood vessels, release complement, or even stimulate an IgE-modulated immune reaction.[144,153,154]

A new ICM using gold nanoparticles is available and undergoing tests prior to use in humans. It has many advantages over iodinated ICM, such as higher radiation absorption, yielding better images with lower x-ray dose, low allergenic response, and longer imaging times due to its nanoparticle size.[155,156]

A thorough preanesthetic assessment for a patient about to undergo CT should include questions pertaining to asthma, allergies, and any previous reactions to any contrast media. Diabetic patients taking metformin must withhold the medication due to the risk of lactic acidosis. This problem is mainly observed in patients with diabetic nephropathy. Other patients at risk for reactions to ICM are patients with multiple medical problems, especially those with cardiac disease or with preexisting azotemia, patients of advanced age, and patients being treated with nephrotoxic agents such as the aminoglycoside antimicrobials gentamicin, tobramycin, streptomycin, amikacin, kanamycin, and neomycin or nonsteroidal antiinflammatory agents. ICM is contraindicated in pregnant patients.[144,153]

Clinicians may use preventive measures in patients who may be at risk for a reaction to ICM. The radiologist should use the smallest amount of contrast agent necessary. To safeguard against the possibility of renal failure, the patient should be adequately hydrated beginning 1 hour before the procedure and continuing for another 24 hours. Patients who are at risk for possible anaphylactoid reactions should be pretreated with corticosteroids such as methylprednisolone or prednisone administered by mouth or intravenously. In cases of moderate or severe previous ICM reactions, a histamine-1 (H_1) blocker such as diphenhydramine and an H_2-blocker such as cimetidine or ranitidine should be given together either intravenously or by mouth.[144,153,154]

ICM is probably the most frequently used agent that causes anaphylactoid reactions. Anaphylaxis recognition and treatment are outlined in Chapter 41 As little as 1 mL of ICM can initiate these reactions.[144,153,154]

Magnetic Resonance Imaging. MRI can take up to an hour or longer. During this time, the patient must remain extremely still to reduce motion artifacts. These artifacts can cause unfaithful representations of the tissues being studied. The motions of breathing, the heart, blood flow, swallowing, and even cerebral spinal fluid flow produce artifacts in a highly sensitive MRI scan.

Patients must remain within the bore of the magnet for an MRI scan for longer periods of time than for a CT scan. During this time, the MRI suite's ambient temperature is cold.

The patient is exposed to varying magnetic fields of up to 4 T, along with additional exposure to variable radiofrequency radiation. Blood flow is decreased by strong magnetic fields, and blood pressure compensates by rising. Patients also have reported symptoms of vertigo, nausea, headache, and visual sensations.[140,143]

The MRI machine produces loud vibratory and knocking noises as coils are switched on and off during the course of the study. The size of the MRI magnet bore may preclude the morbidly obese or claustrophobic patient from MRI scanning, although a more open-bore MRI is available. Most patients are content with an explanation of what to expect during the procedure and with reassurance. Some patients need minimal or moderate sedation. Patients with claustrophobia or those who cannot or will not remain motionless during the study, as well as critically ill patients, may require deep sedation or general endotracheal anesthesia.[140,142,143,145] MRI is not painful, so opioids are not usually required. Sedation has been performed with oral and intravenous midazolam, ketamine, pentobarbital, or propofol.[140-143,145] Minimal sedation requires full monitoring. Deep sedation or general anesthesia requires intravenous access and full monitoring. The LMA has served as an excellent, relatively noninvasive airway for MRI. Some anesthesia providers prefer general endotracheal intubation. Children who cannot or will not cooperate experience better MRI scans with general endotracheal anesthesia in shorter periods of time, despite longer recovery times, when compared with sedation.[35,45]

Because of the intense magnetic field always present in the MRI suite, anesthesia providers must be aware of every item on their persons and every item that is to be used in conjunction with anesthesia administered to the patient. Ferromagnetic (iron-containing) substances are attracted at astonishing rates of speed into the bore of the magnet. Personal items such as pens, certain types of eyeglasses, jewelry, watches, pagers, personal computers, calculators, name badges, coins, audiotapes, videotapes, and credit cards are some of the items that should never enter the MRI suite, as well as any ferromagnetic anesthesia equipment, medication

BOX 52-22

Potentially Harmful Items When in Proximity to MRI

- Automatic implantable cardiac defibrillators (AICD)
- Cardiac pacemakers
- Certain mechanical heart valves
- Cochlear implants
- Deep brain neurostimulators
- Dorsal column stimulators
- Pacing wires
- Penile implants
- Permanent eyeliner or tattoos
- Prostheses (including dental prostheses)
- Implanted pumps (such as baclofen, narcotic, or insulin pumps)
- Internal plates, wires, or screws
- Metallic aneurysm clips (clips manufactured after 1995 and certified MRI compatible can be scanned)
- Certain metallic implants (history of recent orthopedic implants inserted within 3 months, dental implants)
- Metallic sutures
- Shrapnel and metal fragments (especially intraocular metal shrapnel)
- Tissue expanders with metallic ports

MRI, Magnetic resonance imaging.

BOX 52-23

List of Available MRI-Compatible Equipment and Supplies

- MRI-compatible anesthesia machine
- Pulse oximeter
- Intravenous bag pole
- Liquid crystal temperature monitoring strip
- Thermocouple temperature probe with radiofrequency (RF) filter
- Respiratory rate monitor
- Noninvasive blood pressure monitor
- Pulse oximeter
- Electrocardiograph
- Electrocardiograph patches
- Electrocardiograph cable
- Capnograph
- Laryngoscope with lithium batteries and aluminum spacers
- Laryngoscope blades
- Nerve stimulator
- Intravenous infusion pump
- Oxygen tanks
- Precordial stethoscope
- Esophageal stethoscope
- Patient carts
- Tables and trays

MRI, Magnetic resonance imaging.

vials, and supplies. If a patient were present within the bore of the MRI, injury or death could be possible from the missile created. As newer and more powerful 3-T MRI scanners become more prevalent, previously "safe" items could cause injury. Metals known to be safe within the proximity of the MRI bore are stainless steel, nonferrous alloys, nickel, and titanium. Materials and equipment constructed of plastic are safe.[121,141,143]

Patients possessing certain medical therapeutic devices may be prohibited from an MRI scan. MRI lists devices or metal that patients may possess that could be affected by the MRI and cause patient morbidity or mortality (Box 52-22).[141,142-145] Further investigation by the anesthetist in concert with the radiologist or MRI technician regarding the metal content and MRI compatibility of these metal items is necessary.

Cardiac pacemakers may be effected several ways by the electromagnetic field: reprogramming may occur, the pacemaker may be inhibited, it may revert to an asynchronous mode, the reed switch may close, the pacemaker may become dislodged, or it may become heated by the magnetic field.[140,142-143,145]

Manufacturers have developed a host of MRI-compatible anesthesia equipment and supplies (Box 52-23). This host of equipment and supplies allows performance of the anesthetic procedure directly within the MRI suite. Be aware that some equipment designated by the manufacturer as MRI compatible may not be compatible as magnet strengths increase.[145]

Facilities that cannot afford MRI-compatible equipment and supplies can provide anesthetic services to their patients by inducing anesthesia outside the MRI suite. The patient is placed on an MRI-compatible cart or a detachable MRI scanning table that fits within the bore of the electromagnet, where anesthesia may be then induced. With the aid of extra-long circuits, extension intravenous tubing, and properly insulated monitor cables, the anesthesia can be maintained with full monitors and a standard anesthetic machine outside the MRI suite. The patient is then carefully moved on a flat, relatively hard, wheeled platform into the bore of the electromagnet. Attention should be paid to isolate any monitor leads or intravenous tubing from touching the skin of the patient. Any monitor leads and intravenous tubing should be kept in straight alignment, because the intense magnetic fields in the MRI suite can induce current flow in coiled leads or tubing, and severely burn the patient.[145] Flexible LMAs and endotracheal tubes that contain wire windings also can be sources of burns. The American College of Radiology recommends strong attention to and the elimination of induced current, which can be large tissue loops, such as the loop created by the hand touching the hip or thigh, or the loop created when the feet or calves of the legs touch.[145]

Consideration must be given to the MRI contrast media administered to patients. Fortunately, the dyes used for MRI contrast are nonionic gadolinium chelates and have extremely low allergy rates.[144,153-154] Nausea is a common side effect. Urticaria (hives) and anaphylactoid reactions occur in less than 1% of patients.[154] The risk of a reaction to MRI dye is increased in patients with a history of asthma or other allergies or drug sensitivities, especially to iodinated contrast dyes.[153,154] Proper equipment, medications, and supplies must be immediately available for management of a reaction if one occurs. Treatments for anaphylactoid and anaphylactic reactions are discussed in Chapter 41.

Although MRI does not use ionizing radiation, patients and personnel are exposed to constant levels of magnetic force while in the MRI suite. Acute exposure to magnetic fields under 2.5 T have not been shown to have adverse effects in humans. All care providers must make their own determinations regarding how much magnetic exposure they will accept during a patient's MRI scan. Doses both to the patient and to all personnel should be minimized.[141,145] Pregnant anesthesia personnel have no restrictions on presence in the MRI scanner room during all of the required anesthesia preparations necessary to treat the patient, but the American College of Radiology recommends that personnel not be present in the MRI scanner room during the scan. Pregnant patients should discuss risks and benefits with their physician.[145]

If the anesthesia provider is away from the patient during the procedure, it should be ensured that all airway circuitry, monitoring leads, and intravenous connections are secure and tight. A respiratory monitoring apparatus (RMA) built into the anesthesia circuit reservoir bag will soon be available to monitor respiration with both visual and audible signals pertaining to movement of the RMA relative to the patient's respiratory rate and tidal volume.

When the environment could pose physical danger, anesthetists must be cognizant of their own safety and physical well-being while administering anesthesia for patients, especially during repeated exposures of radiation and/or chemicals. Therefore, a means for remote observation and monitoring either via a clear window, a camera, or telemetry must be available, although controversies regarding the traditional standards of physical presence during the conduct of anesthesia exist.[141,145] In conjunction with recognized standards of safety, the anesthetist must use monitors with both audible and visual alarms and have clear and continual view of the patient and the anesthesia monitors. Consideration must be made for safe and rapid access to the patient should the need exist.[141,143,145]

The functional MRI (fMRI) is a tool used to better differentiate residual pathologic tissue from normal healthy tissue to perform higher-quality tumor resection. An fMRI scan requires the patient to remain motionless and cooperative to avoid artifact. It is known that anesthetic agents can alter cerebral blood flow and cerebral oxygen metabolism, which can affect the interpretation of the fMRI scan. Therefore fMRI use for uncooperative or pediatric patients may preclude its use in this cohort of patients. Anesthesia research will provide the anesthetist tools to enable this population to receive both an anesthetic and needed fMRI.[143,145]

Positron Emission Tomography (PET) Scan. Positron emission tomography (PET) scan is used for the imaging and detection of malignant disease, neurologic function, and cardiovascular disease. The isotope fluorodeoxyglucose (FDG) is injected and is then absorbed into metabolically active cells. The absorbed isotope emits minute amounts of positron antimatter, which are detected and produce high-resolution images of diseased tissue. The patient must remain still for about an hour after the injection of FDG to minimize the amount of the muscle uptake of this glucose-like molecule. The patient must have fasted to minimize blood glucose levels. Any sedation medications containing sugar should also be avoided.[157-159]

Interventional Radiology (Vascular and Nonvascular), Radiotherapy, Stereotactic Radiosurgery, Interventional Neuroradiology. As skills, techniques, and technology progress, more procedures will be performed with radiation or under radiologic guidance.[146] These procedures all require the absolute immobility of the patient, with periods of controlled apnea, which assist in the viewing or treatment of the targeted area of the patient, especially during whole-body therapeutic radiation treatment.[146,148-150] These procedures are also time consuming, taking up to several hours to complete. Procedures may be necessary in patients of various age groups from infants to geriatrics and in all states of health.[150,151] A thorough preanesthetic assessment is imperative.

With the exceptions of angiography or radiotherapy, procedures for IR are painful, are physically invasive to the patient, and may need to be accomplished over several treatment sessions. Treatment may be required electively or urgently.[146] Patients may require anesthesia along the continuum from minimal or moderate sedation/analgesia, local or regional anesthesia, with the trend moving toward general anesthesia because of the superior image quality obtained in a motionless patient, especially if the patient is held apneic for a brief period of time by the anesthestist.[146,147,151] Full monitors and intravenous access are required. Additional catheterization and monitoring of arterial pressure and central venous pressure may be necessary.[150,151] Certain procedures require monitoring of the patient's neurophysiologic status for changes. The patient also may need to be assessed awake and then resedated at times during the procedure.[150] Anesthetics that can be used are midazolam, propofol, ketamine, isoflurane, and the other potent inhaled general anesthetics.[146,149,151] Dexmedetomidine, a selective α_2-adrenoreceptor agonist is also being explored for its reduction of intraprocedure and postprocedure anesthetic requirments.[150] To assess and monitor the patient's neurologic functioning, rapid recovery from anesthesia at the end of the case is ideal.[150]

It may be necessary to manipulate or manage normal systemic blood flow, normal cerebral blood flow, or other regional blood flow. The anesthetist may be called on to control deliberate hypertension or deliberate hypotension, manage anticoagulation, and manage unexpected procedural complications.[148-150]

Intraoperative radiation therapy (IORT) is the delivery of radiation to the patient via a linear accelerator, at times in conjunction with tumor surgery. If surgery is performed coincidental to the dose of radiation, normal tissues may be able to be moved away from the ionizing radiation beam. Normal tissues and organs can be shielded with lead beforehand. Some facilities use a dedicated IORT suite, whereas others use an operating room with transport of the patient to the radiation oncology suite. General anesthesia is performed if the surgical and radiation procedures are concurrent. All personnel must leave the room during IORT and stereotactically guided GammaKnife or CyberKnife surgery so that high-dose radiation can be delivered to the patient while personnel are protected from the scattered radiation. The radiation oncology suite is heavily shielded and has a lead or iron door that can take from 30 to 60 seconds to open. The patient is monitored via closed-circuit video and hands-off anesthesia delivery during treatment.[149]

Complications can occur rapidly and be life threatening. Foremost is the possible complication of hemorrhage. A sedated patient experiencing hemorrhage may show sudden signs of headache, nausea and vomiting, and vascular pain. A patient under general anesthesia may experience sudden bradycardia. The airway must be secured first if necessary, followed by support of the cardiovascular system, discontinuation of heparin, and administration of protamine (1 mg/100 units of total heparin dose administered). Other possible complications are radiocontrast reactions, embolization of particles or tissue, perforation of an aneurysm, and obliteration of unintended physiologically necessary arteries. Patient safety necessitates skilled and competent staff assistance in treatment of complications. Complications may necessitate the safe transfer of the patient to the operating room.[148-150]

Postanesthesia Care

Physiologic stability is the goal in any patient undergoing a radiologic or diagnostic procedure. The patient must be observed for possible reactions to dyes administered by the radiologist. The patient must be relieved of pain. Cardiovascular status must be stable. Hospital admission may be necessary for observation after any complication experienced by the patient or suspected to have occurred. One should always err on the side of patient safety and patient welfare.

REMOTE ANESTHETIC MONITORING USING TELECOMMUNICATIONS TECHNOLOGY

Communications technology in conjunction with reliable and accurate electronic monitoring (telemonitoring) have made it possible to perform anesthetic monitoring with the anesthetist

in one location and the therapeutic or diagnostic procedure in another physically remote, geographically isolated, or environmentally extreme environment.

The anesthetist may be involved with communication and monitoring involving land-line telephone, cellular telephone, wireless walkie-talkies, amateur (ham) radio communications, satellite communications, real-time audio and video, computer/monitor interlinks, the internet, and videoconferencing software.

The purposes of telemonitoring are the benefits to patients requiring therapeutic or diagnostic procedures with the added safety of available expert care to assist the anesthetist in performing anesthesia in a challenging environment. Anesthetists can collaborate and use their combined skills during the entire anesthetic procedure—from preoperative planning to postprocedure care and eventual discharge. Telemonitoring also provides a tool for mentoring and teaching.

SUMMARY

New procedures and patient treatments are evolving and moving out of the traditional operating room. This demands evolution of anesthesia providers, equipment, and techniques for the provision of anesthesia services to patients in need of such service. Although anesthesia providers are required to be flexible in order to adapt to these dynamic changes in the healthcare world, this should never be at the cost of patient safety. The same standards that apply in the operating room setting should always be adhered to outside of the operating suite. Clinicians must be absolutely comfortable that all required equipment, medications, and supplies are available, as would be true in a typical, fully equipped operating room. It is easier and safer to prepare beforehand than to gather the items needed for safe anesthesia delivery later or go without them. Where cases of "minor" surgery or patient intervention may exist, cases of "minor" anesthesia do not.

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Anesthesia Complications

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CHAPTER 53

Every day healthcare professionals practice within enormously complex environments; unexpected patient outcomes or complications can occur at any time. Public interest regarding patient safety has increased significantly over the past decade, largely as a result of the staggering number of preventable deaths cited in the Institute of Medicine's (IOM) 1999 landmark report.[1] The results of this report led to implementation of a broad range of improvement efforts concentrating on the prevention and detection of errors in health care. Complications can arise as consequences of another concurrent disease or of mishap. Often these complications appear unexpectedly, and they have been experienced by well-intentioned healthcare professionals who are surrounded by complex clinical conditions, poorly designed processes, and suboptimal communication patterns.[2,3]

This chapter is more than a simple compilation and review of various types of anesthetic complications. Our goal is to provide more insight into common and emerging types of anesthetic complications and to introduce organizational concepts that often surround complications in anesthesia. We discuss how to deal with complications systematically and examine the underlying human factors and lapses in communication involved in the development of critical incidents.

MORTALITY IN ANESTHESIA

Risks related to anesthesia have declined over the past several decades; however, the exact cause of this decline is unclear.[4] Anesthesia has had a 10-fold decrease in mortality since the 1980s and is often cited as reaching a six-sigma defect rate (99.99966% of end-products are statistically free of defects or 3.4 defects per million).[4,5] Outcome measures studied related to the risk of anesthesia include mortality, morbidity, patient satisfaction, and quality of life.[6] Perioperative risk related to anesthesia is multifactorial and depends on several interactions between the anesthesia, surgical procedure, and patient health. Increased safety measures (e.g., use of pulse oximetry) would be expected to improve outcomes, but no randomized controlled trials have been able to document such a conclusion.[7]

It is difficult to use mortality data to extrapolate conclusions about the safety of anesthesia, because no standard definition of what anesthesia mortality really is has been established. In addition, significant morbidity involving patients who do not die has not been considered in regard to safety. Some perioperative mortality data mainly include perioperative death to which human error has contributed versus all causes of death during or after anesthesia.[4,8] Secondly, there is a lack of consensus related to the period of time after anesthesia that should define anesthesia-related mortality. Depending on which studies are referenced, this time frame can vary from 24 hours to 30 days after anesthesia.

Another issue that clouds outcome data related to morbidity and mortality is that older patients with multi-morbidities are now considered operable as a result of improved technology (e.g., less invasive procedures) resulting in higher perioperative surgical and anesthetic risk.[7] Actual data are difficult to analyze because most studies use coroner's registries, voluntary reports, surveys, and malpractice claims as primary data sources for perioperative death. As a result, prevalence data available for anesthesia-related mortality are approximate estimates as documented in Table 53-1.

Death attributable to anesthesia is rare.[9] Anesthesia has evolved significantly regarding drug efficacy, equipment safety, and operative/procedural setting. Over 60% of surgical procedures are now performed in an ambulatory setting. Procedures associated with greater perioperative risk are increasingly being performed on an outpatient basis, and the use of regional techniques has increased.[10] Emerging claim areas in which an increase has occurred over the years include regional anesthesia (16% of all claims), chronic pain management (18% of all claims), and acute pain (9% of all claims).[6] By contrast, claims related specifically to surgical anesthesia have declined from 80% during the 1980s to 65% as compared with all anesthesia malpractice claims since 2000.[6]

The American Society of Anesthesiologists (ASA) classifies the patient's physical status related to incidence of mortality on a scale of 1 to 5 based on comorbid conditions, 1 being the healthiest individual with no comorbidities and 5 being the individual that will likely die if surgery is not performed within 24 hours. The most current incidence of anesthesia mortality in a patient with an ASA physical status of 1 is 0.04 per 10,000 (0.0004%) anesthetics. Patients with comorbid conditions have higher risk. For example, an ASA physical status 2 risk is 0.5 per 10,000 (0.005%) anesthetics, an ASA physical status 3 risk is 2.7 per 10,000 (0.027%) anesthetics, and an ASA physical status 4 risk is 5.5 per 10,000 (0.055%) anesthetics.[9] Death still remains the leading outcome in the ASA Closed Claims Project Database representing 26% of the most common complications from 1990 to 2007. The most common events leading to injury in anesthesia claims included regional blocks (20% of claims), respiratory (17% of claims), cardiovascular events (13% of claims), and equipment problems (10% of claims)[6,8] (Box 53-1).

MORBIDITY IN ANESTHESIA

The term *morbidity* is indicative of disease, incorporating any complication, excluding death occurring during the perioperative period (Box 53-2). The incidence of adverse outcomes with minor morbidity is quite high (18%-22%). For example, hoarseness has been cited to occur in 14% to 50% of patients and may accompany a traumatic lesion in the larynx or hypopharyx in 6.3% of patients. Drug errors (0.1%), equipment malfunction (0.23%), postoperative nausea and vomiting (PONV) (10%-79%), accidental dural perforation (0.5-0.6%) are all fairly common anesthesia-related morbidities. Therefore, if morbidity is included in the definition of harm caused by anesthesia and linked to anesthesia safety within the framework of six sigma, then anesthesia remains far from being 99.99966% free of defects (Figure 53-1).[4]

Anesthesia risk remains even today in several areas including perioperative airway control during general anesthesia, perioperative management of hemorrhage, and circulatory perturbations associated with regional anesthesia. Human error contribution to morbidity is a significant concern identified in 51% to 77% of anesthesia-related deaths.[4,9] It is difficult to quantify human error related to morbidity, and more research should be conducted in this area.

TABLE 53-1 Anesthesia-Related Deaths by Type of Complication (United States 1999-2005)

Type of Complication	Number of Deaths	%
Complications of anesthesia during pregnancy, labor, and puerperium	79	3.6
Cardiac complications	60	2.7
Overdose of anesthetics	1,030	46.6
Inhaled anesthetics	233	10.5
IV anesthetics	419	19.0
Other and unspecified general anesthetics	254	11.5
Local anesthetics	86	3.9
Unspecified anesthetics	38	1.7
Adverse effects of anesthetics in therapeutic use	940	42.5
Opioids and related analgesics	439	19.9
Benzodiazepines	42	1.9
Opioids and related analgesics	40	1.8
Local anesthetics	137	6.2
Unspecified anesthetic	257	11.6
Other complications of anesthesia	162	7.3
Malignant hyperthermia	22	1.0
Failed/difficult intubation	50	2.3
TOTAL	2,211	100.0

Adapted from Haller G, Laroche T, Clergue F. Morbidity in anaesthesia: today and tomorrow, *Best Pract Res Clin Anaesthesiol.* 2011; 25(2):123-132; Li G, et al. Epidemiology of anesthesia-related mortality in the United States, 1999-2005. *Anesthesiology.* 2009;110(4):759-765.

BOX 53-1

Complications of Anesthesia Identified by ASA Closed Claims Database

- Aspiration of gastric contents
- Failed intubation
- Esophageal intubation
- Other problems with the induction of general anesthesia
- Inadequate ventilation
- Airway obstruction
- Respiratory failure
- High spinal or massive epidural
- Neuraxial cardiac arrest
- Local anesthetic toxicity
- Drug reaction
- Anaphylaxis
- Overdose of sedatives
- Prolonged hypotension or hypertension
- Intraoperative cardiac arrest during anesthesia of undetermined etiology

From Metzner J, et al. Closed claims' analysis. *Best Pract Res Clin Anaesthesiol.* 2011;25:263-276.
ASA, American Society of Anesthetists.

Teamwork and communication represent another cause of adverse outcomes contributing to 43% to 65% of sentinel events occurring in the operating room (e.g., wrong side/site, transfusion error). Communication breakdown (oral 36%, written 20%) and absence of help (44% of failures) when needed also contribute to morbidity.[4]

Anesthetic complications are the seventh leading cause of pregnancy-related mortality in the United States, accounting for 1.6% of all pregnancy-related deaths. An 18-year retrospective study of maternal mortality was conducted in the state of Michigan, where all pregnancy-associated deaths within 1 year of the termination of pregnancy for any cause were reviewed. Eight anesthesia-related and seven anesthesia-contributing maternal deaths were cited, and the pattern of deaths illustrates three key points. First, all anesthesia-related deaths from airway obstruction or hypoventilation took place during emergence and recovery, not during induction of general anesthesia. Second, system errors contributed to the majority of deaths, for example, lapses in standard postoperative monitoring, missed diagnoses (e.g., cardiomyopathy, ischemic heart disease, sleep apnea). Third, obesity and African-American race are important risk factors for anesthesia-related maternal mortality.[11]

Future morbidity/mortality issues will likely include more acute and chronic pain issues, regional anesthesia, issues related to oversedation, and management of the difficult airway. Analysis of these rare events is imperative, and can improve practice and ultimately patient safety. According to the Anesthesia Patient Safety Foundation (APSF), anesthesia-related mortality does not directly reflect patient safety during anesthesia. No patient should be harmed during anesthesia, but when a critical event does occur resulting in morbidity, the incident should be explored together with anesthesia-related mortality in order to assess the true level of patient safety during anesthesia.[12]

PATIENT FACTORS AND POSTOPERATIVE MORTALITY IN PATIENTS OVER 70 YEARS

The population of older patients is growing in number, and increasingly these patients require surgery and anesthesia. Preventing, detecting, and managing morbidity and mortality is the greatest challenge facing anesthesia providers. Several large studies using worldwide databases have recently been published with an attempt to identify patient risk factors that could predict postoperative mortality. The most important resource available to date related to exploring complications and mortality after surgery is the National Surgical Quality Improvement Program (NSQIP) database in the United States. The NSQIP was established in the

BOX 53-2

Morbidity Classification

Minor morbidity: Moderate distress without prolonging hospital stay. No permanent complications (e.g., postoperative nausea and vomiting).
Intermediate morbidity: Serious distress prolonging hospital stay vor both. No permanent complications (e.g., dental injury).
Major morbidity: Permanent disability or complication (e.g., spinal cord injury; anoxic brain injury).

From Haller G, Laroche T, Clergue F. Morbidity in anaesthesia: today and tomorrow. *Best Pract Res Clin Anaesthesiol.* 2011;25(2):123-132.

early 1990s as part of the U.S. Veterans' Administration Health System and is now run by the American College of Surgeons, containing data on millions of surgical patients. The database has been associated with hundreds of publications centered on perioperative risk.[13]

One such study from the NSQIP database extracted data on 25,000 patients aged 80 years or more and 550,000 patients aged less than 80 years who had noncardiac surgery under general, spinal, or epidural anesthesia. In the cohort over 80 years of age, the top five variables associated with 30-day mortality were (1) ASA physical status, (2) preoperative plasma albumin concentration, (3) emergency surgery, (4) preoperative functional status, and (5) preoperative renal impairment.[13,14]

The Australian and New Zealand College of Anaesthetists (ANZCA) Trials Group recently published the REASON study (Research into Elderly patient Anaesthesia and Surgery Outcome Numbers), which was a prospective observational study of 4100 patients in 23 hospitals.[14,15] Patients 70 years and older undergoing noncardiac surgery and expected to stay at least one night in the hospital were included. The major findings of this study were that 1 in 20 patients (5%) died within 30 days of surgery, and one in 5 (20%) had at least one major complication within 5 days of surgery. Four preoperative factors emerged predicting postoperative mortality similar to the results of the NSQIP database study: age, ASA physical status, albumin, and those patients who had an accident and needed emergency surgery were at increased risk. A useful statistic from the REASON study is that patients aged 70 years who are an ASA physical status 1 or 2 have a 30-day mortality of 1% for inpatient surgery. Patients 80 to 89 years had an odds ratio for 30-day mortality of 2.1, meaning this age group was twice as likely to die as compared with healthy patients 10 years younger. Additionally, those patients who were 90 years of age had an odds ratio for 30-day mortality of 4.0 or were 4 times as likely to have postoperative mortality as compared with healthy patients in their 70s (Table 53-2). The most important postoperative complications were systemic inflammation, acute renal impairment, and unplanned critical care admission.[14,15]

The National Confidential Enquiry into Patient Outcome and Death database in the United Kingdom provides reports on aspects of patient care and safety. A 2010 report explored remedial factors in the processes of care of patients aged 80 years and older who died within 30 days of a surgical procedure. Out of 1120 patients, 85% had an ASA physical classification of 3 or 4, most having nonelective surgery. Only one third of these patients who died had acceptable perioperative care.[15] The authors concluded that the impact of comorbid conditions upon the frailty of a patient is underappreciated, and that increased vigilance in this patient population is warranted.

TABLE 53-2 Factors Associated with Increased 30-Day Mortality

Factors	Odds Ratio Compared with Healthy 70-Year-Old Patients
Age 80-89	2.1
Age 90	4.0
ASA 3	3.1
ASA 4	12.4
Plasma albumin <30 g/L	2.8
Emergent surgery	1.8
Thoracic surgery	2.6
Systemic inflammation	2.5
Acute renal impairment	3.3
Unplanned ICU admission	3.1

From Story DA, et al. Complications and mortality in older surgical patients in Australia and New Zealand (the REASON study): a multicentre, prospective, observational study. *Anaesthesia*. 2010;65(10):1022-1030.
ASA, American Society of Anesthetists; *ICU*, intensive care unit.

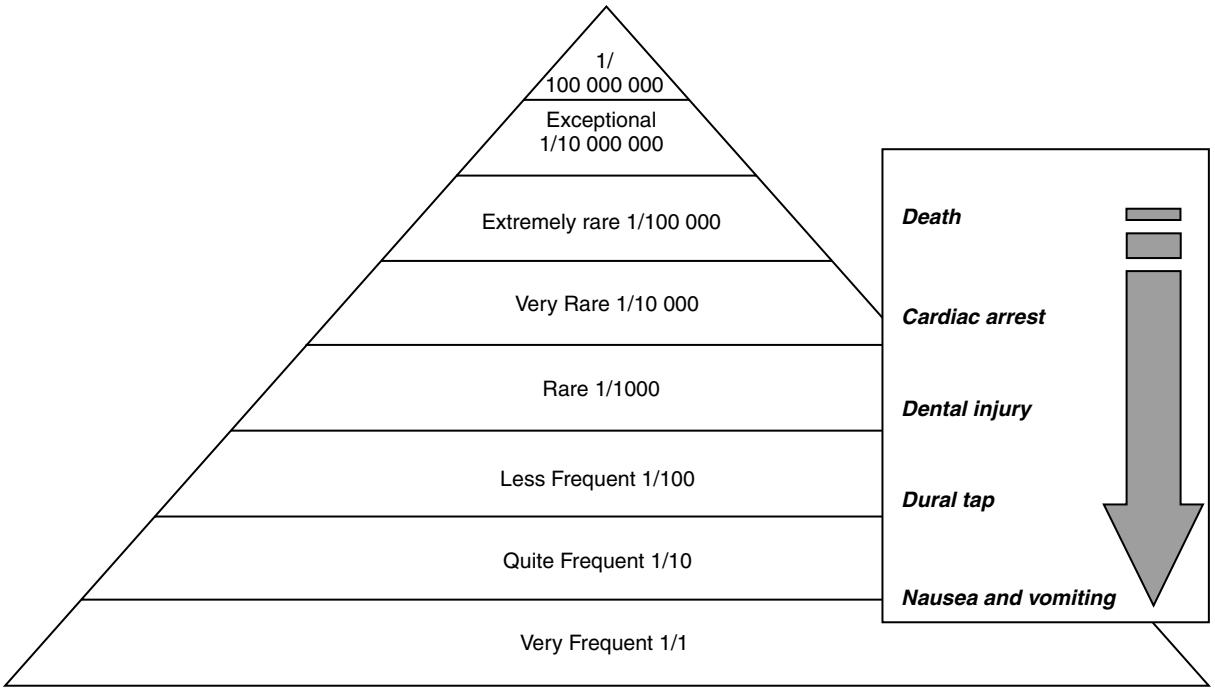

FIGURE 53-1 Anesthesia morbidity. (From Haller G, Laroche T, Clergue F. Morbidity in anaesthesia: today and tomorrow. *Best Pract Res Clin Anaesthesiol*. 2011;25[2]:123-132.)

Until recently the risk of surgery, with accompanying anesthesia, was viewed as the prime determinant of mortality. However, NSQIP data extracted from 8500 patients concluded that after accounting for age, ASA status, albumin, and emergency surgery complexity are important in about 5% of cases.[15] This reinforces the fact that surgery itself is safe, and patient factors are more important than operative procedure factors.

One emerging area in the care of older patients is the attempt to define and quantify frailty and risk of postoperative complications. Five domains of frailty have been described as depicted in Box 53-3. They include age, sex, comorbidities, physical status, and type of surgeries. Patients with 2 or 3 domains were considered to have intermediate frailty, and those having 4 to 5 domains were classified as frail. The odds ratio was 2.0 for postoperative complications in those who were considered to have intermediate frailty and 2.5 for frail patients.[16]

While age has often been the focus of perioperative concern, comorbidity, quantified with ASA physical status, is probably more important. Frailty is the new addition to this paradigm. Risk assessment should begin with patient factors that are more strongly associated with outcome than type of operation. Preoperative albumin should be measured regularly in patients over 70 years of age.

BOX 53-3

Domains of Frailty Measurements

1. Unintentional weight loss greater than 4 kg in the past year
2. Exhaustion measured by assessing effort and motivation
3. Decreased grip strength
4. Slowed walking speed
5. Low physical activity

From Makary MA, et al. Frailty as a predictor of surgical outcomes in older patients. *J American Coll Surg.* 2010;210(6):901-908.

POSTOPERATIVE COGNITIVE DYSFUNCTION

Postoperative cognitive changes after anesthesia have been reported in both the elderly for over a century and more recently in children displaying behavioral and developmental disorders after anesthesia.[17] It has been postulated that anesthetic agents can produce neurotoxic effects leading to postoperative neurologic, developmental, and behavioral complications. Postoperative cognitive problems can be categorized as postoperative cognitive dysfunction (POCD), delirium, dementia, confusion, learning, and memory problems.

Elderly Undergoing Noncardiac Surgery

The two most common postoperative cognitive disorders in the elderly are delirium and POCD and can be difficult to diagnose. A comparison of these two disorders can be found in Table 53-3. Delirium is defined as a disturbance of consciousness that is accompanied by a change in cognition that cannot be attributed to a preexisting psychological state. Presentation of postoperative delirium is variable, and patients may exhibit hyper or hypoactive cognitive or motor states. Postoperative delirium usually occurs during the first postoperative days as an acute, fluctuating loss of orientation and impairment of attention and memory. The incidence of delirium is approximately 20% in hospitalized elderly patients, and 80% in sedated intensive care unit (ICU) patients. Delirium is independently associated with increased hospital stay and mortality. Age and preexisting disease are important risk factors, in addition to medication side effects, electrolyte or fluid defects, and withdrawal symptoms.[17] Delirium research has focused on identification and treatment of risk factors prior to surgery. Factors associated with an increased postoperative delirium include advancing age, sensory deprivation (visual or hearing impairment), sleep deprivation, social isolation, physical restraint, use of bladder catheter, polypharmacy, psychoactive drugs, comorbidities, severe illness, cognitive impairment, hyper-/hypothermia, dehydration, malnutrition, and low serum albumin.[18]

TABLE 53-3 Characteristics of Postoperative Cognitive Problems in the Elderly

Postoperative Cognitive Problem	Onset	Symptoms	Anesthetic Issues
Delirium	Acute Hours/days	Decreased awareness of environment Fluctuating course Hyperactive state • Increased psychomotor activity • Rapid speech • Irritability • Restlessness • Disruptive to others Hypoactive state • Calm appearance • Inattention • Decreased mobility • Difficulty answering simple orientation questions • May be confused with depression/fatigue	Avoid polypharmacy and long-acting sedatives (e.g., benzodiazepines) Use propofol, paracetamol, opioids as needed Regional techniques better Schedule surgery early after injury or illness Early geriatric consultation Effective pain management
POCD	Weeks/months (usually not detectable during first days after surgery)	Affects wide variety of cognitive domains • Memory • Information processing • Executive function Difficult to manage job Impaired attention Normal consciousness	Recognize risk factors Anesthetic issues undefined

Adapted from Monk TG, Price CC. Postoperative cognitive disorders. *Curr Opin Crit Care.* 2011;17(4): 376-381; Björkelund KB, et al. Reducing delirium in elderly patients with hip fracture: a multifactorial intervention study. *Acta Anaesthesiol Scand.* 2010;54(6): 678-688.

Recent randomized controlled trials suggest that pain management and depth of general anesthesia are important modifiable factors for postoperative delirium after hip fracture surgery. Regional anesthesia with light propofol sedation compared with deep sedation was associated with a 50% decrease in postoperative delirium.[19] Another recent study reported a 35% reduction in postoperative delirium after hip arthroplasty using a multifactorial approach. Perioperative interventions consisted of supplemental oxygen, systolic blood pressure greater than 90 mmHg, transfusion for hemoglobin less than 10 g/dL, adequate pain relief, intravenous fluid supplementation, normothermia, avoidance of polypharmacy, spinal anesthesia, propofol sedation, and use of paracetamol as well as opioid as needed.[20] A Cochrane review concluded that regional anesthesia has a slight benefit over general anesthesia in reducing acute postoperative confusion after hip arthroplasty, but could not find a difference regarding mortality or other outcomes.[21]

POCD presents as a subtle deterioration of memory, concentration, and information processing distinct from delirium and dementia and is not a formal psychiatric diagnosis. Neuropsychologic testing is necessary for detection and must show that an individual has new onset of deficits in at least 2 areas of cognitive function lasting for a period of at least 2 weeks, and diagnosis is made when all other neurocognitive disorders can be ruled out. These diagnostic criteria make it impossible to accurately identify POCD during hospital stay, and symptoms can persist for weeks or months postoperatively.

One of the first large prospective studies describing postoperative cognitive decline after noncardiac surgery described an incidence of 25% at 1 week and 10% at 3 months after surgery. Advancing age was the only significant predictor for POCD at 3 months after surgery. Other similarly designed studies report POCD in up to 30% to 40% of adult patients of all ages at hospital discharge.[17]

General anesthesia has been implicated as the cause of postoperative cognitive problems. However, two large recent prospective studies demonstrated that type of anesthesia did not impact long-term cognitive outcome. A study comparing coronary angiography with light sedation, total hip arthroplasty with general anesthesia, and coronary artery bypass graft surgery under general anesthesia found a 16% to 17% incidence of POCD at 3 months in all three groups. Therefore, POCD may be independent of the type of anesthesia and surgical procedure.[22]

The concept of cerebral oxygen reserve offers one hypothesis regarding the significant differences in the degree of cognitive symptoms. Patients with preoperative vascular risk factors may be at greater risk for POCD. Several other etiologies have been proposed, including brain hypoxia caused by arterial hypoxemia or low flow, residual concentrations of general anesthetics such as benzodiazepines, or long-lasting effects of general anesthetics on cholinergic or glutaminergic neurotransmission, as well as psychological factors related to illness and environment during hospitalization.[17]

Elderly Undergoing Cardiac Surgery

The incidence of overall mortality after coronary artery bypass grafting has continued to decline; however, delirium and POCD remain a major concern in patients undergoing cardiac procedures, with an incidence ranging from 30% to 80%.[23] It has been assumed that the use of extracorporeal cardiopulmonary bypass was the primary culprit; however, large prospective randomized studies comparing on-pump versus off-pump bypass techniques have not shown any significant reduction in the incidence of postoperative neurologic injury.[24-26] The etiologic explanation could still involve the increased amount of atheromatous plaques and vascular disease in these patients, but this has yet to be clarified. Therefore, efforts to reduce incidence of postoperative neurologic injury have shifted focus towards patient risk factors (e.g., degree of aortic atherosclerosis, carotid arteries, and brain involvement).[23]

Pediatric Postoperative Cognitive Development Dysfunction

A great deal of concern has recently arisen regarding the safety of anesthesia in the pediatric population. Anesthetic agents have been implicated in pediatric developmental delays that have undergone prolonged procedures and/or multiple procedures (Figure 53-2).[27] A growing body of evidence in animals suggests that under certain circumstances, anesthetic drugs could adversely affect neurologic, cognitive, and social development of neonates and young children.[27,28]

Exposure to certain anesthetic agents during sensitive periods of brain development in animal studies has been postulated to result in widespread neuronal apoptosis and functional deficits later in development. So far *N*-methyl-D-aspartate (NMDA)

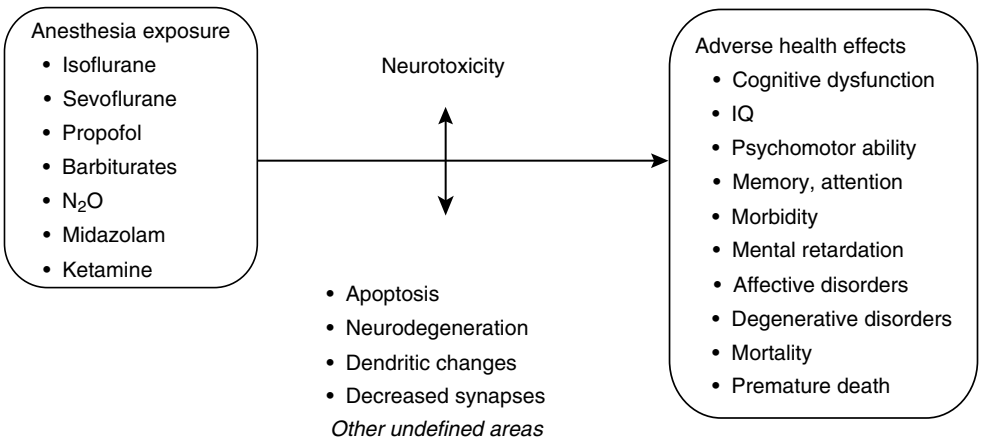

FIGURE **53-2** Conceptual framework for pediatric anesthetic neurotoxicity. (Adapted from Sun L, et al. Early childhood general anaesthesia exposure and neurocognitive development. *Br J Anaesth*. 2010; 105[suppl 1]:i61-i68.)

receptor antagonists and γ-aminobutyric acid (GABA) agonists have been implicated. However, no safe doses of these agents or safe duration of administration of these agents have been defined.[28,29] For example, 5-day-old non-human primates exposed to ketamine for either 9 or 24 hours experienced neuroapoptosis. A similar neurologic damaging effect was observed in the fetuses of pregnant rhesus monkeys (third trimester) exposed to ketamine for 24 hours. No effect was seen when ketamine exposure duration was 3 hours. Neuroapoptosis also has been demonstrated in primates given isoflurane on postnatal day 6.[28] The Food and Drug Administration (FDA) and others are currently conducting more studies to address the neurocognitive and neurobehavioral aspects of anesthetic-induced apoptosis.

Studies in children have attempted to assess effects of anesthetics on the developing human brain. A retrospective cohort analysis followed a birth cohort of 383 children who underwent inguinal hernia repair during the first 3 years of life and compared them with 5050 children in a control sample who had undergone no hernia repair before the age of 3 years. The children who underwent hernia repair were twice as likely as those who did not to have a developmental delay or behavioral disorder.[28] Another recent study retrospectively examined children (younger than 4 years) who were exposed to a single anesthetic (n = 449), two anesthetics (n = 100), or more (n = 44) related to the development of learning disabilities. No increased risk of learning disabilities was found with a single anesthetic. However, significant increased risk of learning disabilities was associated with two or more anesthetics and also increased with greater cumulative exposure to anesthesia.[29] It appears that windows of anesthetic vulnerability exist that are dependent on the exposure time, amount, and type of anesthesia. However, no definitive conclusions can be drawn on the basis of these nonrandomized studies in humans because of the substantial potential for confounding and bias. Interpretation is difficult due to the retrospective nature of the studies, lack of precise information in terms of age, agent, duration, and dose of anesthetics, specific agents used, variable outcome end-points used, and the method outcomes that were assessed.[27] Although withholding anesthesia in children who need surgery is unreasonable, obtaining more information about safe use is imperative. If anesthetic agents are found to affect the developing brain, strategies for mitigating and managing such risks can be implemented.[27-29]

CARDIOPULMONARY COMPLICATIONS

Intraoperative Cardiac Arrest

Currently, cardiac arrest during anesthesia is usually a concomitant and not a causative factor. Incidence of intraoperative cardiac arrest has been cited as 0.2 to 1.1 per 10,000 adults and 1.4 to 2.9 per 10,000 children.[30,31] Cardiac arrest during neuraxial anesthesia is less frequent compared with general anesthesia, with an incidence of 0.04 to 1.8 per 10,000 anesthetics. Etiologic factors can be grouped into categories: preoperative complications (65%), surgical procedures (24%), intraoperative pathologic events (9%), and those attributable to anesthetic management (2%).[31] Excessive surgical bleeding has been identified in 70% of surgical procedure-related deaths, and major causes of intraoperative pathologic events (e.g., myocardial ischemia, pulmonary embolism, and severe dysrhythmias). Fifty-percent of anesthetic management–related events were caused by airway or ventilatory problems, followed by medication errors and infusion/transfusion mishaps. Perioperative cardiac arrest is multifactorial in origin including factors such as patient comorbidities, inadequate risk estimation, inappropriate anesthetic management, and human error or misjudgment.[30,31]

Sudden Cardiac Arrest

Sudden cardiac arrest (SCA) is a leading cause of death in the United States, accounting for an estimated 325,000 deaths each year. Approximately 6 cases per 100,000 individuals have been reported.[32] Ninety-five percent of victims die before ever reaching emergency assistance. The most common underlying substrate of sudden cardiac arrest is ischemia and/or left ventricular dysfunction (Table 53-4).[33] Hypertrophic cardiomyopathy is the most common underlying cause of sudden cardiac death in young athletes.[32] However, there are also patients with preserved left ventricular function who are at risk for sudden cardiac arrest. Many of these individuals are walking around with long QT syndrome (LQTS).[34] Long QT syndrome has gained increased attention because of young athletes collapsing unexpectedly in sudden cardiac arrest. Long QT syndrome is an arrhythmogenic inherited or acquired cardiovascular disorder, with a prevalence of approximately 1 per 2500 to 10,000, causing sudden death as a result of episodes of syncope, seizures, and ventricular tachycardia. Only about 60% of patients are symptomatic at the time of diagnosis. Induction of general anesthesia has provoked LQTS without any prior clinical diagnosis or preoperative abnormal clinical findings.[35] Sudden sympathetic stimulation during intubation may be a cause or it could be QTc (interval corrected for heart rate) prolongation, as well as drugs that have positive adrenergic properties (e.g., ketamine, pancuronium). Careful anesthetic management should include treatment with beta-blockers preoperatively. Heart rate should be maintained below 130 beats/minute. It is recommended to avoid any pharmacologic agents that have the potential to further prolong the QT interval (Table 53-5).[36] Episodes of torsades de pointes may be short lived and self-terminating, but treatment with magnesium sulfate is considered the treatment of choice. Temporary pacing is also an effective method for controlling torsades de pointes (Figure 53-3).[35,37]

Perioperative episodes of sudden cardiac arrest in the pediatric population sparked the formation of the Pediatric Perioperative Cardiac Arrest Registry in 1994 to study the causes and outcomes from perioperative cardiac arrests in anesthetized children. Results from a recent examination of arrests from 1998 to 2004 indicate that cardiovascular causes of arrest accounted for the highest proportion of arrests (41%); among these the most common identifiable single cause was hypovolemia related to underestimation of blood loss and inadequate peripheral IV access (Figure 53-4).[38] Cardiac arrests due to medication errors were most common during the mid-1990s; this statistic has dropped significantly during more recent years. One explanation for this is a decline in the incidence of cardiac depression from decreased use of halothane.[38]

Myocardial Infarction

The Perioperative Ischemic Evaluation (POISE) trial data using surgical data from 56 countries suggests that perioperative myocardial infarction (MI) is the most common cardiovascular complication after noncardiac surgery, with an incidence of 5% in patients 45 years or older with cardiovascular risk factors.[39] Patients who suffer a perioperative MI have a 30-day mortality of between 11.6% and 21.6%.[40] Over 200 million noncardiac surgical procedures are performed annually worldwide, which equates to 10 million perioperative myocardial infarctions and more than 1.1 million deaths. This is a significant public burden considering that perioperative MIs are commonly undiagnosed and undertreated.[39]

TABLE 53-4 Causes of Sudden Cardiac Death

Underlying Heart Disease	Incidence	Description
Ischemic heart disease	Greater than 50% luminal narrowing Less than 20 yr, 0% 20-29 yr, 24% 30-40 yr, 58%	Atherosclerotic coronary artery disease, generally with normal cardiac function
Sudden arrhythmic death syndrome	Brugada syndrome 5:10,000 (0.05%) Long QT syndrome 1:2500 (0.04%) Short QT syndrome Catecholaminergic polymorphic VT 1: 10,000 (0.01%) Wolff-Parkinson-White syndrome 0.9%-3%	Brugada syndrome—hereditary channelopathy with right ventricular conduction delay and ST elevation in right precordial leads (dome or cove-like) associated with incomplete or complete right bundle-branch block and ultimately VF Long QT syndrome—channelopathy with QT interval (greater than 480 ms) Short QT syndrome—channelopathy with QT interval (less than 340 ms) Catecholaminergic polymorphic VT—genetically mediated, cardiac channelopathy induced by exercise or emotional stress with structurally normal hearts Wolff-Parkinson-White syndrome—preexcitation syndrome with an accessory pathway (Bundle of Kent) causing atrioventricular reentrant tachycardia and/or VF with structurally normal hearts; shortened PR, delta waves, and widened QRS may be present
Hypertrophic cardiomyopathy (HCM)	1:500 (0.2%) of general population 36% of all sudden cardiac deaths (additional 10% of cases have unexplained increase in cardiac mass not meeting full criteria for HCM	Inherited disease characterized by myocyte disarray, asymmetric hypertrophy of left ventricle (typically at the septum), occasional LV outflow tract obstruction, and predisposition for unstable ventricular arrhythmias
Arrhythmogenic right ventricular cardiomyopathy	1:5000 (0.02%) general population	Right ventricular wall-thinning and fibrofatty tissue infiltration
Congenital right ventricular cardiomyopathy	18% congenitally abnormal coronary arteries 12% anomalous coronary artery origins and hypoplastic anatomy	Also called *arrhythmogenic right ventricular dysplasia* (ARVD); rare form of cardiomyopathy in which the heart muscle of the right ventricle is replaced by fat and/or fibrous tissue
Commotio cordis	5% (nonspecific causes) 19.9% (athletic injury)	Blunt chest wall impact
Myocarditis	Less than 5%	Myocardial inflammation
Aortic disorder	3%-8%	Thoracic dissection/rupture

Adapted from Cross BJ, Estes M, Link MS. Sudden cardiac death in young athletes and nonathletes. *Curr Opin Crit Care*. 2011;17(4):328-334; Heiner JD, Bullard-Berent JH, Inbar S. Deadly proposal, a case of catecholaminergic polymorphic ventricular tachycardia. *Pediatr Emerg Care*. 2011;27(11):1065-1068.
VT, Ventricular tachycardia; *VF*, ventricular fibrillation; *LV*, left ventricle.

Characteristics and short-term prognosis of perioperative MI have evolved over the past two decades. Fewer patients with nonoperative MI have ST-segment elevation, and more patients have non–ST segment elevation. Short-term mortality is decreasing. A large cohort study using POISE data extracted from over 8000 patients reported that most MIs occur within 48 hours of surgery (74.1%); 65.5% were asymptomatic.[40] Independent predictors of perioperative MI from this cohort are depicted in Table 53-6.

PULMONARY COMPLICATIONS

Perioperative pulmonary complications are common, often equal to or outnumbering cardiac events. There is no unifying definition of what constitutes a postoperative pulmonary complication (POPC). Commonly cited POPCs are listed in Box 53-4.[41] This discussion highlights the complications associated with manipulation and management of the airway.

Complications Associated with Supraglottic Devices

Airway mortality does not happen because of failure to intubate. Airway mortality occurs due to failure to ventilate. A major challenge for any evidence-based evaluation of airway management techniques is the extremely low incidence of severe adverse events directly attributed to inadequate ventilation.

Incidence of difficult mask ventilation has been cited to be 1.4% to 5%.[42-44] A recent study of 94,630 anesthetics reported impossible mask ventilation in 0.2% of patients, and within this group, 25% were also difficult to intubate.[44] Combined difficult mask ventilation and difficult intubation has been encountered 0.4% of the time. Finally, the incidence of cannot ventilate–cannot intubate is a very small, but devastating 0.008%.[42] Complications related to mask ventilation are underappreciated and underestimated and listed in Box 53-5.

Many airway devices exist today to assist with difficult or cannot ventilate and/or difficult to intubate situations. A considerable body of evidence (level 3b and 4) (Table 53-7),[46] over 300 publications (no greater than 3000), exists regarding successful use of the classic laryngeal mask airway (cLMA) in patients with difficult-to-manage airways. The intubating LMA also has been used successfully 97% to 100% of the time for ventilation in both the anticipated and unanticipated difficult airway.[47,48] Level 4 evidence of successful ventilation in patients with difficult airways has been described for many other supraglottic devices in a recent

TABLE 53-5 Pharmacologic Agents Known to Prolong the QT Interval

Type of Drug	Examples
Class 1a antidysrhythmic agents	quinidine disopyramide procainamide
Class 1c antidysrhythmic agents	flecainide
Class III antidysrhythmic agents	sotalol amiodarone
Butyrophenone antipsychotics	droperidol haloperidol
Phenothiazine antipsychotics	thioridazine
Atypical antipsychotics	pimozide quetiapine risperidone zotepine
Selective serotonin reuptake inhibitors	fluoxetine paroxetine sertraline
Macrolide antibiotics	erythromycin clarithromycin azithromycin
5-HT-1 agonists	zolmitriptan naratriptan
Antimalarial agents	halofantrine
Antihistamines	terfenadine
Prokinetic agents	cisapride
Anesthetic drugs	halothane isoflurane sevoflurane succinylcholine atropine glycopyrrolate

From Roden DM. Clinical practice: long QT syndrome. *N Engl J Med*. 2008;358(2):169-176.

review: LMA ProSeal, Supreme LMA, i-gel, Ambu Aura-i and Air-Q intubating laryngeal airways, Cobra perilaryngeal airway, CobraPLUS, and Laryngeal Tube.[47,48] However, even with current evidence of successful use of various supraglottic devices in difficult airways, there is still not enough evidence to judge one individual device superior.

As useful as these devices are, they are not without complications. The LMA has been associated with inadequate seal,

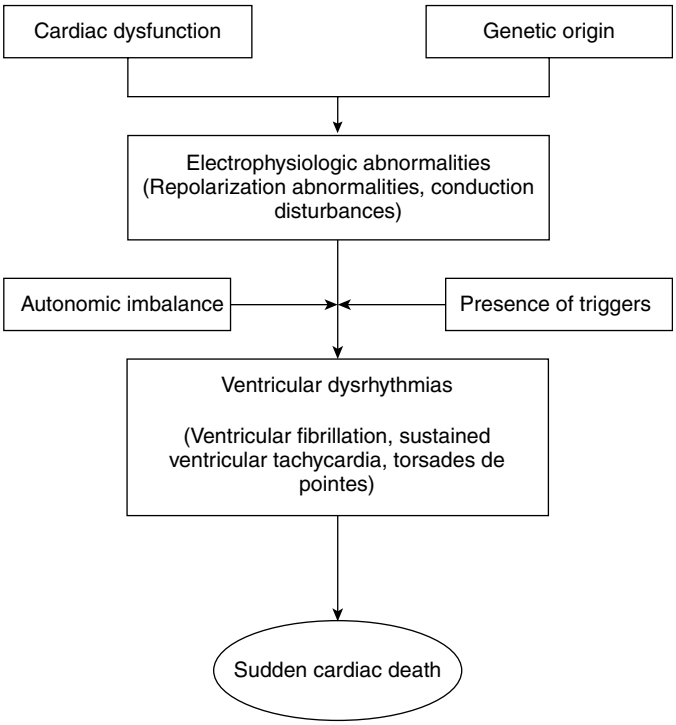

FIGURE 53-3 Mechanisms of sudden cardiac arrest. (From Ikeda T, et al. Risk stratification for sudden cardiac death. *Circ J*. 2007;71[suppl A]:A106-A114.)

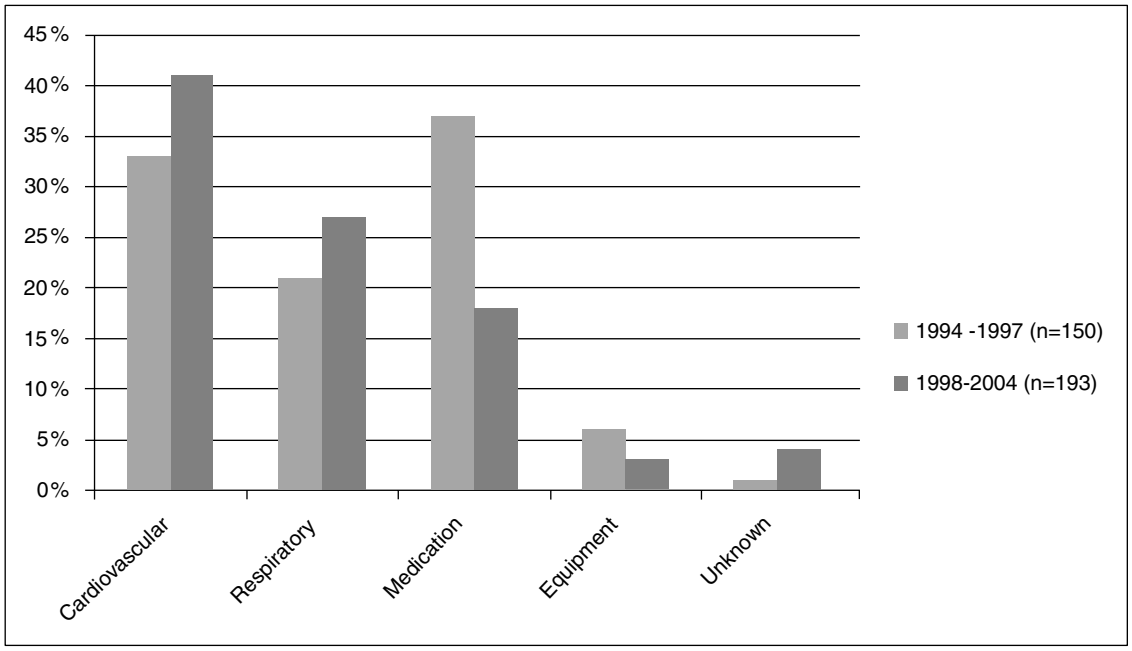

FIGURE 53-4 Causes of anesthesia-related cardiac arrests in children 1 to 18 years of age. (From Bhananker SM, et al. Anesthesia-related cardiac arrest in children: update from the Pediatric Perioperative Cardiac Arrest Registry. *Anesth Analg*. 2007;105[2]:344-350.)

TABLE 53-6 Independent Predictors of Perioperative Myocardial Infarction

Independent Predictor	Adjusted Odds Ratio (95% CI) for Association with Perioperative MI
Every 10-beats/min increase in baseline heart rate	1.29 (1.13-1.50)
History of stroke	2.24 (1.20-4.20)
Undergoing major vascular surgery	2.21 (1.15-4.25)
Preoperative serum creatinine level greater than 2.0 mg/dL	4.33 (2.32-8.09)
Age per decile increase	1.53 (1.20-1.95)
Emergency or urgent surgery	2.94 (1.65-5.26)
Serious bleeding, 2 units or more	3.62 (2.07-6.36)

From Devereaux PJ. Characteristics and short-term prognosis of perioperative myocardial infarction in patients undergoing noncardiac surgery: a cohort study. *Ann Intern Med*. 2011;154(8):523-528.

BOX 53-4

Commonly Cited Postoperative Pulmonary Complications

- Laryngospasm
- Bronchospasm
- Airway obstruction
- Desaturation
- Pneumonia
- Pulmonary embolism
- Aspiration pneumonia
- Reintubation/mechanical ventilation without identifiable cause
- Severe coughing
- Stridor
- Pleural effusion
- Pneumothorax
- Respiratory infection not otherwise specified
- Aspiration pneumonitis

From Johnson DC, Kaplan LJ. Perioperative pulmonary complications. *Curr Opin Crit Care*. 2011;17(4):362-369.

induced laryngospasm, and aspiration of gastric contents, to name a few. Failed placement has been documented to occur in 1% to 5%, although this decreases with operator experience.[45] Other supraglottic device complications tend to be similar to those found with the LMA and result from cuff overfilling, dislodgment, trauma during insertion, and insufficient anesthesia depth during insertion.[45]

Complications of Endotracheal Intubation

The phrase "cannot intubate" represents an infrequent, but serious challenge for the provider, but also represents an increased anesthetic risk to the patient. There is a close relationship between difficult intubation and traumatic intubation. Difficult intubation has been documented as a significant factor in 39% of all airway injury claims. Eight-seven percent of these were temporary, and 8% resulted in death. In 21% of claims, the standard of care was not performed.[45]Airway management plans when dealing with difficult airways must have backup plans that require the same level of thought as the primary airway plan. All airway plans can fail. Early recognition by the anesthesia provider that the current plan is not working and good communication throughout the procedure are both crucial. This may seem obvious, but unless all plans have been thought out, the clinical situation can quickly deteriorate. To date, fiberoptic intubation of the spontaneously breathing patient is the gold standard for elective intubation in the anticipated difficult airway.[49]

Video laryngoscopy has recently emerged as an alternative for anticipated difficult airway cases and has become widely available.[50] These devices may seem like a panacea for difficult airway management, but they have several limitations. Most devices are primarily designed for orotracheal intubation and require some mouth opening to allow the device to pass. Several case reports citing pharyngeal mucosal perforation and trauma while using the GlideScope have been published.[51-53] This complication could be minimized by increased vigilance and visual observation when passing the rigid stylet because there is a potential blind spot in the oropharynx when attention is focused on the GlideScope monitor. Care should be taken to cautiously pass the endotracheal tube and not use unnecessary force during insertion or a too-large laryngoscope blade.

Complications of endotracheal intubation encompass both hemodynamic pathophysiologic effects as well as associated anatomic injuries as depicted in Box 53-5. Fifty percent of dental trauma occurs during laryngoscopy; sore throat occurs as often as 40%, and occurs greater than 65% when blood is noted on airway instruments. Trauma to the larynx, although not as common, has been documented in 6.2% of cases; 4.5% of these developed hematomas of the vocal cords. Granulations of the laryngeal area can occur as a result of long-term intubation, and vocal cord paralysis can cause long-term hoarseness. Supraglottic complications induced by long-term intubation may be prevented by early tracheostomy.[45] For a more comprehensive list see Box 53-5.

INTRAOPERATIVE AWARENESS

Unintended awareness during the administration of anesthesia is a dreaded complication for the anesthesia provider and a significant source of fear for many patients. Awareness can occur during general anesthesia or monitored anesthesia care primarily as a result of underdosing of anesthesia relative to specific patient circumstances. An estimated 20,000 to 40,000 patients experience awareness during anesthesia annually in the United States alone, an incidence of approximately 0.1% to 0.4%.[54] The actual incidence of intraoperative awareness remains uncertain and likely is underestimated because of the limited nature of most postoperative interviews, which include the following: (1) no standardized or structured approach, and (2) single postoperative visitation by anesthesia personnel. As a result, many cases of awareness may not be elicited. The Brice Questionnaire developed in 1970 has been traditionally acknowledged as an accepted tool for detecting awareness postoperative and has been modified over the years in recent studies (Box 53-6). A multicenter study in the United States estimated an incidence of awareness under general anesthesia with explicit recall (specific recollection of events) of approximately 0.023%, slightly lower than other large studies (0.13%).[55,56] High-risk cases (e.g., trauma, obstetric, cardiovascular) possess 10 times the risk for awareness with an incidence of 1 case in 100.[57] See Table 53-8 for a list of risk factors for awareness.

Episodes of awareness occur most often during maintenance of anesthesia, less during induction, and least during emergence. Patient movement has been cited in about 1 out of every 7 awareness case reports, and development of tachycardia and hypertension occurs in about 1 out of every 5 episodes of awareness.[58]

BOX 53-5

Airway Management Complications

Mask Ventilation

- Mucosal, skin irritation, conjunctivitis due to cleansing agents
- Soft-tissue damage from excessive pressure
  - Corneal abrasion, retinal artery occlusion, blindness
  - Damage to mandibular branch of facial nerve causing transient facial nerve paralysis
  - Damage to mental nerves causing lower lip numbness
- Broken teeth, mucosal tears
- Worsening obstruction from malposition of tongue
- Subluxation of the temporomandibular joint
- Gastric distention increasing risk for aspiration
- Gastric rupture
- Subcutaneous emphysema

Laryngeal Mask Airway

- Folding of epiglottis tip causing labored breathing, coughing, laryngospasm, and obstruction
- Excess lubricant that causes coughing or laryngospasm
- Lack of protection from aspiration of gastric contents
- Laryngospasm, coughing
- Sore throat
- Increased intracuff pressures with prolonged procedures using nitrous oxide and carbon dioxide
- Dysarthria
- Edema of epiglottis, uvula, posterior pharyngeal wall
- Hypoglossal nerve paralysis
- Postobstruction pulmonary edema
- Tongue cyanosis

Endotracheal Intubation

- Damage to teeth
- Mucosal injuries
- Lip injuries
- Swelling tongue
- Sore throat
- Trauma to larynx/vocal cords
- Arytenoid dislocation/subluxation
- Tracheobronchial trauma
- Barotrauma
- Nerve injury
- Cervical spine injury
- Vocal cord paralysis
- Temporomandibular joint injury
- Laryngospasm
- Bronchospasm
- Hemodynamic perturbations

Extubation

- Hemodynamic perturbations
- Laryngospasm
- Laryngeal edema
- Bronchospasm
- Negative-pressure pulmonary edema
- Aspiration
- Airway compromise
- Difficult/accidental extubation

From Hagberg C, Georgi R, Krier C. Complications of managing the airway. *Best Pract Res Clin Anesthesiol.* 2005;19(4):641-659.

TABLE 53-7 Levels of Evidence

Level of Evidence	Descriptor
1a	Systematic review of RCTs
1b	Single RCT
1c	All or none study (e.g., all individuals died before therapy was available, but some now survive on the therapy, or when some individuals die before the therapy became available, but now none die on the therapy)
2a	Systematic review of cohort studies
2b	Single cohort study or low-quality RCT
2c	Outcome studies investigating outcomes of healthcare practices using epidemiology to link outcomes (e.g., quality of care, quality of life)
3a	Systematic review of case-control or historical-control study
3b	Single case-control or historical-control study
4	Case report or case series
5	Expert opinion or ideas based on theory

Adapted from Centre for Evidence-Based Medicine, 2011. Accessed April 28, 2011, at http://www.cebm.net/; Pandit JJ, et al. The difficult airway society ADEPT guidance on selecting airway devices: the basis of a strategy for equipment evaluation. *Anaesthesia.* 2011;66(8):726-737.
RCT, Randomized controlled trial.

BOX 53-6

Assessing Incidence of Awareness

Modified Brice Interview

- What was the last thing you remember before going to sleep?
- What is the first thing you remember after waking up?
- Do you remember anything between going to sleep and waking up?
- Did you dream during your procedure?
- What was the worst thing about your operation?

From Mashour GA, Tremper KK, Avidan MS. Protocol for the Michigan Awareness Control Study: a prospective, randomized, controlled trial comparing electronic alerts based on bispectral index monitoring or minimum alveolar concentration for the prevention of intraoperative awareness. *BMC Anesthesiol.* 2009;9:7.

Surprising cases of awareness have been recently cited by Mashour et al.,[55,56] in a large study (n = 22,885) of patients who did not undergo general anesthesia, but received monitored anesthesia care 1:3269 (0.03%). This provocative finding indicates that awareness is not simply related to pain, but awareness itself was a source of distress. Several patients reported hearing unwanted conversations and remembered bright lights during their procedure inconsistent with their expectations, making them distraught. Therefore, it might be prudent to spend more time preparing patients for such experiences in order to avoid disparities in expectations that could lead to complications of awareness discussed later in this section.

The concept of consciousness involves not simply brain arousal and recall, but also subjective experience involving higher-order processes including memory. Explicit recall requires

TABLE 53-8 Risk Factors for Awareness

Situation Posing Increased Awareness Risk	Examples
Unsafe to administer sufficient anesthesia	• Trauma with severe hypoperfusion/hypotension • Cardiac cases using cardiopulmonary bypass • Obstetric emergency under general anesthesia
Mistake/failure in anesthesia delivery	• Inhalational agent not turned on/empty vaporizer • TIVA not begun or failure of device • Provider abuse of anesthetic drugs • Discontinuation of anesthesia too early
Anesthetic technique results in inadequate anesthesia	• Failed neuraxial technique • Use of neuromuscular blockade results in underappreciation of light anesthesia • Difficult airway with prolonged intubation attempts • TIVA techniques (e.g., IV infiltration, dosage miscalculation)
Patient needs are underappreciated	• Pharmacodynamic resistance (e.g., opioid, benzodiazepine tolerance) • Altered P450 metabolism (e.g., chronic alcohol use) • Increased P450 3A activity caused by efavirenz, nevirapine, barbiturates, carbamazepine, glucocorticoids, phenytoin, rifampin, St. John's wort • Mutations of melancortin-1 gene associated with red hair phenotype

From Mashour GA, Orser BA, Avidan MS. Intraoperative awareness: from neurobiology to clinical practice. *Anesthesiology*. 2011;114(5):1218-1233.
TIVA, Total intravenous anesthesia; *IV*, intravenous.

not only consciousness, but also involves memory. One of the most potent actions of general anesthetics is memory blockade or amnesia. Intravenous and inhalation anesthetics cause amnesia at doses considerably lower than those required for loss of consciousness and immobility. Propofol and midazolam cause greater memory blockade than fentanyl at equisedative doses. Retention of memory (studied after 24 hours) is also impaired by all anesthetics at relatively low concentrations (e.g., 0.2% isoflurane, 0.3% sevoflurane, 0.44% desflurane, 20% nitrous oxide). Finally, most anesthetics cause anterograde amnesia (i.e., loss of memory for a period after administration of the drug) but not reliable retrograde amnesia (i.e., loss of memory for events before administration of the drug). Intravenous anesthetics, including propofol and etomidate, cause anterograde amnesia and can also interfere with memory consolidation, or stabilization of memories after the initial acquisition.[56]

Awareness is often associated with a high rate of post-traumatic stress disorder (PTSD), increases patients' apprehension of future surgery, enhancing medicolegal risks associated with anesthesia. The B-Aware trial, one of the most recent randomized controlled trials studying awareness, reported a 71% incidence of post-awareness PTSD.[59] Not all patients who have documented intraoperative awareness develop PTSD, but initial emotional distress and the experience of paralysis have been cited as most predictive of developing PTSD. Postoperative sequelae reported related to PTSD include sleep disturbances (19%), nightmares (21%), fear of future anesthetics (20%), and daytime anxiety (17%).[58]

Preventing intraoperative awareness may appear straightforward: give patients adequate anesthesia doses, keep them deep, and ensure that patients receive more-than-sufficient doses of intravenous and inhalational anesthetic agents. Unfortunately, there are no fail-safe methods for what constitutes sufficient dosing for each individual patient. It could be argued that routine administration of muscle relaxants is inhibiting observation of voluntary movement and should be minimized or avoided when possible. Nonetheless, patients who are distressed or in pain can be expected to manifest pain with sympathetic stimulation if anesthesia is light, thereby alerting the anesthesia provider to deepen the anesthetic. Vigilance is imperative.

Brain monitoring using bispectral index (BIS) values has become relatively common during general anesthesia to detect light anesthesia and decrease risk of awareness, although it does not ultimately prevent intraoperative awareness. BIS monitoring theoretically serves as an alert and to guide the titration of anesthesia along with other hemodynamic parameters. Currently, all available brain-monitoring technologies have a nonlinear dose-response relationship, plateauing as doses reach higher levels. Therefore, titration of anesthesia according to these devices may not be reliable. The risk of postoperative recall appears to be low if patients become light only briefly (less than 30 seconds), but increases if patients are awake for more than 30 seconds.[56]

Studies hypothesizing that BIS monitoring protocols decrease intraoperative awareness have produced conflicting results. The B-Aware trial, involving 2500 patients, demonstrated that administration of anesthesia using a BIS monitoring protocol (maintaining BIS values between 40 and 60) compared with traditional anesthesia practice (end-tidal anesthetic concentrations) decreased intraoperative awareness by 0.74 percentage points in patients at high risk for awareness.[58] However, the B-Unaware trial demonstrated no reduction between a BIS monitoring protocol and using end-tidal anesthetic concentrations.[54] Both studies had lower than average incidences of awareness. A more recent trial, the BAG-RECALL trial, also demonstrated no significant differences in intraoperative awareness in high-risk populations related to monitoring for awareness or not.[60]

Incidence and consequences of pediatric intraoperative awareness data have been limited. Three recent studies evaluated awareness using semi-structured interviews modified for use in children with reported incidences between 0.6% and 2.7%.[61-63] Forty-three percent of children reported feeling scared, and 21% reported hurting during their surgery. Psychological follow-up was deemed unnecessary in all cases, and none of the children or parents expressed concern. Additionally, 14% of children with possible/probable awareness stated they would feel worse if they had to undergo another anesthetic procedure in the future, which was similar to reports from children who did not experience awareness (15%). Data seem to suggest that children with awareness do not develop PTSD, but a child's report of intraoperative recall should not be readily dismissed and should be addressed with appropriate follow-up.[64]

MANAGEMENT OF COMPLICATIONS

The aftermath of critical incidents and complications is equally as important as the incident itself, because incident investigation is a prerequisite for learning about the actions and events

surrounding the critical incident and prevention.[65,66] It is important to view the critical incident from an organizational point of view after it has occurred. There are many documented systematic approaches for handling critical incidents. One approach is discussed in this chapter. It would be helpful for anesthetists to explore their individual institution's approach to handling critical incidents.

Organizational learning is an important strategy for improving patient safety. For quite some time, the focus on medicolegal risks has diverted attention from the system-wide improvements with the potential to meet the needs of patients, families, and healthcare providers. Patients, their families/supporting individuals, and healthcare professionals involved are all affected and suffer from a critical event or complication. Taking care of the spectrum of these individuals is an important element of handling adverse events. Every healthcare organization should have a framework for handling critical events and complications embedded in effective communication between all parties involved, while also supporting the healthcare provider in the process.[65,66]

Incident Reporting

Not all critical incidents lead to adverse outcomes or complications. Once a critical incident has occurred, it must be reported and investigated systematically. Any death occurring within 48 hours of an anesthetic should be evaluated for potential relevancy.[10] Effective risk management depends crucially on establishing a reporting culture.[66] All critical incidents should be reported whether or not the outcome is negative.[67] Each hospital or healthcare institution should have a written, accessible policy to guide individuals in how to best support patients and families and also how to learn in a systematic way from the critical incident to minimize the likelihood of recurrence.

When a critical incident occurs, the anesthesia provider's first obligation is to protect the patient from further harm, providing the care required and mitigating further injury. Continuation of patient care, by the same team, for at least a short period of time is up to the individuals involved in the critical incident.[65,66,68] After the critical incident is stabilized, actions to secure the area, brief the team, and analyze the incident should be taken. First, secure implicated drugs, equipment, and records for further investigation. Brief all members of the care team as soon as possible so all members are fully aware of the issues and all subsequent communications are consistent with the patient and family. Decide immediately who will have primary responsibility for communicating with the patient and family about the event. Determine the circumstances surrounding the adverse events and factors contributing to it as quickly as possible while memories of those involved are fresh. This information can be crucial to the immediate clinical treatment plan for the patient, as well as for analysis of the situation. Report the event to the appropriate institutional officer.[69]

Root Cause Analysis

A retrospective analysis of the critical incident should ensue. One common example of this is called a *root cause analysis* (RCA). Root cause analysis is based on the premise that adverse events are caused, not by individual human errors, but by combinations of factors linked to organizational processes and structures by which errors are missed and adverse events are not prevented.[70] The objective of an RCA is to systematically uncover multiple factors or causal chains that contribute to a critical incident, developing systems changes to make it less likely that the incident will recur. During this process, the importance of unbiased investigation and blame avoidance is important. The RCA process is organized in sequential steps including: (1) identifying the incidents/problem statement, (2) organizing a multidisciplinary team to conduct the RCA, (3) exploring processes involved, (4) collecting facts and written statements from all involved, (5) performing an evidence-based literature review, (6) identifying possible causes, (7) analyzing the data, (8) proposing possible actions, (9) writing a report, and (10) reevaluating actions taken.[71-73] There is also broad consensus that RCA represents a toolbox of approaches rather than a single method, but a commitment to using a systematic and disciplined approach should remain.[73]

TABLE 53-9 Components of a Problem Statement When Conducting a Root Cause Analysis

What	What happened or should not have happened, or what change in performance is desired?
Where	Where specifically was the problem? This can be geographic, where in a process, and/or location on a piece of equipment.
Who	Who does this problem directly affect, either individual or group?
When	When was the problem first found or when did it begin?
How much	The frequency or magnitude of the problem: numbers provided should be absolute values plus percentages.

From Okes D. *Root Cause Analysis: The Core of Problem Solving and Corrective Action*. Milwaukee: American Society for Quality: Quality Press; 2009.

The first vital step in any RCA process is to identify the problem. Okes[72] has five components that should be answered when developing a problem statement, as shown in Table 53-9. The problem statement should represent cogent thinking and contain definitive, straightforward terminology that is well recognized and not misunderstood.

Step 2 calls for assembling a multidisciplinary group that will facilitate the process.

Step 3 seeks to understand the processes involved in and around the critical event. Why focus on process? Because everything individuals do on a daily basis is a process. Understanding the process is about stepping back and taking a broad view of the problem before jumping to possible causes. This step is especially important if the problem was thought to have been solved previously, but has recurred.[72] Keep the process boundaries internal to the organization, and limit them to those circumstances over which there is control. A flowchart diagram can be helpful for understanding the steps. An example scenario would be a 48-year-old male undergoing a redo 3-level laminectomy who awakens with bilateral blurry vision, only barely able to see shadows. Previous medical history includes secondary hypertension and dyslipidemia. Vital signs are 145/88, heart rate 78 beats/min, respiratory rate 14 breaths/min, and room air saturation is 96%. Recent laboratory results include sodium 136 mEq/L, chloride 108 mEq/L, potassium 3.8 mEq/L, hemoglobin/hematocrit 14.3/44%, and platelets 240. The surgical procedure lasted 5.5 hours and the total anesthesia time was 6.2 hours. Estimated blood loss was 850 mL. Figure 53-5 shows a sample flowchart diagram related to the postoperative visual loss.

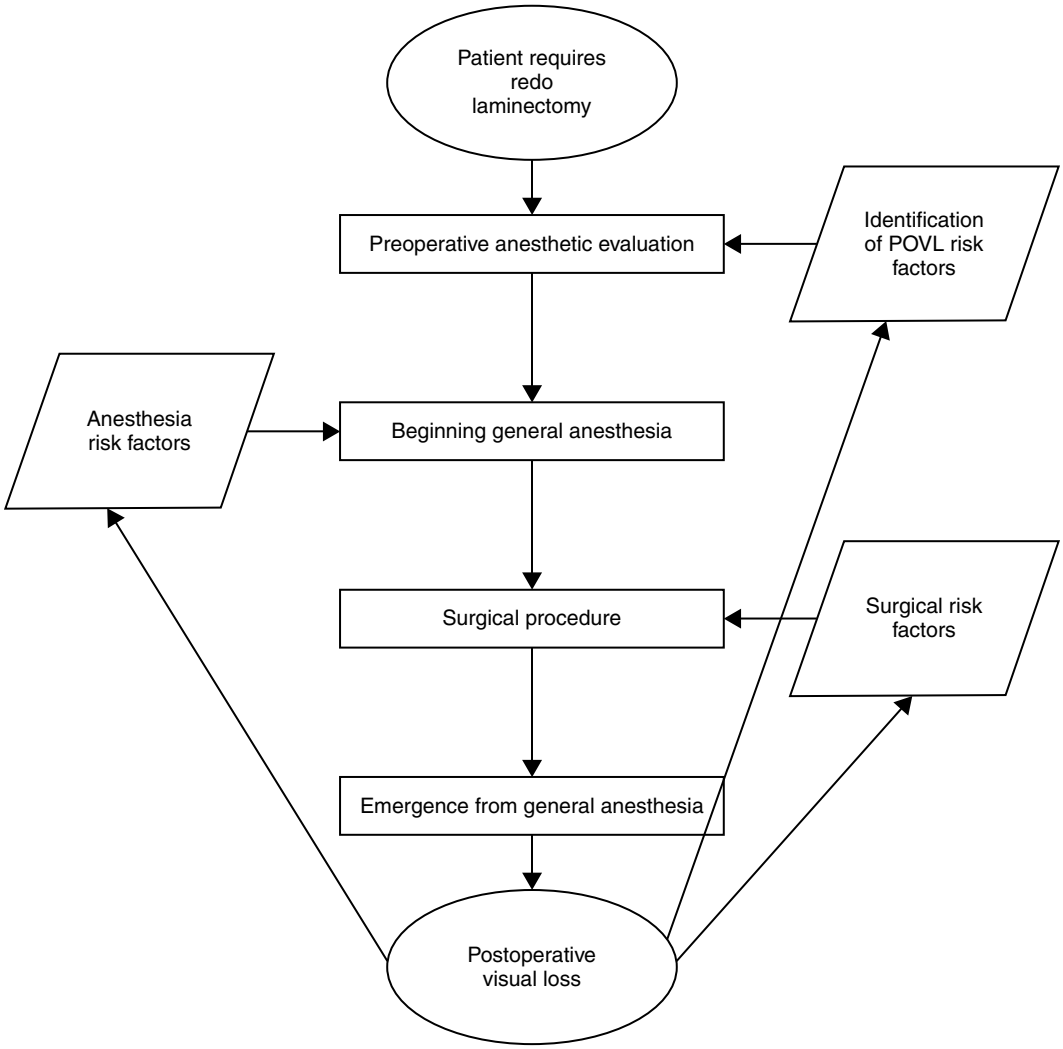

FIGURE **53-5** Sample flowchart diagram for Step 3, understanding the process, in a root cause analysis.

Step 4 involves collecting factual information and perspectives from individuals involved. This should be performed by one individual and compiled for future use by the multidisciplinary group.

Step 5 involves developing a search strategy to locate meaningful, quality evidence to support, refute, or reveal new evidence for the critical event being studied. The essence of evidence-based decision making includes locating the latest and highest-quality information combined with practitioner experience and skill, and incorporating the patient's desires as much as possible.[74] Locating needed information can be easily achieved by visiting the National Center for Biotechnology Information (NCBI) web-based database, which provides access to the National Library of Medicine and PubMed at http://www.nlm.nih.gov. The user should click on PubMed/MEDLINE and search using relevant terms. This website has multiple tools to help with searches. The Cochrane Library of Systematic Reviews and the Cumulative Index of Nursing and Allied Health Literature (CINAHL) databases are also helpful, quality web-based resources that can facilitate an evidence-based search. Other quality web-based resources exist, but the databases mentioned provide a solid, evidence-based foundation.

Once all pertinent data have been accumulated, brainstorming for all possible causes occurs in Step 6. Each brainstormed cause from the multidisciplinary group should ask the question "Why?" in order to form a connection to the critical event. A logic tree is helpful for depicting this thought process and for formulating relationships between each potential cause. An example of a logic tree related to the topic of postoperative visual loss in the scenario described earlier is shown in Figure 53-6.[72] Notice that the tree is hierarchical; the top level of the logic tree is the problem statement (or shorter description), and the next level below lists potential causes across on the same level. Then each level below should describe the causes. Each level of the tree is developed by asking "Why?" or how the step above could have occurred.

Step 7, data analysis, examines which of the causal theories appear plausible and which do not. Being clear about the theory (problem) to be tested and the data acquired to test whether it is true or not is important in analyzing each of the potential causes. Ask questions such as the following: What would the data look like if the theory (problem) were true? Do data collected support or deny the theory (problem) being tested? It is important to consider other conclusions the data might support, other ways to look at the same data, and other data that might confirm or deny the same conclusions. This is where the multidisciplinary group becomes very helpful. There are many ways to analyze data using a variety of diagrams and tools that

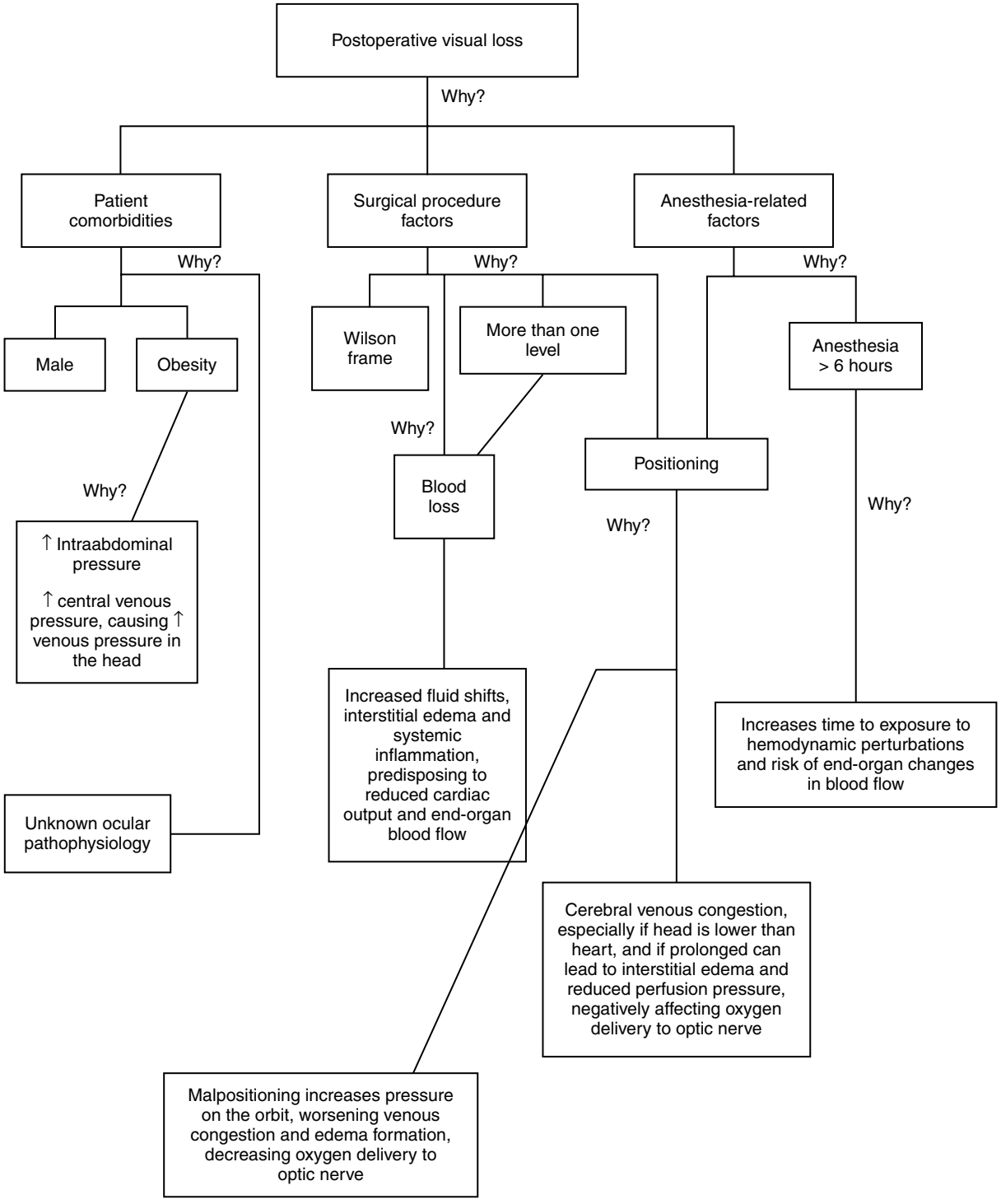

FIGURE **53-6** Sample logic tree diagram for Step 6, identifying potential cause, in a root cause analysis.

are beyond the scope of this chapter. Please see the References section of this chapter as an excellent source for a more detailed approach to data analysis.[72]

Step 8 involves proposing possible actions, which can engender a tendency to formulate only one idea that everyone thinks will work and then immediately implement it. Many tend to think that doing otherwise wastes time, but what is likely to happen is that the institution misses the opportunity to identify and implement breakthrough ideas. If a central idea has emerged, create a concept map, expanding on that idea. The central idea is in the center of the diagram with lines connecting it to expanded or related concepts.

Writing a formal report related to the RCA process is vital. This encompasses Step 9. There are many methods for constructing a report, but primarily the report must be logical, cogent, and factual and devoid of emotion or blame (Box 53-7).

Step 10 calls for reevaluation of actions taken within a certain predetermined time frame. Taking action without checking

BOX **53-7**

Elements of an Root Cause Analysis Report

Executive Summary

- Incident description and consequences
- Pre-investigation risk assessment
- Background and context
- Terms of reference
- Members of the investigation team
- Scope and level of investigation
- Involvement and support of patient and relatives
- Involvement and support for staff involved
- Information and evidence gathered
- Chronology of events
- Detection of incident
- Notable practice
- Care and service delivery problems
- Contributory factors
- Root causes
- Lessons learned
- Recommendations
- Arrangements for shared learning
- Distribution

From Nicolini D, Waring J, Mengis J. Policy and practice in the use of root cause analysis to investigate clinical adverse events: mind the gap. *Soc Sci Med.* 2011;73(2):217-225.

to see whether the process improvement worked is like shooting in the dark.[72]

A vital aspect of RCA is that during discussions of adverse events, the focus on the individual is removed. Therefore, it is less likely that defensive behavior will occur and more likely that reflection on practice will occur openly. RCA can be used to reinforce good practice, support individuals involved in incidents so that they can come to terms with the event, and to explain to patients and families why care was suboptimal and what staff will do to prevent the event from recurring.[70]

Disclosure

Open disclosure of a critical incident and timely communication with patients and families is increasingly being emphasized and is largely responsible for decisions regarding legal action.[65,66] Open disclosure includes accurate information about the critical incident, immediate consequences and remedial action, expression of regret, and other information about preventing such an incidence from occurring again. A survey of 958 adults (31% reported experience with medical errors involving either themselves or another family member) revealed that not disclosing information was associated with lower patient satisfaction, less trust, and stronger negative emotional responses. Patients and families have interpreted healthcare provider silence as hiding information, covering up errors, or showing a lack of respect. Patients and families who take legal actions related to critical incidents do so in an effort to prevent that incident from ever happening again; they want an explanation and feel abandoned, and they desire to make the physicians/healthcare providers realize what they had done.[65,66] A recent interview study (n = 23) using open disclosure after a critical incident supported the positive aspects of open disclosure. All interviewees appreciated the opportunity to meet with staff to receive an explanation of the incident.[75] More research needs to be conducted in this area related to the full impact and techniques of open disclosure

BOX **53-8**

Process for Effective Disclosure

- Continuation of care
- Acknowledgement of incident and patient consequences
- Information on what happened and what to expect
- Apology (when appropriate)/expression of regret
- Advice about necessary treatment
- Information about preventing recurrence
- Tangible support regarding physical, psychological, social, and financial consequences

From Iedema R, et al. Practising Open Disclosure: clinical incident communication and systems improvement. *Sociol Health Illn.* 2009; 31(2):262-277.

on patients, families, and healthcare providers. It is imperative that anesthesia providers comply with state law and/or institutional policies regarding disclosure and not view disclosure as an individual endeavor (Box 53-8).

THE SECOND VICTIM

Complications, in the healthcare provider's eyes, have been described as the darkest hour of one's professional career.[76] Involvement of healthcare providers in critical incidents and the emotional turmoil that ensues is often regarded as taboo and to be avoided at all costs. No one wishes to be involved in the drama. Psychological stress and negative emotional responses can engulf the practitioner, creating serious health and performance deficits.[65,66,76,77] This practitioner is called *the second victim*, or a healthcare provider involved in an unanticipated adverse patient event who becomes victimized. The second victim is traumatized by the critical/adverse event. Frequently these individuals feel personally responsible and believe they have failed their patients and begin second-guessing their clinical skills and knowledge.[65,66,76] Some healthcare providers even report developing post-traumatic stress disorder, sleep disturbances, and problems with irritability. As a result, it becomes harder to work clinically and have job satisfaction. Published evidence addressing emotional and health-related effects of critical incidents on healthcare providers have looked only at short-term outcomes. However, a recent prospective longitudinal study examining medical errors by residents (n = 184) over a 3-year period found that self-perceived errors were common among trainees. These errors were associated with significant personal distress, burnout, loss of empathy, and increased risk of making another error.[78] Time to recovery from these symptoms can last for several months.[77]

Stages of Recovery

Participants develop their own unique way of coping, yet each describes a predictable recovery trajectory. Six stages of recovery are listed in Box 53-9.[76] At the moment the critical incident occurs, the involved clinician can usually describe chaotic and confusing scenarios of external and internal turmoil that ultimately lead to a realization about what happened. There is a period immediately after the incident of rapid inquiry to verify exactly what happened. Additional clinicians are summoned to provide support. The victim is frequently distracted, immersed in self-reflection, while also trying to manage a patient in crisis. The second stage is characterized by haunted reenactments, often accompanied by feelings of internal inadequacy.

BOX **53-9**

Stages of Second Victim Recovery

1. Chaos/accident response
2. Intrusive reflections
3. Restoring personal integrity
4. Enduring inquisition
5. Obtaining emotional first aid
6. Moving onward

From Scott SD, et al. Caring for our own: deploying a systemwide second victim rapid response team. *Jt Comm J Qual Patient Saf*. 2010; 36(5):233-240.

The victim reevaluates the situation repeatedly with "what if" questions. Stage 3 is entered when the victim seeks support from a trusted individual, usually a colleague or supervisor, friend, or family member. One of the biggest challenges in this stage is an inability to move forward and introspection related to "what will others think of me" and "will I ever be trusted again." Then in Stage 4 the individual wonders what the ramifications from the institution will be and "will I ever practice again." Second victims in Stage 5 seek out respected and safe colleagues to confide in. Litigation issues are often discussed. Stage 6 is a unique stage describing the second victim as moving on—dropping out, surviving, or thriving.[76]

What do practitioners need emotionally and professionally after a critical incident involvement? Little evidence exists to address this issue, but four primary needs have been identified after a critical incident involvement: (1) talking to someone about what happened, (2) validation of decision-making process, (3) reaffirmation of professional competence, and (4) personal reassurance.[65,66] Colleagues and supervisors are perceived as being the most helpful people with whom to discuss the situation. However, evidence suggests that little support is obtained at an organizational level. This lack of support after a critical incident often causes the negative emotional responses and psychological stress to be sustained.[76] Along with emotional needs, there are definite professional needs that should be met as well. The anesthetist should consider speaking with the appropriate hospital administrators and possibly an attorney if there is litigation or expected litigation.[79]

THE HUMAN FACTOR IN COMPLICATIONS

Human Error

Human error is inevitable. The most important component of anesthesia is the anesthesia provider, the human performance embedded in a larger system of care. Human failures have been identified in 51% to 77% of anesthesia-related deaths.[9] Most cases are related to lack of experience or competence observed in 89% of human failures–related deaths. Less frequently, errors of judgment or analysis were detected in 11% of these deaths.[4]

The topic of human error is rich in myths, such as error is intrinsically bad; bad people make bad errors; and errors are random and highly variable.[67] Errors are not intrinsically bad, but instead are essential for coping with trial-and-error learning in novel situations. One of the basic rules of error management is that the best people can make the worst errors. Many times the best people tend to push at the limits of existing practice by trying out new techniques. Errors do not occur "out of the blue," but do take on recurrent and predictable forms. Different errors occur in different situations. Errors happen when individuals know what they are doing, but actions do not go as planned, taking the form of absent-minded slips and memory lapses. Errors also can happen when individuals think they know what they are doing, as in dealing with what appears to be a trained-for problem, but then misapply a normally good rule, apply a bad rule, or fail to apply a good rule. Errors are certain to occur when the individual is not sure what he or she is doing.[67]

Past concepts related to human error in health care have not embraced the statement that human error is inevitable, but tried to avoid or prevent human error, doing so without success.[80] It has been argued that judgments of human error should form the starting point of accident investigations, not be the explanation for the failure.[80,81] Human involvement in complex systems is necessary and beneficial, because of our ability to adapt, our creativity, and our ability to be flexible.[80] This relevance of human factors in improving safety cannot be overstated. Even though we cannot change the human condition, we can change the conditions under which humans work.[67]

The aviation industry realized, embraced, and acted upon human factors more than 20 years ago. A systematic approach to safety at an organizational level is currently in practice in the aviation industry and has been recommended as an approach to dealing with human factors in anesthesia. This type of safety culture possesses certain features such as standard operating procedures, operations manuals, and checklists that could be incorporated into anesthetic practice; however, there is a certain amount of reluctance to embrace these tools, perhaps for fear of being constrained in exercising clinical judgment and critical thinking as well as being forced to forego practical long-standing techniques.[80]

A key concept related to human factors is the concept of resilience. Resilience is an everyday word synonymous with *buoyant*, *elastic*, and *flexible*, and it can describe an individual's ability to recover readily from illness, depression, or some other life adversity. A human factors perspective of resilience refers to the ability to understand how failure is avoided and how to learn from successes and error avoidance rather than simply conduct a reactive search for causes and remedies. It offers a systems-based approach to understanding how to stay safe proactively. Resilience is a positive human attribute that can be used to bounce back from errors made, learn from mistakes, and move forward. Resilience has the potential to provide significant advances in patient safety by shifting focus from an emphasis on human error and error counting to preventing these errors from being repeated.[82,83]

Human factors that contribute to complications often include nontechnical skills and behaviors. Lack of communication and teamwork have been shown to contribute to 43% to 65% of sentinel events occurring in the operating room (e.g., wrong side, transfusion error). Poor team performance has been the trigger for the development of crew resource management, which has been adapted to health care and anesthesia in the form of crisis resource management.[84] Communication is fundamental to workplace efficiency and safety. Elements of good communication are not just verbal, but nonverbal as well (Box 53-10). Good communication is a major part of good teamwork. Teamwork represents a distinguishable set of two or more people who interact dynamically, interdependently, and adaptively toward achieving a common goal, who have each been assigned specific roles or functions to perform, and who have a limited life span of membership (Box 53-11). Effective teamwork and communication do not happen alone, but must be developed through training. Training individuals working in a team is based upon developing competence, knowledge, skills, and attitude of individuals as well as training objectives. Teams should develop identity, in which team

BOX 53-10

Elements of Good Communication

- Send information clearly and concisely
- Include context and intent during information exchange
- Receive information, especially by listening
- Identify and address barriers to communication

From Flin R, O'Connor P, Crichton M. *Safety at the Sharp End: A Guide to Non-Technical Skills*. Burlington, VT: Ashgate Publishing Ltd; 2008.

BOX 53-11

Elements of Teamworking

- Supporting others
- Solving conflicts
- Exchanging information
- Coordinating activities

From Flin R, O'Connor P, Crichton M. *Safety at the Sharp End: A Guide to Non-Technical Skills*. Burlington, VT: Ashgate Publishing Ltd; 2008.

members learn their own roles and tasks and understand those of other team members.[67,85] Simulation provides a teaching and learning methodology that allows team members to practice crisis resource management and develop nontechnical skills and behaviors to improve teamwork and communication.[4]

Fatigue

Fatigue is the largest identifiable and preventable cause of accidents. The aviation industry estimates that fatigue may involve 4% to 7% of civilian aviation accidents, and anywhere between 4% to 25% of military aviation accidents. Fatigue, anesthesia, and complications have not traditionally been discussed together, but are an expanding science of interest and a significant safety concern. Anesthesia care is a 24-7 profession, and consequently this can require long working hours, sustained vigilance, unpredictability of stressful situations, and production pressure.[85] Currently no quantitative data exist regarding the incidence of complications in anesthesia related to the fatigued provider. Reducing work hours and allowing 24 hours of sleep time between shifts significantly impacted attentional failures (i.e., intrusion of slow rolling eye movements into confirmed episodes of wakefulness during work hours) in a small prospective study with interns.[86] The Joint Commission has published evidence-based actions that healthcare organizations can incorporate to help mitigate the risks of fatigue (Box 53-12).[87]

Stress

Every anesthesia provider knows what it feels like to be under stress, both professionally and personally. Stress can have both acute and chronic effects. Acute stress in humans can be related to the classic fight, flight, or freeze response.[85] Chronic stress is related to conditions in the workplace and the individual's reaction to these over a period of time. Stress has been linked to safety outcomes, such as accident involvement. Because stress has been linked to accident involvement and safety outcomes, the ability to recognize and manage stress in self and others is an important nontechnical skill. Job demands, control over work activities, support or lack thereof from managers or coworkers, poor relationships, uncertain work

BOX 53-12

The Joint Commission Action Suggestions for Healthcare Provider Fatigue

1. Assess organizational fatigue-related risks (e.g., shift hours)
2. Assess patient handoff processes
3. Invite staff input for schedule design to promote less fatigue
4. Create and implement a fatigue management plan to help fight fatigue
   a Conversation
   b Strategic caffeination
   c Short naps (less than 45 minutes)
5. Educate staff about sleep hygiene and effects on patient safety
6. Provide opportunities for expressing concerns about fatigue
7. Encourage teamwork as a strategy to support staff working extended hours
8. Consider fatigue potentially contributing to adverse events

From Jeffcott SA, et al. Improving measurement in clinical handover. *Qual Saf Health Care*. 2009;18(4):272-277.

roles, uncertainty about change, and family-personal problems are all considered stressors. How each individual handles these with the resources available to them using prior experience, training, personality, fitness, social support, and coping strategies will indicate whether the stress will have a positive or negative effect on the individual. The effects of stress on behavior are generally the most readily observable by work colleagues (Table 53-10). For example, a placid coworker becomes irritable, or a colleague who generally has a neat appearance begins to take less interest in how he or she looks.[85]

Patient Handoff/Communication

Communication issues and breakdowns in communication have been estimated to contribute between 15% and 67% to the development of critical incidents.[88] In particular, communication at organizational interfaces (e.g., care transitions, shift changes) with changing responsibility for care is a key target for improvement.[89] A surgical patient undergoing elective surgery can have direct patient care change a minimum of at least four times (e.g., admission area to surgery/anesthesia to postanesthesia care area to unit/floor).

A clinical handover/handoff or transfer of care is by definition, "the transfer of professional responsibility and accountability for some or all aspects of care for a patient, groups of patients to another person or professional group on a temporary or permanent basis."[65,66,89,90] The Joint Commission defines handoffs as the real-time process of passing patient-specific information from one caregiver to another or from one team of caregivers to another for the purpose of ensuring the continuity and safety of patient care.[91]

Historically, patient handover has not been studied systematically, which is in stark contrast to other high-risk industries where handovers have received considerable attention. Qualitative studies and surveys across different healthcare settings cite that handover processes are highly variable with widespread dissatisfaction among physicians and nurses.[65,66,88] As a result, patient handover has been recognized as a safety initiative by the World Health Organization (WHO) Alliance for Patient Safety and the WHO Collaborating Center for Patient Safety for over 5 years and is listed as one of the National Patient Safety Goals by The Joint Commission.[91] There has been a substantial increase in research activity and literature reviews across healthcare disciplines focusing on a specific type of handover in a specific clinical setting (e.g., nursing, physicians, perioperative care area)[88,92,93] (Figure 53-7).

TABLE 53-10 Indicators of Chronic Stress

Behavioral	Emotional	Somatic	Thinking	Organizational
• Absenteeism • Abuse of drugs • Hostile behavior • Apathy • Reduced productivity • Distracted • Careless errors	• Anxiety • Hopelessness • Cynicism • Resentfulness • Depression • Irritability	• Decline in physical appearance • Chronic fatigue • Frequent infections • Health complaints (e.g., headache, stomach)	• Lack of concentration • Reduced attention • Difficulty in remembering • Impaired decision making • Failures in planning	• High staff turnover • Absenteeism • Poor timekeeping • Decreased productivity • Increased client complaints • Increased employee compensation claims • More near-misses and accidents

From Flin R, O'Connor P, Crichton M. *Safety at the Sharp End: A Guide to Non-Technical Skills*. Burlington, VT: Ashgate Publishing Ltd; 2008.

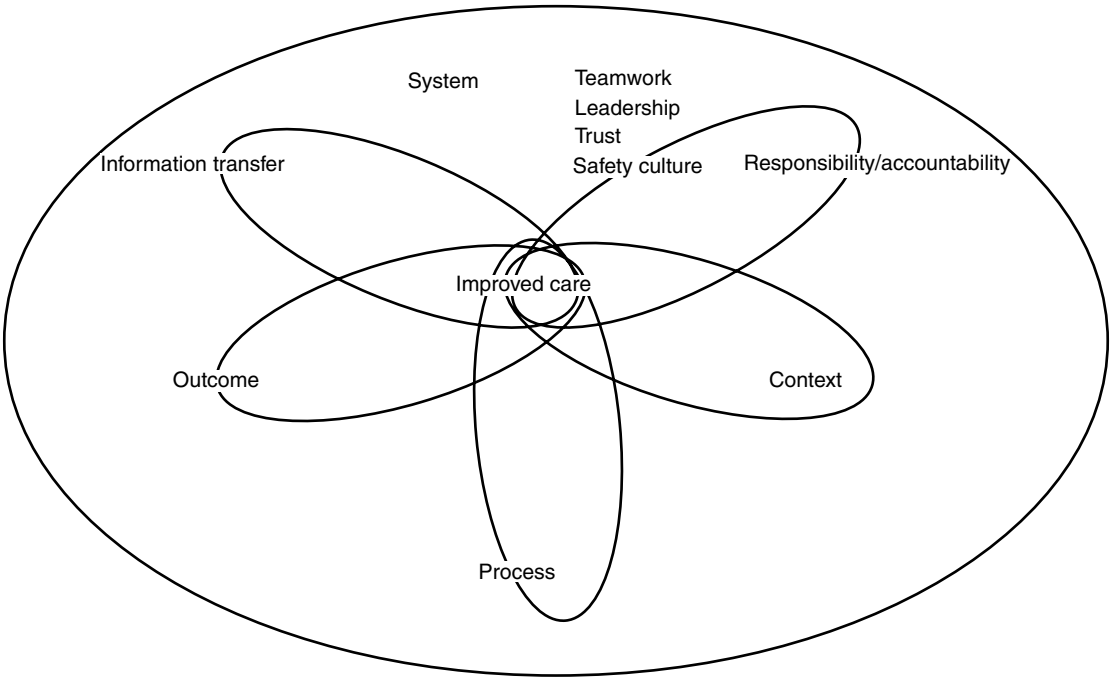

FIGURE **53-7** Conceptual model of handover elements. (From Jeffcott SA, et al. Improving measurement in clinical handover. *Qual Saf Health Care*. 2009;18[4]:272-277.)

Certain handoff attributes contribute to potential complications such as truncated handoffs and omission of information due to work demands or time constraints, unfinished diagnostic and care activities, or a perceived lack of trust or familiarity with the participating individual.[94,95] A self-reporting survey among 133 residents found that 31% had experienced an issue for which the handover had not prepared them.[96] Another recent study reviewing 2729 critical incidents found that the most frequent type of handover incident reported besides an incomplete handover (45.2%) was no handover at all (29.3%).[97]

Nagpal et al.[92,93] studied information transfer and communication (ITC) across the entire surgical care pathway in patients undergoing major gastrointestinal procedures. Most ITC failures were observed during the preoperative phase (61.7%) and postoperative handover (52.4%). Seventy-five percent of patients had clinical incidents or adverse events because of ITC failures.

So what constitutes a handover that contributes to the quality and safety of patient care? Quality of the handover depends on the perception as to what is the primary function of the handover (e.g., information or responsibility transfer, shared decision making).[65,66,89,90] Handover quality measures can be grouped into five areas: (1) information delivery or transfer, (2) responsibility/accountability, (3) context and environments, (4) the handover process, and (5) handover outcome.[83,88] For a conceptual model of handover elements, see Figure 53-7.

Measures of handover content appear to be straightforward, but which items should be included in a list for a quality handoff can vary depending on the clinical setting, timing, and individual perceptions and experience.[65,66] The list can often become lengthy and generate heated discussions. Most handover content should concentrate on completeness and accuracy of information and related errors. Purely verbal handovers have been found to be the most incomplete when compared with information available in the patient record or located in a predefined protocol.[89,90,94] A noisy operating room and an anesthetist that is in a hurry may not create the optimal handover process, leaving a gap for crucial information to be missed. The generation of evidence in this area is extremely limited, and there is still an open question regarding how various process measures translate into safe care.[65,66,89,90]

Handover outcome measures usually include healthcare provider satisfaction. An observational study conducted in three different clinical settings (e.g., paramedic to emergency room, anesthetist to

postanesthesia care unit [PACU], and PACU to floor/unit nurse) found that although information transfer was the key characteristic, overall handover quality was predicted by three factors: information transfer, shared understanding, and working atmosphere.[65,66,89,90]

Professional organizations have published guidelines for handover communication, and standard approaches do exist that can improve handover communication. Study outcomes evaluating adherence to a protocol for handovers demonstrated statistically significant improvement in handover quality and improved teamwork.[98] Another approach focuses on general interaction structures and does not define actual content, but instead focuses on an order of topics to be covered. Both approaches have demonstrated improvements in teamwork and communication, which are factors that have translated into a significant reduction in morbidity and mortality in surgical patients.

An emerging area related to communication and handovers is incorporating a shared understanding among a healthcare team during a handover so that a handover is not a one-person–one-way process. An ideal patient handover conducted as a team-based activity would comprise an episode of shared cognition and understanding among healthcare providers and an opportunity for collaborative cross-checking. In this view, handovers represent a source of resilience for healthcare systems.

Standardized handovers in anesthesia have been proposed. One approach to handover content defines specific content to be included and also an order in which the information should be presented using a checklist-type format. A second approach focuses on the environment and general interaction structures without any defined content.[65,66]

The electronic medical record (EMR) system has been proposed as one solution that provides a handover sheet that can easily be extracted to improve completeness of handover information. Arora et al.[89,90] systematically reviewed studies reporting interventions for improving patient handovers and found that technology solutions were associated with a reduction in preventable adverse events and improved satisfaction with handoff quality and also improve provider identification. Technology, however, ignores behavioral and cultural aspects of communication and does not necessarily improve communication.

SUMMARY

It is important to recognize the effect of local culture as a key underpinning for processes for improvement. A culture of blame is no longer acceptable and should not be supported.[65,66] Learning from a critical incident can be both prospective (deliberating in advance of process changes and how they might affect safety) and retrospective (learning from events that have already transpired). It is important in these educational interventions to reinforce that errors are not always the cause of accidents, and blaming an individual may hinder uncovering a latent error or problem in the system. If reporting is safe and provides useful information from expert analysis, then it can measurably improve safety. Transfer of care is complex—much more involved than one-way communication—and is a major source of error, yet specific contribution to these errors and their evaluation remain unclear. A more complete understanding of the processes involved is needed. Safety is a dynamic "non-event" when individuals employ foresight, coping, and recovery to bridge gaps, thereby avoiding failure.

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